GAS TRANSPORT CHARACTERISTICS OF HEMOCORRECTORS AND PERFUSATES BASED ON PERFLUOROCARBON BLOOD-SUBSTITUTING EMULSIONS

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GASNO TRANSPORTNE KARAKTERISTIKE HEMOKOREKTORA I PERFUZATA ZASNOVANIH NA PERFLUOROKARBONSKIM EMULZIJAMA KOJE SE DODAJU U KRV

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Received/Primljen: 18.05.2020. Accepted/Prihvaćen: 28.05.2020.

ABSTRACT

This review summarizes the data regarding the gas transport characteristics of hemocorrection and perfusates on the basis of low concentrated drugs nano-sized perfluorocarbonic 20% Perftoran (a blood substitute, it is allowed for clinical use in Russia), 20% Ftoremulsion III (an improved blood substitute, registered in Russia), 10-20% Perfusol (a perfusion solution for perfusion of the isolated heart), 20% Ftorem (a cardioplegic emulsion for surgeries on the stopped heart) used in the biomedical field. The compensation of blood loss using traditional plasma substitutes without the gas transport function or with low gas transport characteristics leads to a decrease in the oxygen capacity of the resulting mixture and subsequently to deterioration in the oxygen transport characteristics of blood. The synthetic gas-transport blood substitutes can be used in the treatment of various forms of ischemia, such as carbon monoxide poisoning. Furthermore, recent results regarding the mechanism of COVID19 infection indicate a possible use of the synthetic gas-transport blood substitutes in the treatment and therapy of COVID19 infected patients.

***Keywords**: perfluorocarbon; synthetic gas-transport blood substitutes; ischemia treatment*

SAŽETAK

Ovaj rad sumira podatke koji se tiču gasno transportnih karakteristika hemokorekcije i perfuzata na osnovu lekova niske koncentracije perfluorokarbonskog 20% Perftoran velicine nano cestica(supstituta krvi koji je dozvoljen za kliničku upotrebu u Rusiji), 20% Ftoremulsion III (poboljšan supstitut krvi, registrovan u Rusiji), 10-20% Perfusol (perfuzioni rastvor za perfuziju izolovanog srca), 20% Ftorem (kardioplegijska emulzija za operacije na zaustavljenom srcu) korišćenih u biomedicinskoj oblasti. Kompenzacija gubitka krvi korišćenjem tradicionalnih supstituta plazme bez gasno transportne funkcije ili sa nisko gasno transportnim karakteristikama dovodi do smanjenja u kapacitetu kiseonika rezultujuće mešavine i zatim pogoršanju u transportnim karakteristikama kiseonika u krvi. Sinteticki gasno transportni supstituti krvi mogu se koristiti u lečenju različitih oblika ishemije, kao što su trovanje ugljen monoksidom, Osim toga, skoriji rezultati što se tiče mehanizma infekcije COVID-om 19 ukazuju na moguću upotrebu sintetičkih gasno transportnih supstituta krvi u lečenju i terapiji pacijenata inficiranih COVID-om 19.

***Ključne reči:** perfluorokarbon, sintetički gasno transportni supstituti krvi, lečenje ishemije*

sciendo
UDK: 615.384.033
Ser J Exp Clin Res 2020; 21 (2): 147-155
DOI: 10.2478/sjecr-2020-0020

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INTRODUCTION

One of the main pathophysiological problems in clinical practice is the elimination of hypoxia and delivery of oxygen to tissues and organs during blood loss using the oxygen-carrying blood substitutes.The compensation of blood loss using the traditional plasma substitutes without the gas transport function or with low gas transport characteristics leads to a decrease in the oxygen capacity of the resulting mixture and, accordingly, to ‘ deterioration in the oxygen transport characteristics of blood. A decrease in the blood oxygen capacity may not always be compensated by an increase in the blood flow rate and other adaptation mechanisms. Therefore, the creation and use of full-fledged hemocorrectors based on the gas-transport blood-substituting with perfluorocarbon drugs, that can compensate blood loss without reducing the oxygen capacity of the blood and its rheological characteristics, are currently becoming an urgent pathophysiological problem.

Since the last century, the gas-transport hemocorrectors based on perfluorocarbon blood-substituting emulsions-binary or multiphase systems, are actively used in the medical and biological field as multifunctional drugs, in particular, as the gas-transport substitutes for donor blood and perfusates for transplantation and preservation of organs and tissues (1,2,12,18-22).

