EFFECT OF AN EMULSION OF FLUORINATED HYDROCARBONS ON THE PROTECTIVE PROPERTIES OF CARDIOPLEGIC SOLUTIONS

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UDC 616.127-005.4-084:615.22:615.451.23

KEY WORDS: emulsion of fluorinated hydrocarbons; cardioplegia; resting tension, membrane potential.

Analysis of traditional methods of protecting the myocardium against anoxic damage during open heart operation (cardioplegia with hyperpotassium and procaine-containing solutions) has shown that the main factor causing exhaustion of the energy reserves of the myocardium is membrane depolarization during entry of the cold cardioplegic solution into the coronary vessels. The result of this depolarization is an increase in the Ca^{++} concentration in the cytoplasm, which requires additional expenditure of energy to maintain calcium homeostasis [7]. Prevention of excess inflow of calcium into the cytoplasm and a better oxygen supply to the myocardium can evidently make traditional methods of protecting the myocardium against ischemia more effective. Unfortunately, traditional blockers of Ca channels have no protective action during hypothermia, which is an essential component of myocardial protection [7, 10]. Oxygenation of crystalloid cardioplegic solutions does not give the desired effect because of their low oxygen capacity. The writers previously suggested a new kind of cardioplegic solution based on an emulsion of fluorinated hydrocarbons which, in its gas-transporting and membranotropic properties, proved to be exceptionally effective in protecting the myocardium during open heart operations on patients with acquired heart defects [2].

The aim of this investigation was to study the effect of an emulsion of fluorinated hydrocarbons (EFH), developed at the Institute of Biological Physics, Academy of Sciences of the USSR, on the protective properties of a hyperpotassium cardioplegic solution.

EXPERIMENTAL METHOD

Experiments were carried out on 118 rat hearts. There were six series of experiments, in each of which the resting tension (RT), membrane potential (MP), and heat production were determined. The experimental conditions were as follows (for each series): myocardial ischemia at 35°C (RT and MP were determined in 10 investigations, heat production in 6); myocardial ischemia at 17°C (10 and four investigations, respectively); cardioplegia with balanced salt solution (BSS) at 35°C (six and six); cardioplegia with BSS at 17°C (40 and four); cardioplegia with BSS based on EFH at 17°C (16 and five). A hyperpotassium balanced crystalloid solution of the following composition (in mM) was used as the control cardioplegic solution: NaCl 71.8, KCl 29, MgCl 2.1, $NaHCO_3$ 15, NaH_2PO_4 1.4, mannitol 44, glucose 28, calcium gluconate 1.2. A similar ionic composition also was present in the EFH. Before use, both preparations were oxygenated with carbogen (pO_2 350-400 mm Hg). After excision, the rat heart was placed in physiological saline at the corresponding temperature. In the experiments with cardioplegia, the cardioplegic solution was infused into the coronary vessels for 1 min. The heart was fixed at the aorta and apex, to produce tension of 1-2 mm Hg. Isometric tension (in mm Hg/g weight of the heart), amplified tenfold, was recorded as the parameter of RT. Since the volume of RT depends on the calcium concentration [6, 8], its approximate concentration in the sarcoplasm was calculated by the formula:

$$Ca^{2+} = \frac{10 \cdot F \cdot K}{m},$$

where F is the resting tension of the heart (in mm Hg/g), m the weight of the heart (in g),

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Laboratory of Medical Biophysics and Biochemistry, Institute of Biological Physics, Academy of Sciences of the USSR, Pushchino. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 8, pp. 183-185, August, 1986. Original article submitted July 9, 1985.

 0007-4888/86/0008-1078 $12.50

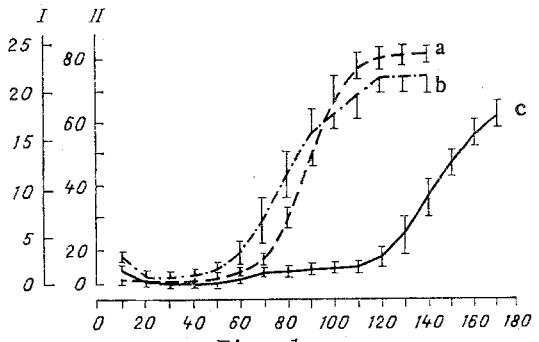

Fig. 1

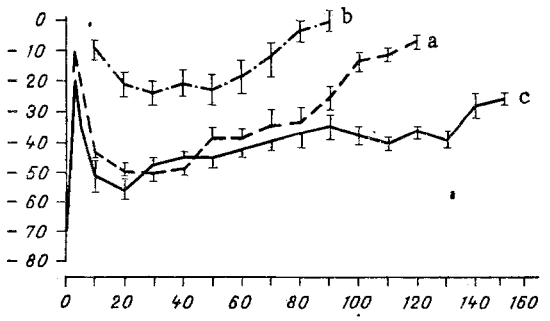

Fig. 2

Fig. 1. Time course of RT and corresponding change in Ca^{++} concentration in myocardium (t = 17°C). Abscissa, time (in min); ordinate: I) Ca^{++} concentration (in nanomoles/g); II) RT (in mm Hg/g). a) Crystalloid hyperpotassium cardioplegia; b) ischemia; c) cardioplegia with EFH.

