EFFECT OF PERFLUOROCARBON EMULSION IN DIFFERENT DOSES ON THE HEMODYNAMICS AND CONTRACTILITY OF THE ISCHEMIC HEART

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Perfluorocarbon emulsion (PFCE) is a promising preparation for protecting the heart against ischemic damage, thanks to its unique rheologic and oxygen-transporting properties [4, 6, 7]. Usually PFCE is used in high doses (blood replacement 20-40 ml/kg) together with inhalation of pure oxygen [7, 9, 12]. From the practical point of view, however, this approach to the treatment of acute myocardial ischemia is undesirable, because blood replacement in large volumes, especially in patients with initial hypovolemia, leads to lowering of the blood hemoglobin level and, consequently, depression of oxygen transport to the tissues, and a high arterial pO_2 may have undesirable side effects [10]. Meanwhile there have been only isolated studies, which have revealed the beneficial effect of small doses of PFCE (3-6 ml/kg) on the hemodynamics in patients with myocardial ischemia [11], and the ability of the emulsion to improve the oxygen supply to the tissues in normoxia [8]. Previously [4] we found that the emulsion may have an antiischemic action on the myocardium in a dose of 10 ml/kg, with arterial pO_2 = 120 mm Hg.

The aim of this investigation was to determine the effect of different PFCE on the hemodynamics and contractility of the ischemic heart.

EXPERIMENTAL METHOD

Experiments were carried out on 30 mongrel dogs of both sexes weighing from 12 to 20 kg. After premedication with trimeperidine (10 mg/kg intramuscularly 30-40 min beforehand) and under thiopental sodium anesthesia (10-15 mg/kg), the trachea was intubated and the lungs artificially ventilated with a mixture of air and oxygen (2:1), by means of an RO-2 volume respirator, so that the arterial pO_2 could be maintained at 110-130 mm Hg. Thoracotomy was performed in the fifth intercostal space, after which the pericardium was divided and a small segment of the anterior descending branch of the left coronary artery was isolated in its upper third, and a special screw clamp was fixed around it [5]. In the presumed zone of ischemia, two or three nickel-plated electrodes were sutured to the epicardium to record the epicardial electrogram on an "Astra" cardioscope. To measure the pressure in the left ventricle and vessels the left ventricle was catheterized through the apex of the heart, the aorta through the carotid artery, and the superior vena cava through the jugular vein. Pressure curves were recorded in the aorta and left ventricle on a "Mingograf" ("Elema," Sweden). The mean arterial pressure (BP_m), +dp/dt, −dp/dt, and the end-diastolic pressure of the left ventricle (EDPLV) were calculated from the pressure curve. The central venous pressure (CVP) was determined by means of Val'dman's apparatus. The cardiac output was determined by the thermodilution method, using a "Swan Gans" catheter introduced into the pulmonary artery. The cardiac index (CI) and total peripheral resistance (TPR) were calculated by the usual method. The heart rate (HR) and degree of depression of the ST segment, used as an indicator of the degree of subendocardial ischemia [2], were determined from the epicardial electrogram. The above-mentioned parameters were recorded before ischemia and also 60, 90, 150, and 210

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TABLE 1. Effect of Intravenous Injection (between 60th and 90th minutes of experiment) of Perfluorocarbon Emulsion on Parameters of Hemodynamics in Dogs with Occlusion of Anterior Descending Branch of Left Coronary Artery

Parameter	Dose injected, ml/kg	Time of experiment, min				
		before occlusion		ischemia		
		0	60	90	150	210
CI, %	0 (control)	100	78±6	67±4!	67±7!	64±4!
	5	100	79±4	79±6	54±8!	51±5!
	10	100	80±4	111±4*!	91±7*!	81±4*
	15	100	88±8	113±12*!	77±7	65±7!
TPR, %	0 (control)	100	116±16	133±6	138±18	147±16
	5	100	117±11	131±12	200±18	198±23
	10	100	125±11	95±7*!	114±7!	126±8
	15	100	117±12	102±9*!	136±15	153±8!
EDPLV, mm Hg	0 (control)	0,8±0,8	3,3±1,4	4,0±1,7	6,6±3,5!	7,3±1,7!
	5	5,1±1,2	7,3±1,6	5,2±0,6!	5,7±0,6!	6,1±0,6
	10	3,4±0,8	5,4±0,5	4,7±0,6	5,2±0,8	5,1±0,9
	15	3,1±1,0	5,9±1,6	4,6±1,6!	4,0±1,1!	6,1±1,6
HR, %	0 (control)	100	96±4	98±4	103±6	100±5
	5	100	110±13	103±13!	107±14	106±11
	10	100	100±6	91±6	92±3	93±6
	15	100	98±14	112±8!	88±11!	93±13