It should be noted that the organic perfluorine compounds (PFOC) themselves dissolve any gases, including oxygen and carbon dioxide, much more than donor blood. Thus, in Russian perfluoroorganic compounds such as perfluorodecalin (PFD), perfluoromethylcyclohexylpiperidine (PFMCP) and perfluorotributylamine (PFTBA), the solubility of oxygen is about 40 vol.%, and carbon dioxide is 140-150 vol.% (16,17).

However, due to the low concentration (10-20%) of organofluorocarbon compounds (PFOS, gas carriers) in Russian perfluorocarbon preparations of the type 20% perfluorocarbon (approved for the clinical use) (9), 20% Fluoroemulsion III (registered) (11), 10-20% Perfusol (perfusion emulsion) (4), 20% Fluoroem (cardioplegic emulsion) (3,7), respectively, the preparations have a low oxygen capacity (5-7 vol.%), compared with donor blood (15-20 vol.%), which raises the question about the effectiveness of hemocorrection and these perfusates.

This review article is dedicated to the clarification of this issue.

Gas-transport characteristics of the perfluorocarbon blood-substituting drug Perftoran during compensation for 60-70% of acute blood loss in the experiment

To determine the gas transport efficiency, the perfluorocarbon blood-substituting emulsion Perftoran was studied. In an experiment on animals, blood loss was compensated with the drug Perftoran, in control experiments, blood loss was compensated with the classic plasma substitute drug Polyglucin (Dextran with mol. weight 60 thousand D). Under pressure control in dogs, in the aorta and superior vena cava, exchange replacement of 50 ml of blood per kg of body weight was performed in an isovolemic mode. During blood replacement and during the first 2 hours, pH, pO_2 and pCO_2 in arterial and venous blood were studied, the concentration of hemoglobin in the blood and the content of PFOS in the blood flow were calculated. The total content of O_2 in arterial and venous blood, chemically bound and physically dissolved oxygen was calculated.

For both groups, blood loss is characterized by a sharp decrease in the oxygen capacity of the blood (table 1). However, the content of physically dissolved oxygen in arterial blood when using the drug Perftoran is 3.5 times higher (2.94 ± 0.31) than in the group with the drug Polyglucin (0.88 ± 0.02) ($p<0.05$). This partially compensates for the decrease in the total value of the arterio-venous difference (a-vO_2 diff.) in oxygen and provides almost equal to the original (66.5±0.85) value of real oxygen transport, which is 70±0.4 ml/min.m2. In the group with Polyglucin with an equal amount of blood loss, the volume of infusion and identical values of the heart index (2.2±0.1; 2.1±0.1), this value is 37% lower and is 44±0.3 ($p<0.05$), which indicates an insufficient supply of oxygen to the tissues in the control.

As shown in studies (5.9), despite the low oxygen capacity in comparison with donor blood, the drug Perftoran during the compensation of blood loss in 60% -70% of the volume of circulating blood (BCC) successfully performs the gas transport function and maintains the normal value of oxygen transport, compared to the traditionally used hemodynamic plasma substitute – the drug Polyglucin.

Table 1. Indicators of oxygen supply of blood in the experiment on dogs when compensating for blood loss of 60-70% with Perftoran and Polyglucin

INDICATORS	Before blood substitution (control group)	After blood substitution (after 2 hours)	
		Polygluckin	Perftoran
Concentration of Hb (%)	12 ± 0,95	4,7 ± 1,2	3,6 ± 0,34
pO2 art. (mm Hg)	234 ± 13,6	259 ± 58	360 ± 42
pO2 ven. (mm Hg)	52 ± 8	53 ± 8,4	45 ± 3,4
pCO2 art. (mm Hg)	53 ± 3,1	40,5 ± 3	57 ± 7
pCO2 ven. (mm Hg)	59 ± 2,5	47,7 ± 4,1	61 ± 4,5
pH art.blood	7,35 ± 0,06	7,33 ± 0,10	7,34 ± 0,08
pH ven. Blood	7,23 ± 0,02	7,26 ± 0,10	7,24 ± 0,16
Concentration of O2 of art. blood bound to Hb (%)	16,1 ± 1,2	6,30 ± 0.7	5,06 ± 0,6
a-vO_2 diff. bound with Hb (%)	3,96 ± 0,9	1,41 ± 0,1	0,96 ± 0,05
Concentration of O_2 in art. blood in the physical solution (%)	0,86 ± 0,01	0,88 ± 0,02	2,94 ± 0,31
a-vO_2 diff. in the physical solution (%)	0,67 ± 0,01	0,69 ± 0,01	2,40 ± 0,30
Total value a-vO_2 diff. (%)	4,58 ± 0,9	2,01 ± 0,1	3,35 ± 0,3
Real transport of O_2 (ml/min m^2)	66,5 ± 0,35	44 ± 0,3	70 ±0,4 (!)

