PRESERVATION OF MYOCARDIAL CONTRACTILITY IN DOGS AFTER BLOOD-INDUCED CARDIOPLEGIA

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KEY WORDS: blood-induced cardioplegia; potassium-induced cardioplegia; preservation of the heart; myocardial contractility.

Cardioplegia induced by coronary perfusion with cooled whole blood has not given a high protective effect against myocardial ischemia [1, 5, 6, 8, 11]. This method has been replaced by the use of cardioplegic solutions [2-4, 7, 12-14]. Their optimal composition is not yet known. Dissatisfaction with the practical results of the use of cardioplegic solutions has renewed interest in blood-induced cardioplegia [9, 10].

To enhance the anti-ischemic action of cooled blood, it was corrected in order to create hemodilution, hyperosmolarity, hyperkaliemia, and alkalification. Periodic perfusion during prolonged exclusion of the heart were aimed at removing metabolic products, supplying oxygen and oxidation substrates, and maintaining hypothermia. To obtain direct data on the effect of the suggested method of anti-ischemic protection of the myocardium, the contractility of a fragment of the auricle of the left atrium at different stages of preservation of the heart was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 17 dogs weighing 4-9 kg. The animals were anesthetized by intramuscular injection of trimeperidine (7 mg/kg), droperidol (0.5 mg/kg), and atropine (0.2 mg); 30 min later pentobarbital (25-30 mg/kg) was injected intravenously. During artificial ventilation of the lungs, thoracotomy was performed and heparin injection in a dose of 3 mg/kg. In 17 experiments strips of the auricle of the left atrium were taken before the heart stopped (control).

Autologous blood was collected with the pressure in the ascending aorta stabilized at 70 mm Hg. The autologous blood was used to prepare a perfusion fluid, with the addition of rheopolyglucin (hemodilution 20-25%, Hb 8-9 g%, osmolarity of the perfusion fluid 320 milliosmoles/liter), 5% KCl (K^+ in the perfusion fluid 20-25 meq/liter), and 0.2 M Tris-buffer (pH of the perfusion fluid 7.7). The perfusion fluid was cooled to 15°C and injected into the coronary arteries under a pressure of 60 mm Hg in a dose of 3 ml/g weight of the heart. The arrested heart was preserved in physiological saline at 15°C for 120 min. Every 20 min perfusion with the cardioplegic mixture was resumed at the rate of 1 ml/g weight of the heart. In 6 experiments fragments of the auricle of the left atrium was taken after preservation of the heart for 60 and 120 min in order to study their contractile activity.

The preparation was fixed in a continuous flow chamber with a capacity of 0.5 cm^3, through which oxygenated Krebs' solution (pH 7.3, temperature 37°C, pO_2 500 mm Hg) was passed. Contractions close to isometric were recorded with the 6MKh1S mechanotron. For the first 50 min the myocardium was stimulated by square pulses 5 msec in duration and with an amplitude 1.5-2 times above threshold, with a frequency of 1 Hz. After "warming up," the frequency—strength curve was recorded while the rhythm of stimulation was increased from 0.2 to 1 Hz in steps of 0.2 Hz, and again at 2 Hz. Myocardial contractility was estimated from the change in shape of the frequency—strength curve and the amplitude of the first contractile responses after various (10, 30, 60, and 300 sec) intervals of rest. The following parameters were analyzed: amplitude (P), maximal rate of contraction (P'), duration of the

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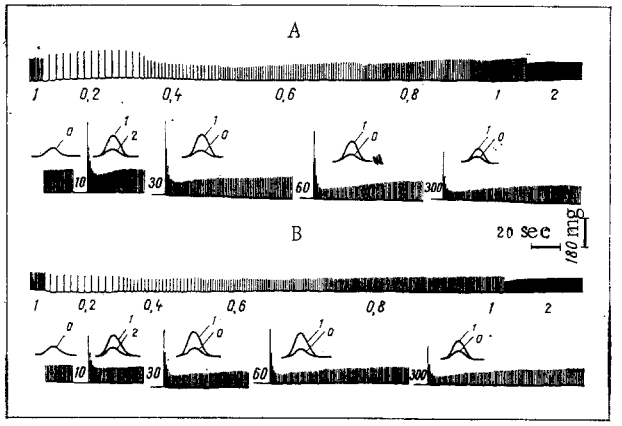

Fig. 1. Frequency—strength relations in control (A) and in experiments with preservation of dogs' heart for 2 h (B). Top trace — change in amplitude of myocardial contractions during variation in frequency of stimulation, values of which, in Hz, are shown. Bottom trace, amplitudes of contractions after various intervals of rest, above which first high-amplitude contractions after rest (1) and steady-state contractions in rhythmic series (0) are shown with faster sweep. Numbers in front of traces indicate duration of cardiac arrest (in sec).