Legend. Here and in Table 2: M ± m (M denotes arithmetic mean, m denotes mean error of the mean); CI) cardiac index, TPR) total peripheral resistance, EDPLV) end-diastolic pressure in left ventricle, HR) heart rate, *) difference from control ($p < 0.05$); !) difference from 60th minute ($p < 0.05$).

TABLE 2. Effect of Intravenous Infusion (between 60th and 90th minutes of experiment) of Perfluorocarbon Emulsion on Peak Rates of Contraction (+dp/dt) and Relaxation (−dp/dt) of Left Ventricular Myocardium

Parameter	Dose injected, ml/kg	Time of experiment, min				
		before occlusion	ischemia			
		0	60	90	150	210
+dp/dt, %	0 (control)	100	79±6	78±4	73±4	70±3!
	5	100	77±7	76±4	74±7	74±8
	10	100	77±4	90±4!	88±6	79±6
	15	100	86±6	97±11!	93±9	78±8
−dp/dt, %	0 (control)	100	80±5	81±4	72±3	67±6!
	5	100	79±6	89±8	84±10	89±12
	10	100	88±7	91±7	94±4*!	88±8
	15	100	86±5	97±8!	101±12*!	86±7

min after the beginning of myocardial ischemia. Ischemia of the anterior wall of the left ventricle was produced by partial occlusion of the anterior descending branch of the left coronary artery and its upper third by means of the screw clamp by 70-80%. The amount of occlusion was determined by Stroganova's method [5]. PFCE was injected 60 min after occlusion of the coronary artery intravenously into the animals in the course of 30 min in doses of 5 ml/kg (n = 7), 10 ml/kg (n = 8), and 15 ml/kg (n = 8). The control group (n = 7) received no injection. The PFCE contained 10 vol. % of perfluorocarbons (perfluorodecalin and perfluoromethylcyclohexylpiperidine, in the ratio of 7:3), 4% of the surfactant proxanol, and the following salt composition (in mM): NaCl 102, KCl 5, $MgSO_4$ 1.2, $NaHCO_3$ 15, NaH_2PO_4 1.2, glucose 11. The results were subjected to statistical analysis by traditional methods, using Student's t test.

EXPERIMENTAL RESULTS

The Effect of PFCE on the Hemodynamics (Table 1). BP_m in all groups did not change significantly in the course of the experiment, but averaged 98 ± 4 mm Hg. A decrease in CI was observed in all groups 60 min after the beginning of occlusion, on average to 80% of the initial level, TPR increased to 119%, and EDPLV by 2 mm Hg.

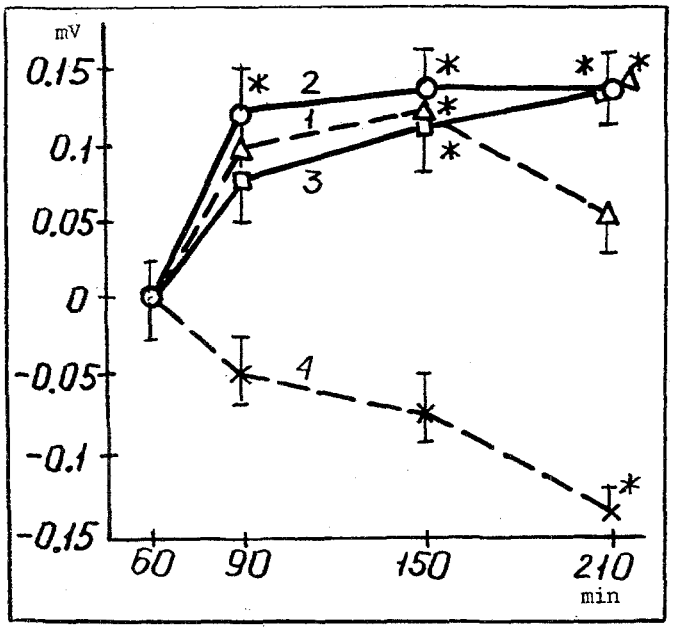

Fig. 1. Changes in depression of ST segment (mV) on epicardial electrocardiogram in zone of ischemia after injection of perfluorocarbon emulsion at 60th minute of ischemia in doses of 5 ml/kg (1), 10 ml/kg (2), and 15 ml/kg (3). 4) Control group without injection. M ± m (M denotes arithmetic mean, m mean error). Abscissa, time of experiment (in min); ordinate, change in depression of ST segment (in mV). Asterisk indicates significant difference from 60th minute ($p < 0.005$).