Fig. 2. Time course of myocardial MP (t = 17°C). Abscissa, time (in min); ordinate, MP (in mV). Remainder of legend as to Fig. 1.

K a conversion factor equal to 0.34 (in nanomoles/mg Hg) [5]. The resting MP was recorded simultaneously by means of a floating electrode. The microcalorimetric investigations were conducted by the known method on a "Setoram" microcalorimeter (France) [1]. In cases of cardioplegia, calorimetry began after a delay of 3 min, which was necessary for infusion of the corresponding solutions into the coronary vessels.

EXPERIMENTAL RESULTS

The investigations showed the considerable advantage of the cardioplegic solution based on EHF in myocardial protection, which was expressed as follows. Emulsion-induced cardioplegia delayed the development of ischemic contracture to 2 h as a result of a single infusion of the solution, whereas the traditional cardioplegic solution lengthened this time by only 10-15 min compared with ischemia. At the same time, accumulation of Ca^{++} in the myocardium took place more slowly during emulsion-induced cardioplegia (Fig. 1). The study of the time course of MP revealed a lower level of depolarization of the cell membranes and greater stability of depolarization in cardioplegia induced by EHF (Fig. 2). This fact may be linked with the membrane-stabilizing action of fluorinated hydrocarbons [3].

When the emulsion was used, a lower degree of diastolic contracture was observed, a direct result of accumulation of less Ca^{++} in the cytoplasm. The writers' previous experiments on isolated preparations of myocardium show that this effect is linked with blocking of the transmembrane inflow of Ca^{++} under the influence of EHF. It is noteworthy that this property of fluorinated hydrocarbons is preserved at a low temperature (Fig. 3), in contrast with known Ca antagonists, which can no longer block Ca channels at temperatures below 25°C [7, 10].

It will be clear from Table 1 that in cardioplegia with EHF a higher level of heat production was observed. In experiments with traditional hyperpotassium cardioplegia, heat production was less than that of the ischemic heart. This evidently is due to the considerable energy expenditure in the initial period of cardioplegia, which is characterized by a sharp rise of dia-

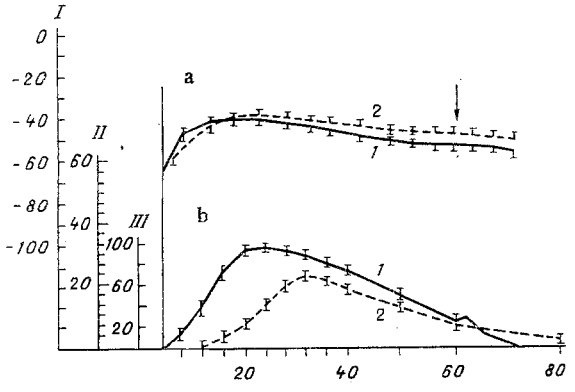

Fig. 3. Time course of MP (a) and RT (b) in initial period of cardioplegia (t = 17°C). Abscissa, time (in sec); ordinate: I) MP (in mV); II) Ca^{++} concentration (in nanomoles/g); III) RT (in mm Hg/g). 1) Crystalloid solution; 2) EFH. Arrow indicates end of infusion of cardioplegic solutions.

TABLE 1. Total Quantity of Heat Liberated by the Heart during Dying, mcal·(min^{-1}·2^{-1})

Experimental conditions	35 °C	17 °C
Myocardial ischemia	1544±23	1260±21
Cardioplegia with BSS based on EFH	1789±62	1442±48
Cardioplegia with traditional BSS	1367±25	1179±67

stolic tension and a parallel rise of the intracellular Ca^{++} concentration (Fig. 3). The high heat production of the heart in the emulsion version can be taken as evidence that the energy resources are better preserved during survival of the heart.

The cardioplegic solution based on EHF thus reduces Ca^{++} accumulation in the cytoplasm, and thereby leads to economical utilization of the energy reserves of the myocardium, and improvement of the oxygen supply ensures better conditions for resynthesis of high-energy compounds in the myocardium. Both these processes are ultimately reflected in the total increase of heat production (by 31% under normothermic conditions, by 22% in hypothermia) and the almost doubling of the safe period of myocardial ischemia compared with that observed when traditional methods of cardioplegia are used. All the above-mentioned effects of the emulsion are extremely important for myocardial protection during complicated reconstructive operations on the heart with an artificial circulation. In our view the use of cardioplegic solutions based on EHF for the prevention of ischemic damage to the myocardium can widen the scope of cardiac surgery and of organ conservation.

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