Gas-transport characteristics of the perfluorocarbon blood-substituting drug Fluoroemulsions III during compensation of blood loss in the clinic

The results of a clinical trial of the drug Fluoroemulsions III revealed its good clinical effectiveness. In most cases, patients who used the drug had severe comorbidities. Infusion of the drug to 24 patients was performed during endotracheal anesthesia under conditions of the oxygen content in the supplied gas mixture of 20-40 %. Out of the total number of patients (32 patients), only in one case, a minor adverse reaction to the drug was detected (chills, tachycardia, hypertension and hyperemia), after stopping the infusion, the patient's condition with acute intestinal bleeding normalized. The amount of intraoperative blood loss was from 0.5 to 1 liter. When evaluating the effect of the drug 20% Fluoroemulsions III, as a means with the gas transport characteristics, such indicators were important regarding the gas transfer as: Hb, pO_2, sO_2, measured before and after the surgery.

Studies have shown that the infusion of Fluoroemulsions III during the surgery, even in small doses of 200-600 ml, caused positive changes in hemostasis and acid-base state of the blood in patients. In all cases, without exception, after the drug infusion, even against the background of a decrease in hemoglobin, an increase in oxygen tension over 40% and an increase in sO_2 were observed (Table 2).

This clearly confirms the gas transport characteristics of the drug. The return of oxygen in the perfluorocarbon emulsion Fluoroemulsion III occurs more intensively and completely than in blood, since in perfluorocarbon, oxygen is physically bound and its return to tissues occurs along a concentration gradient, in contrast to blood, where oxygen is chemically bound and cleavage is completely different, more difficult. In the control group (table 3), where the traditional blood substitutes such as Polyglucin were used, the gas transport and hemodynamic indicators were significantly worse than in the experimental group. This occurred due to the fact that traditionally used drugs and salt solutions are ineffective gas carriers. So, if 20% perfluorocarbon emulsion Fluoroemulsion III at pO_2=760 mm Hg dissolves about 7 vol.% oxygen, then traditional drugs, under the same conditions, dissolve oxygen at the water level, about 2.3 vol.%, which is almost 3 times lower.

It is necessary to note an important fact, that, in the group of patients who received the perfluorocarbon preparation in the post-operative period, despite the fact that the level of hemoglobin significantly decreased due to blood loss from 142±2.5 (before the surgery) to 126 ± 2.4 g/l (after the surgery), the oxygen pressure of pO_2 in arterial blood significantly increased from 74.8±4.5 (before the surgery) to 131.6±5.5 mm Hg (after the surgery). This effect emphasizes the gas-transport characteristics of the drug Fluoroemulsions III. In addition, the oxygen saturation in the group of patients (who received Fluoroemulsion III in the postoperative period) increased from 90.6±3.2 (before the surgery) to 95.2± 3.4% (after the surgery), in comparison with the group on the drug Polyglucin, where the oxygen saturation in the blood of patients began to decrease from 90.1±2.4 (before the surgery) to 85.1±3.6% (after the surgery).

Table 2. Some indicators of the blood gas transfer during the intravenous administration of the drug Fluoroemulsions III in correction of blood loss in the clinic

INDICATORS	Before surgery	After surgery
Hb (g/l)	142 ± 2,5	126 ± 2,4*
pO_2 art. (mm Hg)	74,8 ± 4,5	131,6 ±5,5*
sO_2 (%)	90,6 ± 3,2	95,2 ± 3,4

*p < 0.05 compared to the indicators before the operation

Table 3. Some indicators of the blood gas transfer during the intravenous administration of the drug Polyglucin in correction of blood loss in the clinic

INDICATORS	Before surgery	After surgery
Hb (g/l)	138 ± 3,4	119 ± 3,8
pO_2 art. (mm Hg)	73,6 ± 2,6	69,2 ± 2,4
sO_2 (%)	90,1 ± 2,4	85,1 ± 3,6

As shown in studies (11), despite the low oxygen capacity of the drug Fluoroemulsion III in comparison with donor blood, clinical trials of the perfluorocarbon drug revealed its positive gas transport characteristics and clinical effectiveness.

