METHODS

The Use of Perfluorinated Emulsion for Prolongation of the Endurance Period in Lethal Hypoxia

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The apnea model with venovenous perfusion and blood oxygenation in a membrane oxygenator was used to study the gas transport characteristics of perfluorinated emulsion with the aim to prolong the endurance period in lethal hypoxia. The use of PFOS emulsion (40 ml/kg) as a hemodilution agent at relatively low rate of assisted perfusion (35 ml/kg×min) produced no improvement of oxygen supply during the critical period in comparison with conventional plasma substitutes. However, perfusion with oxygenated perfluorinated emulsion prolonged survival as compared with polyglucin perfusion, mainly due to the maintenance of the vitally important organs (heart and brain) and due to the improvement of microcirculation.

Key Words: *perfluorinated emulsion; apnea; assisted circulation; gas transport properties*

Among a large number of recent works on perfluorinated emulsion (PE), a rather small part are devoted to its investigation under the conditions of artificial circulation [2-4,10]. Of particular importance are the studies of gas transport, as well as other properties of PE, under conditions of assisted artificial circulation in critical situations [5].

The aim of this work was to study PE as a hemodilution agent for artificial circulation, which determines the endurance period in hypoxia caused by complete ventilation arrest.

MATERIALS AND METHODS

The study was performed on 22 randomly bred dogs of both sexes weighing 10-12 kg. The animals were intubated and switched to artificial ventilation (a RO-6 apparatus) under ketamine anesthesia (3-4 mg/kg) and dithyline (1 mg/kg) myorelaxation. After making an access to femoral and jugular veins, the venovenous shunt was applied, which had a built-in Masterflow-51 (Dideko) membrane oxygenator (MO) for drainage, oxygenation, and blood transport with the help of a roller pump and Tygon communications going from inferior vena cava to the pulmonic heart ventricle. To fill the extracorporeal contour (filling volume 0.4 liter) polyglucin (2nd group, n=6) or PE (3rd group, n=7) was used. In the control group (1st group, n=9) only the venovenous shunt was applied.

Under myorelaxation and artificial ventilation oxygenated venovenous perfusion was performed during 10 min with a flow rate of 35 ml/kg×min and oxygen supply of 0.6-0.7 liter/min, which stabilized the indices of initial basal hemodilution. The main stage of the experiments was then started: in the control group, after switching the artificial pulmonary ventilation off and applying clamp on the endotracheal tube, the animal was brought to the critical state (zero arterial pressure). After apnea, assisted perfusion with oxygenation in MO was performed in the 2nd and 3rd groups.

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The animal condition was estimated on the basis of hemodynamic indices, blood gases content, the acid-base balance, both against the background of initial hemodilution and 5 min after every apnea.

The study employed an AME-1 acid-base analyzers (Radiometer), an oxymeter Elema and an electrocardiograph. The results were statistically analyzed by Student's t test.

RESULTS

In the control group (total apnea followed by anoxia), the survival was restricted by 10.1±1.2 min period, in which the tissue oxygen consumption was performed under conditions of its maximum extraction from hemoglobin and activation of anaerobic glycolysis. In 4-5 min after clamping the endotracheal tube, the classical hypoxia-evoked stress reaction was observed as a short-term hypertension followed by rapid drop in arterial pressure to zero, when clinical death was documented. The indices of partial pressure of blood gases, hemoglobin saturation with oxygen, and acid-base balance during experiment are listed in Table 1, which shows the dynamics of critical condition manifested by rapid hypoxemia, hypercarbia, and metabolic and respiratory acidosis.

Inclusion of artificial circulation into the apnea model, i.e., the venovenous perfusion with blood oxygenation in MO, makes it possible to prolong the animal's life due to partial substitution of the lung respiratory function. It should be stressed that the volume rate of perfusion used in this study (35 ml/kg×min) could not provide prolonged survival of animals under conditions of complete arrest of ventilation, because extracorporeal blood oxygenation in MO supplied less than half oxygen that is necessary for organism under critical conditions. Such experiments reveal both the potentialities of oxygenated venovenous perfusion and efficiency of various infusion media used to fill the extracorporeal contour, which is estimated from the viewpoint of survival during acute respiratory inefficiency.