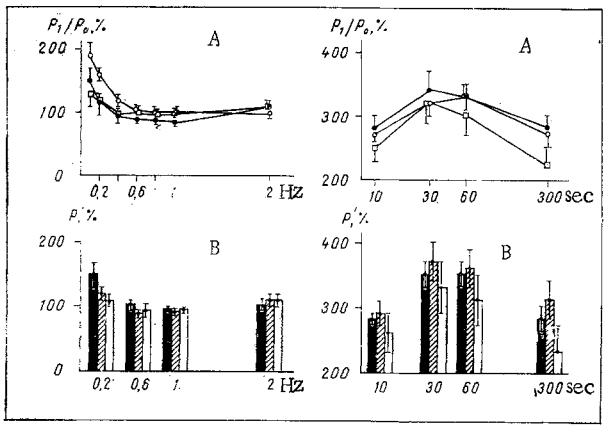

Fig. 2 Fig. 3

Fig. 2. Dependence of steady-state amplitude (A) and maximal rate of contraction (B) of myocardial fragment on frequency of stimulation in control and after preservation of the heart. A) empty circles — control; filled circles — after preservation for 1 h; squares — after preservation for 2 h; P_o) amplitude of steady-state contractions to stimulation with a frequency of 1 Hz in control, P_1) amplitude of steady-state contractions at different frequencies. B) Black columns — control; obliquely shaded — after preservation for 1 h; unshaded — after preservation for 2 h. Ordinate, maximal rate (P'), normalized P_{max} to stimulation with a frequency of 1 Hz (in percent).

Fig. 3. Dependence of amplitude (A) and maximal velocity (B) of first contraction after rest on duration of rest interval in control and after preservation of the heart. A) Empty circles — control; filled circles — after preservation for 1 h; squares — after preservation for 2 h; P_o) amplitude of contraction during stimulation with a frequency of 1 Hz, P_1) amplitude of first contractions after various rest intervals. B) black columns — control; obliquely shaded — after preservation for 1 h; unshaded — after preservation for 2 h. Maximal velocity of contraction normalized on maximal velocity of contraction to stimulation with a frequency of 1 Hz.

phases of contraction and relaxation, and also the total time of the contractile responses measured at the level of 10% of amplitude.

EXPERIMENTAL RESULTS

Frequency—strength curves in the control are illustrated in Fig. 1A (top trace) and Fig. 2A. With an increase in the frequency of stimulation the established amplitude of contractions fell initially. However, when the rhythm of stimulation was increased above 0.6 Hz a tendency was observed for a small increase in amplitude of contractions. The maximal rate of development of tension was independent of the frequency of stimulation (except contractions to stimulation with a frequency of 0.2 Hz).

During stimulation of the preparation by series of pulses (Fig. 1A, bottom trace) the first stimulus after rest evoked a high-amplitude contraction. The amplitude of the subsequent five or six contractile responses decreased progressively. The amplitude of contractions then gradually increased. Dependence of the amplitude of the first contractile response on the interval of rest is shown in Fig. 3A. The greatest contractions were observed after interruption of stimulation for 30-60 sec. The same dependence on the rest period also was found for the maximal rate of rise of tension in the first contractile response (Fig. 3B).

Preservation of the heart for 1 h caused no significant changes in the characteristics recorded (Figs. 2 and 3). The threshold of excitability did not increase. The frequency—strength curve was practically the same as initially, and only at frequencies up to 0.6 Hz was a small decrease in the steady-state amplitude of contraction recorded (Fig. 2A). Differences in the maximal velocity of contractions were not statistically significant (Fig. 2B). During tests interruptions of stimulation, the "ladder" remained biphasic in type. Dependence of amplitude of contractions (Fig. 3A) and of the maximal rate of development of contraction (Fig. 3B) on the rest interval remained unchanged.

Preservation of the heart for 2 h also had hardly any effect on myocardial contractility. The threshold of excitability was not raised, the frequency—strength curve (Fig. 2A) and the shape of the "ladder" were preserved (Fig. 1B, bottom trace), and dependence of the amplitude of the first contraction after rest on its duration also was unchanged (Fig. 3A).

After a rest period of 300 sec a small decrease in amplitude was observed. Irrespective of the conditions of stimulation, the maximal velocity of contraction was the same as originally (Figs. 2B and 3B).

Many investigations have shown that arrest of the heart and its exclusion from the circulation lead to inhibition of its contractility. This is expressed as a decrease in the amplitude of contractions, a decrease in the rate of development of contraction and relaxation, impossibility of rhythm binding at high frequencies, an increase in the relaxation time, and so on. These changes, as well as absence of the first high-amplitude contraction after rest, characteristic of the atrial myocardium of most warm-blooded animals, are connected with worsening of the functional state of the Ca^{++}-transport systems (sarcoplasmic reticulum, Na—CA exchange diffusion), and with a decrease in the Ca^{++} flow along electrically excitable slow Na—Ca channels [15].

A cause of the changes described above during ischemia is a disturbance of the energy supply to the myocardial cells which, in turn, leads to disturbance of the metabolism, structure, and function of the organ as a whole. Protection of the heart when excluded from the circulation is aimed chiefly at abolishing the leading mechanisms of ischemic injury.

Experiments to assess the protective action of the cardioplegic perfusion fluid derived from blood showed that preservation of the heart for 1 and 2 h by means of this method can prevent considerable changes in the recordable characteristics of myocardial contractility. This indicates that the suggested method can be successfully used to protect the myocardium during exclusion of the heart from the circulation.

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