Gas transport characteristic of the perfluorocarbon preparation 20% Perfusol emulsion (without a hemodynamic agent) for normothermic 4-hour perfusion of the isolated heart in the experiment

This section presents the gas transport characteristics of perfusates on the model of the isolated rabbit heart perfused during normothermy using the Langendorff method. Our research was conducted on 2 groups of hearts: 1-a group of control hearts perfused with Krebs-Henseleit solution (KNS); 2 - a group of experimental hearts perfused with perfusate based on 20% Perfusol emulsion.

When comparing the gas transport characteristics of the control solution and the Perfusol emulsion, it was found that the oxygen content in the arterial sample during perfusion with the Krebs-Henseleit solution was maintained at the level of 0.84 - 1.16 vol.% during 4 hours of perfusion, and in the venous - 0.55-0.38 vol.%. it was as an increase in the arterio-venous difference in oxygen, which was initially 0.3 vol.%, and at the end of the control time - 0.79 vol.%. With this oxygen supply, the heart, perfused according to Langendorff with a Krebs-Henseleit solution, consumes 1.9 ml/min*g in the initial state and 0.98 ml / min*g - after 4 hours of perfusion (table 4). A decrease in PO_2 after 4 hours of perfusion is associated with a sharp decrease in the value of the coronary flow (by 75%) and the development of edema. At the same time, the water content in the myocardial tissues increased from 78.1 ± 0.4% (intact hearts) to 84.9 ± 0.8% - by the end of the 4th hour of perfusion.

As it is known, the gas characteristics of the emulsion Perfusor are significantly higher than that of the conventional crystalloid solutions. Therefore, the oxygen content in the arterial and venous samples at an equal value of pO_2 (250-350 mm Hg) was 3 times higher than in the corresponding samples of the Krebs-Henseleit solution. Thus, the content of oxygen in the blood sample of the emulsion of Perfusal is 3,34-3,62 % during the entire perfusion time (4 hours). The arterio-venous difference in oxygen is significantly higher than in a similar indicator of a traditional solution. The oxygen consumption of the myocardium made up 5.45 and 4.6 ml/min . during the entire perfusion period. The coronary flow and degree of myocardial edema after 4-hour coronary perfusion with the Perfusol emulsion (without a hemodynamic agent) were, respectively, 5.2-3.6 ml/min . g and 81.1%, which is significantly better than in the group of hearts perfused with the traditional Krebs-Henseleit solution (KNS) (table 5).

Table 4. Oxygen supply to the myocardium during normothermic 4-hour perfusion of the isolated rabbit heart with the Krebs-Hanselate solution

INDICATORS	Result (after 15 min)	After 4 hours
pO_2 art. (mm Hg.)	269±31	370±18*
pO_2 ven. (mm Hg)	172±18	121±16*
Concentration of O_2 art. (v%)	0,84±0,1	1,16±0,07*
Concentration of O_2 ven. (v%)	0,55±0,06	0,38±0,05*
a-vO_2 diff. (v%)	0,3±0,05	0,79±0,08*
O_2 perfusion (ml/min · g)	1,9±0,3	0,98±0,2*
Coronary flow (ml/min · g)	6,1±0,72	1,5±0,26 *
Utilization of O_2 (v%)	37±7	56±6*

where *) < 0.05 in comparison with the initial indicators

As it is shown in studies (4,5),the adequate delivery of oxygen to tissues during perfusion of the isolated heart with perfusate-20% Perfusol emulsion provides a significantly better preservation of the myocardium than when using the traditional Krebs-Henseleit crystalloid solution.

Table 5. Oxygen supply to the myocardium during normothermic 4-hour perfusion of the isolated rabbit heart with the perfluorocarbon perfusol emulsion

INDICATORS	Result (after 15 min)	After 4 hours
pO_2 art. (mm Hg.)	358±41	392±64
pO_2 ven. (mm Hg)	235±39	250±34**
Concentration of O_2 art.(v%)	3,34±0,36 **	3,62±0,6**
Concentration of O_2 ven. (v%)	2,18±0,38**	2,33±0,36**
a-vO2 diff. (v%)	1,16±0,08**	1,3±0,24
O_2 perfusion (ml/min · g)	5,45±0,4**	4,6±0,8**
Coronary flow (ml/min · g)	5,2±0,6**	3,6±1,2**
Utilization of O_2 (v%)	31±6	35±8**