Assisted circulation with polyglucin (40 ml/kg) used to fill the extracorporeal contour (2nd group) makes it possible to maintain the animal life for 26±2.7 min, which is 2.5-3-fold longer than in the control group. The hemodynamic indices, blood gases content, and the acid-base balance during perfusion were significantly different from these parameters of the 1st group (Tables 1 and 2).

The use of PE for hemodilution and filling the extracorporeal contour showed a number of aspects. Thus, there was no essential difference in the blood gas content and acid-base balance in comparison with the 2nd group (Table 2). On the 5th min of assisted venovenous perfusion with PE, arterial Po_2 was 29.8±3.2 mm Hg (with polyglucin it was 24.6±0.87 mm Hg, $p>0.05$), which then decreased on 20th min to 22.2±3.2 mm Hg. At the same time, Po_2 in the 2nd group was 20.6±2.7 mm Hg, ($p>0.01$). These data show that PE has no particular advantage over the standard plasma substitutes.

However, the life duration in experiments with PE was 50.7±4.3 min, which is twofold longer than in experiments with polyglucin. In addition, there was no pronounced stress-reaction in the form of a short-term arterial pressure increase and drastic decrease in hemodynamic indices against the background of profound endotoxicosis and hypoxia, and ECG variations were negligible.

TABLE 1. Variation of Hemodynamic Indices, Blood Gases and Acid-Base Balance in the Control Group ($M±m$)

Indices		Apnoe		
		initial	in 5 min	in 10 min
Arterial pressure, mm Hg		120±7.4	168±6.9	10±1.7
Po_2, mm Hg	arterial	110.2±8.4	23.6±2.5	20.1±2.8
	venous	50.1±6.2	22.1±3.1	16.1±1.9
	arteriovenous difference	58.7±4.5	1.9±0.12	3.9±0.43
Pco_2, mm Hg	arterial	40.5±5.6	61.3±6.9	71.1±5.4
	venous	53.2±4.9	62.2±6.0	74.5±5.1
BE, mmol/liter	arterial	-8.4±0.84	-7.7±0.43	-15.4±1.12
	venous	-7.4±0.77	-7.6±0.69	-15.1±0.82
pH	arterial	7.26±0.098	7.10±0.102	7.00±0.078
	venous	7.17±0.068	7.10±0.087	6.93±0.119
SO_2, %	arterial	98.1±1.9	29.1±0.89	16.2±1.1
	venous	65.0±2.3	22.3±0.92	13.4±0.77

TABLE 2. Variation of Hemodynamic Indices, Blood Gases and Acid-Base Balance during Venous Perfusion with Polyglucin (2nd Group) and PE (3rd Group) (*M±m*)

Indices	2nd group						3rd group					
	initial	in 5 min	in 10 min	in 15 min	in 20 min	in 25 min	initial	in 5 min	in 10 min	in 15 min	in 20 min	in 25 min
Arterial pressure, mm Hg	121.6±6.0	166.7±6.7	126.7±6.7	78.3±14.8	56.6±8.8	33.3±17.6	106.2±9.4	113.7±5.5	113.7±5.5	91.2±9.6	88.7±10.8	80.0±12.2
P_{O_2}, mm Hg arterial	121.8±7.25	24.6±0.87	22.0±2.45	21.7±3.5	20.6±2.7	—	105.2±23.6	29.8±3.2	27.2±2.5	22.2±1.8	22.2±3.2	25.6±2.0
venous	47.5±6.1	20.8±3.7	16.1±2.2	15.5±1.15	14.6±2.2	—	44.6±10.5	29.5±4.2	19.5±2.4	13.9±0.9	13.8±2.1	14.6±1.05
arteriovenous difference	76.8±5.1	3.9±0.7	5.4±1.1	5.6±0.5	5.9±1.1	—	65.7±7.1	0.8±0.2	8.1±0.7	7.9±0.5	8.2±0.6	9.7±1.1
P_{CO_2}, mm Hg arterial	39.7±3.3	48.5±4.8	59.8±5.1	69.1±7.3	77.8±6.1	—	40.6±6.5	59.7±5.4	59.5±3.6	61.1±0.45	71.9±2.1	74.9±3.3
venous	50.8±3.5	57.4±4.2	63.5±6.9	73.8±8.5	84.2±6.4	—	45.9±4.1	61.4±1.7	63.6±1.0	67.4±2.9	71.2±5.9	74.3±5.4
BE, mmol/liter arterial	-9.4±1.23	-9.6±0.97	-9.7±0.41	-11.2±0.35	-12.2±0.56	—	-10.3±0.46	-9.3±0.88	-10.4±0.67	-12.4±0.45	-13.4±0.99	-14.6±0.30
venous	-8.3±0.85	-9.2±0.44	-9.3±0.43	-10.7±0.95	-12.0±0.72	—	-8.4±1.2	-9.3±0.77	-10.3±0.54	-11.8±0.30	-12.8±0.17	-14.4±0.55
pH arterial	7.24±0.03	7.12±0.03	7.05±0.05	7.01±0.04	6.98±0.07	—	7.24±0.05	7.12±0.04	7.12±0.01	7.08±0.01	7.04±0.03	6.98±0.01
venous	7.19±0.01	7.11±0.05	7.03±0.07	7.01±0.05	6.97±0.06	—	7.20±0.04	7.09±0.07	7.11±0.02	7.08±0.01	6.96±0.03	6.078±0.08
SO_2, % arterial	97.6±0.5	27.1±0.55	22.1±0.32	22.4±4.2	21.2±3.0	—	93.3±4.4	56.0±3.3	31.2±4.1	20.1±2.4	21.2±3.7	22.1±3.7
venous	69.7±8.2	20.1±3.6	13.1±2.7	11.3±4.4	10.1±0.35	—	61.9±12.9	34.6±9.8	17.6±3.5	8.75±1.1	8.64±3.1	8.2±1.2