Later, in the control group, a progressive disturbance of the hemodynamics was observed (CI fell to 64%, TPR rose to 147%, and EDPLV rose by 4 mm Hg). Injection of PFCE into the animals at the 60th minute of ischemia in a dose of 5 ml/kg led only to significant slowing of the heart (by 7%) and to a decrease in EDPLV (by 2.1 mm Hg). However, these changes were of short duration and disappeared 2 h after infusion. Changes in the remaining parameters were identical to those in the control group.

Higher doses of the emulsion (10 and 15 ml/kg) had a more marked effect on the hemodynamics, restoring CI and TPR to their initial level and reducing EDPLV. Injection of the emulsion in a dose of 10 ml/kg also lowered HR (by 9%) temporarily, whereas a large dose caused an increase in HR (by 14%), followed by a decrease (to 88%), which was accompanied by a faster decrease in CI (to 65%) than with a dose of 10 ml/kg, and by an increase in TPR (up to 153%).

Effect of PFCE on +dp/dt and −dp/dt (Table 2). The maximal rates of contraction and relaxation of the left ventricular myocardium were significantly reduced 1 h after occlusion of the coronary artery, on average to 80 and 83% respectively, followed by a progressive decline, both in the control group and in the group receiving PFCE in a dose of 5 ml/kg. Injection of the emulsion in larger doses significantly increased contractility and the rate of relaxation of the myocardium on average to 93 and 98% respectively. Toward the end of the experiment these parameters fell to 79 and 87%.

Effect of PFCE on Depression of the ST Segment (Fig. 1). Immediately after occlusion of the coronary artery marked depression of the ST segment was observed on the epicardial electrogram (on average to 0.36 mV), and in the control group this continued to increase in the course of the experiment (to 0.54 mV). Unlike in the control, the emulsion in all doses caused a significant reduction of depression of the ST segment (on average by 0.13 mV). However, only in groups receiving the emulsion in doses of 10 and 15 ml/kg was this effect preserved until the end of the experiment.

Analysis of the results shows that the cardioprotective effect of PFCE on the myocardium depends on the injected dose. Injection of small doses of the emulsion (5 ml/kg) causes a decrease in EDPLV and slowing of the rhythm, which places the heart under relatively advantageous conditions from the energy point of view, and arrests

the development of the ischemic process (reduction of depression of the ST segment). However, first, these effects are of short duration, and second, this dose of the preparation does not compensate for the disturbances of the hemodynamic and myocardial contractility observed in acute myocardial ischemia.

This is evidently attributable to the high dilution of the emulsions with blood and, as a result, the weak manifestation of its rheologic and acid-transporting properties. An increase in the dose of PFCE to 10 ml/kg was sufficient for a marked antiischemic effect to appear. As our previous investigation showed [4], the cardioprotective index of the emulsion is linked with its two principal components: proxanol (which improves the rheologic properties of the blood) and perfluorocarbons (oxygen transport). It can be postulated that an increase in the concentration of these substances in the blood potentiates the antiischemic action of the emulsion. It is on these grounds that many workers have been led to use PFCE in the treatment of ischemia, as replacement of blood by large doses of the emulsion (20-40 ml/kg) [7, 9, 12]. In our investigations, however, a further increase in the dose of emulsion injected did not increase its effect, possibly due to the negative influence of hypervolemia, and also the cardiodepressive action of proxanol [3], which is manifested as a rapid fall of CI after its transient rise. With this in mind, and also the side effects of preparations based on perfluorocarbons (accumulation of perfluorocarbons in the tissues [1]), the use of a dose of 15 ml/kg cannot be advised. For the reasons given above, it can be concluded that a dose of PFCE of 10 ml/kg is optimal for antiischemic protection of the myocardium.

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