** p<0.05 compared to the indicators in table 2

Gas transport characteristics of the perfluorocarbon preparation of 10% Perfusol emulsion (with a hemodynamic agent) for hypothermic 24-hour perfusion of the isolated heart in the experiment

Hypothermic 24-hour perfusion of the dog heart with 10% Perfusol emulsion began immediately after isolation of the heart from the dog's body, without registering the initial level of vital activity of the graft, using the control group data as initial indicators. The heart started to be cooled by perfusing 10% Perfusol emulsion through the coronary arteries at temperature of 18-20 ℃. Then, the preservative was connected to a perfusion system located in a household refrigerator, and perfused retrograde with a peristaltic pump in a recirculating mode at temperature of 4-8 ℃.

Studies have shown (6) that the oxygen consumption of the myocardium during the heart preservation with 10% Perfusol emulsion was 0.31-0.37 ml / min.*100g. In the recovery period, the functional capabilities of the myocardium were measured after 24-hour hypothermic perfusion with 10% Perfusol emulsion on the stand. The heart activity was restored independently in all cases. The attention is drawn to the fact that before the heterotopic attachment to the neck vessels of the recipient dog, all the hearts were soft to the touch, and after switching to the stand, they contracted rhythmically during the entire observation period (6 hours). In total, the perfusion of the isolated heart was 30 hours, including 24 hours of the hypothermic perfusion on 10% of the Perfusol emulsion, 6 hours of perfusion after blood-feeding on the recipient dog.

Within 6 hours after the hypothermic perfusion, the isolated heart was switched to perfusion on a stand to load samples. So, 6 hours after the recovery, there was no difference between the control data and similar indicators in the experiment.

Table 6. Changes in the hemodynamic parameters, contractile function of the dog's myocardium and oxygen consumption by the myocardium after 24-hour hypothermic perfusion with 10% Perfusol emulsion

INDICATORS	Control group (without perfusion)	Experimental group after 6 hours of 24-hours perfusion
Heart rate (u./min)	121,5 ±8	132±4
BP system. (mm Hg)	127±4	120±4
BP diastolic. (mm Hg)	61,6 ±8	83,2±7
BP average (mm Hg)	94±3	100,5±4
Pressure in left ventricle (mm Hg)	125,3 ±3	117,2±4
End-diastolic pressure in left ventricle (mm Hg)	4,2 ±1,3	7,5± 1,3
Coronary flow (ml/min·100g)	104,3 ±5	102,5±6
Pressure in right atrium (mm H20)	100*	100*
Cardiac output (ml/min·100g)	612 ±69	575± 61
Utilization of O_2 (ml/100 g)	5,2 ±0,7	4,2± 0,4
CVR (mm Hg ·min ·100 g/ml)	0,9± 0,03	0,96± 0,05
Work of left ventricle (kg· m/min·100g)	0,77± 0,05	0,76± 0,08
+ dp/dt (mm Hg/sec)	2149± 182	2097± 231
- dp/dt (mm Hg/sec)	2126± 132	2306± 262
V_{max} (sec^{-1})	4,6± 0,4	4,4± 0,4
VCE (sec^{-1})	2,95± 0,3	2,97 ±0,2
O_2 perfusion (ml/min·100g)	7,07± 0,3	6,65± 0,5

Thus, the evaluation of functional capabilities of the heart with loading tests revealed a statistically significant difference between different blood flow to the left atrium (volume burden) and immediate response in the aorta and left ventricle, while there were no differences with similar indicators of the control group, which indicates a full recovery of the heart activity after 24-hour hypothermic perfusion of the isolated heart with 10% Perfusol emulsion.

Gas transport characteristics of the perfluorocarbon preparation 20% of the Ftorem - cardioplegic emulsion for perfusion-free preservation of the isolated heart in the experiment

A promising area of application of the perfluorocarbon emulsions is the cardioplegic solution for heart operations, which does not enter the major blood flow, but is used only when filling the coronary vessels.

Studies have shown (7) that use of the cardioplegic composition based on the perfluorocarbon - Ftorem emulsion while preserving the rabbit heart for 6 hours (14-16 °C) has a significant advantage compared to the crystalloid hyperkalic solution. Thus, after 6 hours of cardioplegia with the Ftorem emulsion (with 3 reperfusions), the cardiac activity was restored independently after the beginning of coronary perfusion. The amplitude of heart contractions in 30 minutes after the recovery was 89±6% of the initial level.