Presumably, in the critical state the vitally important organs (heart and brain) are in more favorable conditions when the assisted venovenous circulation is performed together with PE hemodilution and oxygenation in MO. The input of highly oxygenated blood and PE into the right heart chambers and then to lungs and brain may provide the largest oxygen extraction by these organs, which makes it possible to maintain satisfactory hemodynamic parameters during a longer period. The small amount of oxygen, which is carried by PE, is probably sufficient for the heart and brain. An important factor is the ability of PE to improve microcirculation and augment oxygen diffusion between erythrocytes and tissues [1] even at relatively low Po_2 and SO_2 in blood samples taken from the vessels of distal subdivisions of the vascular bed. It is confirmed by greater arteriovenous Po_2 difference at PE hemodilution (8-10 mm Hg) than at polyglucin hemodilution (4-6 mm Hg) throughout entire experimental period.

Intracorporeal administration of PE even in a high dose (40 ml/kg) does not markedly improve the oxygen supply in the critical conditions compared with the standard plasma substitutes. At the same time, such a high PE concentration in the vascular bed is dangerous and can provoke various complications: allergic reactions, rapid phagocytosis of PE particles by macrophages, blockade of reticuloendothelial system and, hence, disturbance of the immune status [6,11]. However, perfusion by oxygenated PE showed a high efficacy of this agent in maintaining the functional state of vitally important organs (heart and brain), which made it possible to prolong the endurance period of lethal hypoxia. Therefore, it seems to be a good practice to utilize PFOS emulsions in perfusion of individual organs, but not to improve gas exchange in the whole organism. For example, application of PE as a component of cardioplegic solution (30-40 ml/kg heart weight) would provide a better protection of the heart against ischemia and reperfusion complications during cardiac surgery with artificial circulation. There are preliminary data on the use of PFOS emulsion for these purposes [7-9]. Penetration of PE into the vascular bed can be avoided by draining the cardioplegia solution from the coronary sinus to the waste, though even penetration of emulsion into coronary sinus (for example, during aortocoronary bypass surgery) is not dangerous, as the maximum PE concentration in the peripheral bed (even after several cardioplegia procedures) will be only 1.5-2.0 ml/kg.

Thus, the following inferences can be made. When the rate of assisted perfusion is insufficient, PE does not markedly improve the oxygen supply in the organism under critical conditions in comparison

with the standard plasma substitutes. The venovenous perfusion with oxygenated PE prolongs the endurance period in lethal hypoxia by maintaining the functions of the heart and brain. The use of PFOS emulsions as a component of cardioplegic solutions for improvement of myocardium protection against ischemia and reperfusion damage during the open-heart surgery with artificial circulation is prospective.

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