ANTIARRHYTHMIC ACTION OF AN EMULSION OF FLUORINATED HYDROCARBONS

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Considerable attention is currently being paid in the USSR and elsewhere to the development and testing of blood substitutes in the form of oxygen carriers based on emulsions of fluorinated hydrocarbons [1, 2]. The indications for the use of such emulsions could be considerably widened if their gas transport effect was combined with antiarrhythmic action. The basis for this hypothesis is the well-known data showing that hypoxia is the leading pathogenetic factor in the onset of cardiac arrhythmias [3, 6]. There is also evidence of the successful prophylactic action of hyperbaric oxygen on the development of electrical instability of the heart [4]. However, experimental data on the effect of new blood substitutes on the genesis of cardiac arrhythmias are still in sufficient.

In the investigation described below the reproducibility of ventricular fibrillation was studied in rats during perfusion with a solution containing an emulsion of fluorinated hydrocarbons.

EXPERIMENTAL METHOD

Experiments were carried out on isolated hearts of albino rats. Perfusion was carried out by Langendorff's method through the aorta under a pressure of 60 mm Hg. Four perfusion solutions were used. Solutions Nos. 1 and 2 had the following composition (in mM): NaCl 140, KCl 3, $NaHCO_3$ 2, $CaCl_2$ 2.25, $MgCl_2$ 1, glucose 10, Tris-HCl buffer, 2 (pH 7.4). Solution No. 2 also contained (12% by volume) an emulsion of fluorinated hydrocarbons (perfluorodecalin and perfluorotributylamine in the ratio of 7:3, with P-268 emulsifier). By means of solutions Nos. 3 and 4 (low sodium concentration) ventricular fibrillation was induced. The two solutions had the following composition (in mM): NaCl 30, sucrose 200, $NaHCO_3$ 2, KCl 3, $CaCl_2$ 2.25, $MgCl_2$ 1, glucose 10, Tris-HCl buffer 2 (pH 7.4). Solution No. 4 also contained 12% by volume of the emulsion of fluorinated hydrocarbons. All solutions were heated to 37°C and oxygenated continuously with oxygen. When the perfusion solutions were prepared, a correction was introduced for the potassium concentration in the emulsions, which reached 0.9 mM. No trace of sodium was found in the emulsions. Cardiac electrical activity was recorded by means of a suction electrode [5] on the Elkar electrocardiograph. To determine the concentrations of ATP, ADP, and lactic acid, the heart was quickly frozen by contact with aluminum forceps, cooled in liquid nitrogen, and after crushing, the sample was extracted in 5% TCA. The concentrations of nucleotides and lactate were determined enzymically by the use of "Test Combination Boehringer Mannheim" (West Germany) kits on the SF-26 spectrophotometer. The concentrations of metabolites of energy metabolism were determined at the following times: after 15 min of perfusion with solution No. 1; after perfusion for 15 min with solution No. 2; after perfusion for 15 min with solution No. 1 followed by perfusion with solution No. 3 for 30 sec; after perfusion with solution No. 2 for 50 min and solution No. 4 for 30 sec.

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TABLE 1. Content of Adenine Nucleotides and Lactic Acid in Rats' Heart During Perfusion with Solutions of Different Composition (in μmoles/g wet weight of tissue)

Parameter studied	Solution No. 1 (15 min)	Solution No. 2 (15 min)	Solution No. 1 (15 min) + solution No. 3 (30 sec)	Solution No. 1 (15 min) + solution No. 4 (30 sec)
ATP	20,4±0,31	19,8±0,40 $P_1>0,2$	15,0±0,65 $P_1<0,001$	18,4±0,36 $P_2<0,05$
ADP	4,7±0,17	3,45±0,14 $P_1<0,001$	7,2±0,31 $P_1<0,001$	3,92±0,26 $P_2>0,1$
Lactic acid	6,7±0,58	4,6±0,10 $P_1<0,01$	9,5±0,46 $P_2<0,01$	5,4±0,41 $P_2>0,05$

EXPERIMENTAL RESULTS

After perfusion with solution No. 1 (not containing emulsion of fluorinated hydrocarbons) and subsequent perfusion with solution No. 3 ventricular fibrillation developed 23 ± 0.7 sec from the time of action of the solution with a low sodium concentration. In experiments in which the heart was perfused initially with solution No. 2 (containing the emulsion of fluorinated hydrocarbons), and then with solution No. 4 with low sodium concentration, but also containing the emulsion, fibrillation appeared much later — on average after 89 ± 13.0 sec. In 7 of 18 cases either fibrillation did not develop at all, or single or grouped extrasystoles appeared. Simultaneous determination of metabolites of energy metabolism showed that perfusion of the heart with solution No. 1 for 15 min resulted in a high level of ATP resynthesis, and a low concentration of ATP and lactic acid in the myocardium (Table 1). Perfusion of the heart with solution No. 2 (containing emulsion of fluorinated hydrocarbons) did not change the ATP content but led to a decrease in the ADP and lactic acid concentrations. The increase in oxygen capacity of the perfusion solution on account of the emulsion of fluorinated hydrocarbons evidently stimulated ATP resynthesis from ADP and delayed glycolytic processes in the myocardium. The action of low-sodium solution No. 3 after perfusion with solution No. 1 (solutions not containing the emulsion of fluorinated hydrocarbons) was followed by a considerable fall in the ATP level (by 27%) and by an increase in the concentrations of ADP and lactic acid. As pointed out above, ventricular fibrillation developed toward this time. In experiments in which low-sodium solution No. 4 was administered after preliminary perfusion with solution No. 2 (these solutions contained the emulsion of fluorinated hydrocarbons), the ATP concentration did not fall so appreciably (by 7%) as in the previous series of experiments, but the ADP and lactic acid concentrations remained at the initial level.

The results show that emulsion of fluorinated hydrocarbons not only performs a highly effective gas transporting function, but also has a marked antiarrhythmic action, in the mechanism of which activation of energy metabolism plays a part. Significant lengthening of the latent period from the time of administration of the low-sodium solution to the time of onset of fibrillation is important evidence of the need for a high intensity of oxidation in the myocardial cells and to preserve the stability of the electrophysiological state of the heart muscle.

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