In the study of the Ftorem emulsion in cardioplegia on isolated hearts of dogs (3), in comparison with the traditionally used crystalloid solutions, under the same conditions, the restoration of heart activity on the traditional solutions was not observed, only single muscle contractions or ventricular fibrillation were recorded. As a comparison, 6-hour cardioplegia was used on the standard solutions: hyper potassium / hypertonic and novocain-containing. After initial assessment of the functional state of the isolated dog heart, the studied cardioplegic compounds were once introduced into the mouth of the aorta. In group I, where the hypertonic solution was used, it was not possible to restore the heart activity. In group II, when using the novocain-containing solution, only sluggish idiopathic muscle contractions of the myocardium were registered. In group III, the Ftorem emulsion was used in 5 out of 10 cases, spontaneous recovery of the heart contractions with the preservation of sinus rhythm was observed, and in the remaining cases, the rhythm was restored after 1-

2 defibrillator discharges. After switching to the stand, despite the burden, the hearts continued to contract rhythmically without conduction disturbances during the entire observation period. After the restoration of electrical and contractile activity, the majority of hemodynamic parameters did not differ from the control values. The cardiac output, blood pressure, and coronary blood flow were kept at the stable level. The heart rate decreased by 13%, and the speed indicators of myocardial contractility were reduced by the 15th minute (Vmax by 27%, VCE by 31%). +dp/dt did not differ from the original. Of course, the diastolic pressure in the left ventricle increased, but remained within the normal range, as well as the pressure in the left atrium. A comparative evaluation of the results of approbation of three cardioplegic solutions shows clear advantages of a solution based on the fluorocarbon emulsion- Ftorem.

The analysis of the conducted research allows us to identify the following positive effects of the perfluorocarbon emulsions of the Ftorem type on the myocardium:

- reducing the loss of intracellular potassium ions;
- inhibition of the entry of calcium ions into the cell;
- reducing the frequency of arrhythmias in the recovery period;
- reducing the sensitivity of the myocardium to catecholamines;
- slowing down the development of acidosis in the stopped myocardium;
- increasing the degree of relaxation of myofibrils;
- reduction of the tissue edema.

All the listed effects of the perfluorocarbon emulsion and its gas-transport characteristics provide the following advantages in comparison with the traditional cardioplegic solution: a single infusion of the perfluorocarbon emulsions stops the development of ischemic myocardial contracture, while the hypertonic crystalloid cardioplegic solution extends this period for only 10-15 minutes. In addition, the perfluorocarbonic emulsion type Ftorem:

- reduces the depolarization of the cell membrane and stabilizes it during cardioplegia;
- increases twice the oxygen supply of the myocardium after infusion of the cardioplegic solution;
- contributes to better preservation of the myocardium;
- stabilizes the pH of the myocardium;
- supports the aerobic and anaerobic metabolism;
- slows down the development of tissue edema even without a colloidal component;
- eliminates the risk of serious heart rhythm disorders;
- reduces the reperfusion reoxygenation damage;
- reduces the coronary vascular resistance;
- creates the additional relaxation, which facilitates free manipulation of the open heart;
- reduces the damaging effect of endogenous catecholamines at the beginning of cardioplegia and in the reperfusion period.

All this helps to preserve better the state of the myocardium after cardioplegia.

Table 7. Oxygen supply to the myocardium during the cardioplegic arrest of the isolated rabbit heart with the perfluorocarbon 20% Ftorem emulsion

INDICATORS	Before cardioplegie	1 hour after 6-hours cardioplegic heart failure
pO_2 art. (mm Hg)	158±29	190±39
pO_2 ven. (mm Hg)	22±1,8	31±3,9
Concentration of O_2 art. (v%)	12,5±1,2	15,4±1,1
Concentration of O_2 ven. (v%)	7,9±1,5	10,6±1,1
a-vO_2 diff. (v%)	4,6± 0,5	5,57±0,7
O_2 perfusion (ml/min·g)	6,4±0,7	5,78±0,5
pH art.	7,7± 0,08	7,6± 0,09
pH ven.	7,64±0,06	7,57±0,03

Thus, the pronounced protective effect of anoxia of the perfluorocarbon emulsion of the Fluoroem type, allows us to advise introduction of the cardioplegic perfluorocarbon solution for use in the cardiac surgery practice during the surgical treatment of severe patients with the acquired heart leaflet's defects.

Gas transfer and oxygen dissolution in the perfluorocarbon emulsions

According to calculations, contribution to the transport of O_2 of various blood components after an infusion of 10 ml/kg of the perfluorocarbon emulsion is: red blood cells carry 98.3% of total blood O_2, plasma-1.29%, PFOS emulsion-0.5% (10). It is clear that the role of PFOS in O_2 dissolution is small in comparison with red blood cells. However, if we take into account that the direct exchange of gases between cells, their environment and blood is carried out by free O_2 and CO_2 molecules, then the circulation of emulsion particles in the vascular flow significantly increased the oxygen capacity of plasma with physically dissolved oxygen (by 38%), especially its buffer capacity in relation to the consumed O_2, firstly. Secondly, the PFOS emulsion improves the oxygen supply of tissues by enhancing the extraction of oxygen by emulsion particles from erythrocyte hemoglobin. Third, an increase in mass transfer of O_2 to the presence of PFOS is much greater than in plasma, due to the accelerated diffusion of O_2 to PFOS. This is due to the fact that the Krog diffusion constant for O_2 and CO_2 is an order of magnitude greater in PFOS than in plasma. Fourth, an increase in O_2 mass transfer in the presence of PFOS occurs due to a higher rate of O_2 saturation in PFOS, since the rate of PFOS oxygenation is an order of magnitude greater than the oxygenation of red blood cells. Fifth, an increase in O_2 mass transfer in the presence of PFOS is associated with a large gas exchange surface in submicron particles of the PFOS emulsion. It is known that when the oxygen voltage decreases, the total amount of diffusion is preserved by increasing the gas exchange surface. In the PFOS emulsion with a relatively high oxygen voltage (pO_2 up to 100 mmHg), the total surface of the PFOS emulsion particles, for example, in 100 ml, is 1200 m^2, which allows to maintain the necessary amount of diffusion.

In addition, contribution of the PFOS emulsion to the model of anaemic hypoxia in the presence of perfluorocarbon particles in the bloodstream significantly affects the state of the blood-tissue gas balance, increasing the total flow of mass of oxygen from the blood to the tissues and carbon dioxide in the opposite direction. This is due to the fact that the rate of return and addition of O_2 and CO_2 by PFOS particles are not factors that limit the transport of gases. Thus, it was noted that when a small dose of the PFOS emulsion was monitored, the total CO_2 content in venous blood of experimental animals was significantly higher compared to the control. It turned out that the absolute amount of CO_2 dissolved in the PFOS particles (mm/l) at the pCO_2 of venous blood is 3 times lower than the values of total carbon dioxide. Therefore, the difference in the total carbon dioxide content between the experimental and control animals cannot be explained by a simple increased solubility of CO_2, but it can be attributed to the accelerated diffusion of CO_2 in the presence of its carrier (14,15). The main reason for this phenomenon is a change in the total mass transfer of blood gases.

CONCLUSION

It should be noted that the effective use of synthetic gas-transport blood substitutes is in various forms of hypoxia, caused, for example, by carbon monoxide poisoning, when CO binds with hemoglobin of red blood cells, forming carboxyhemoglobin and blocks the transfer of oxygen to organs and tissues; anemia, caused by the autoimmune acute intravascular hemolysis in severe infectious disease such as babesiosis (piroplasmosis, babesiasis) when there is a rapid destruction of both, its own and donor red blood cells with the release of large amounts of hemoglobin into plasma. With all these pathologies, the correction of hypoxia is not possible with the help of donor blood or red blood cell mass.

With the current situation in the world when there is the spread of coronavirus infection, which is accompanied (as noted by some authors) (23) by the penetration of the virus proteins into red blood cells and their binding with hemoglobin in such ways that "knocked out" iron ion from the blood plasma, hemoglobin loses its ability to bind enough oxygen. The use of synthetic gas perfluorocarbonic hemocorrectoring drugs like the Perftoran and Ftoremulsion III would be, as we believe, advisable for the treatment and correction of hypoxia.

In conclusion, it can be emphasized that hemocorrectors and perfusates based on the synthetic nano-sized perfluorocarbon emulsions are effective and safe for the gas transport in the medical and biological field for anti-ischemic protection of isolated organs and relief of various forms of hypoxia, when the use of donor blood is not possible due to any kind of reasons.

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