REVIEW

Perfluoran: Plasma Substitute with Oxygen Transporting Function

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Research carried out in Russia in the 1970s and 1980s, was aimed at creation of plasma substitute with gas-transporting function, and resulted in development of perfluoran. Perfluoran normalizes gas exchange and metabolism, transports oxygen and carbon dioxide, stabilizes cell membranes, corrects blood rheology and microcirculatory disorders, improves central hemodynamics, and exhibits adsorption and diuretic activities. It is effectively used in the treatment of hemorrhagic shock, intoxications, hemodynamic and cerebral circulation disorders, and hypoxia, in cardiosurgery, ophthalmology, and transplantology.

Key Words: *perfluoran; plasma substitute; oxygen transport*

The search for oxygen-transporting blood substitutes was started in Russia in late 1970s — early 1980s [3,31]. In 1981 the USSR State Committee for Science and Technology approved the program aimed at creation and introduction in clinical practice of blood substitutes based on organoperfluorine compounds (OPFC). The head institution was the Institute of Biological Physics of the USSR Academy of Sciences. A preparation with commercial name Perfluoran (PF) was created in 1984 and its clinical trials were started. New-class OPFC fit for medical use were synthesized [45]. PF is an OPFC-based submicron emulsion with polyfunctional characteristics. It improves gas exchange and tissue metabolism, increases oxygen transport, normalizes central hemodynamics and microcirculation, stabilizes cell membranes, blocks calcium currents, elicits adsorption and diuretic effects, and protects the myocardium. PF emulsion includes two OPFC and proxanol as emulgator.

Morphological studies (acute and chronic toxicity tests) showed that macrophages with small vacuoles in the cytoplasm appear in the spleen, liver, lymph nodes, and bone marrow during the first hours after plethoric infusion of PF emulsion [18-20,25]. Histochemically, these macrophages do not react to proteins, lipids, and carbohydrates. Gas chromatography showed perfluorocarbons in these organs, which permitted us to call these macrophages perfluorophages. They formed small accumulations (granulomas) in organs, which gradually disappeared and did not provoke fibrosis. No dystrophic changes in internal organs and the central nervous system were observed early after infusion of PF emulsion.

PF administration was associated with a lower destructive effect of phospholipase A_2 on the myocardium [11]. This is due to a reversible decrease in Ca^{2+}-currents. Block-copolymers (proxanol) may block calcium-dependent activation of endogenous phospholipase A_2. The presence of perfluorocarbons in cardiomyocyte sarcoplasmatic membranes increases myocardial resistance to destruction. Moreover, PF emulsion adsorbs cytotoxic lysophospholipids formed during phosphoglyceride fatty acid hydrolysis by phospholipase A_2.

PF stimulates the primary immune response [8]. Combined administration of PF emulsion and antigen to rats resulted in a two- or three-fold increase in the count of antibody-producing splenocytes in

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comparison with animals challenged with the antigen alone. Activation of humoral immunity results from stimulation of the macrophagal component and increased activity of T helpers.

Experiments with murine peritoneal neutrophils showed neutrophil modification by PF emulsion [15]. Addition of PF emulsion resulted in a short-term flash of luminol-dependent chemiluminescence. PF modified cellular response to opsonized zymosan. These results indicate that PF emulsion does not modify the chemiluminescent response of cells, but alters neutrophil metabolism in the presence of agents activating the cells by different factors. The emulsion corpuscles activate phagocytosis.

Our studies demonstrated that the absolute counts of neutrophils and macrophages increases more than two-fold after injection of PF emulsion into the abdominal cavity of rats [22]. Neutrophils and macrophages with vacuolized cytoplasm (perfluorophages) actively phagocytize staphylococci. The mean number of phagocytosed bacteria increases in comparison with the control. Analysis of phagocytosis showed high phagocytic capacity of neutrophils and macrophages in rats treated with PF. Similar results were obtained in studies of fixed macrophages after plethoric infusion of PF [23].

Perfluorophagal capacity to phagocytize and digest microorganisms was studied in rat and rabbit experiments [21,23]. PF emulsion was injected intraperitoneally to rats, and after phagocytosis of OPFC corpuscles, virulent staphylococcal culture was injected. In rabbits, blood loss was compensated by intravenous infusion of PF emulsion, after which a one-day culture of staphylococci was injected. This helped follow up phagocytic and digesting activity of free and resident macrophages cumulating OPFC corpuscles. The number of macrophages cumulating OPFC varied from 9 to 43% in different organs. The proportion of phagocytic perfluorophages reached 92% (bone marrow) and that of digesting cells 67-100%. Therefore, macrophages which actively cumulated OPFC corpuscles participated in phagocytosis and digestion of microorganisms. These results indicate that therapeutic doses of PF emulsion do not block the mononuclear phagocyte system.

The reactogenicity caused by activation of the complement system by OPFC emulsions (by the alternative route) is a problem attracting the attention of experimentators and clinicians [13,14]. In some cases perfluorocarbon emulsions cause side effects: a sensation of obstruction in the chest, dermatological reactions, and lumbar pain. The redistribution reaction of blood cells is an indicator of the formation of bioactive products of complement activation. It manifests itself by an immediate short-term decrease in the count of neutrophils in peripheral blood vessels and their accumulation in lung blood vessels [4]. The neutropenic index is to be no higher than 2-3 arb. units. Agents with a neutropenic index of higher than 3 arb. units are highly reactogenic and cannot be used for intravenous infusion. Emulsions with a considerable content of large corpuscles increase the neutropenic index and are therefore reactogenic. Modification of the technology of emulsion production and pretreatment with agents preventing activation of the complement are feasible approaches to the problem of reactogenicity of perfluorocarbon emulsions. It is noteworthy that x-ray contrast agents, polygluquin (colloid plasma substitute), and dextran-based agents with molecular weight higher than 30 kD activate the complement system. During homogenization, large corpuscles are not always evenly coated with proxanol. Uncoated hydrophobic sites can react with the complement. Submicron size of the emulsion corpuscles impedes their opsonization by C3B component. C3B factor creates the base for reactions with cells possessing CR-receptors after covalent fixation to the activator. For example, macrophage plasma membrane has receptors for C3B complement. The complex of submicron emulsion corpuscles with C3B factor is characterized by a weak chemotactic signal for macrophages, as a result of which side effects are the minimal or none at all. Methods permitting evaluation of OPFC emulsion reactogenicity *in vitro* have been developed [40].

If the emulsion corpuscles are larger and the proportion of large corpuscles is higher, the neutropenic reaction of the organism (the indicator of complement-activating effect of perfluorocarbons by the alternative pathway) is more expressed [13]. The results helped solve many technological problems ameliorating the quality of PF emulsion.

The mechanism of oxygen transport by PF emulsion is still unclear [32]. Oxygen capacity of PF is 2-3 times higher than that of blood plasma but lower than that of whole blood. On the other hand, oxygen flow does not depend on oxygen capacity; according to Fick's law, it is determined by the oxygen diffusion coefficient and the difference of oxygen potentials in blood and tissue. When PF emulsion corpuscles form a chain, oxygen conduction increases and oxygen delivery from erythrocytes to tissue increases.

Dynamic, but not absolute oxygen capacity, is an important characteristic of RF emulsion. Size and dispersion of corpuscles also play an important role in the frequency of channel formation. PF emulsion corpuscles moving in the bloodstream can create great numbers of channels (chains) between erythrocytes and vascular walls.

Besides the diffusion coefficient, diffusion constant determined according to Krog [39] acquires special significance in the course of gas exchange. This constant for blood gases in OPFC is by an order of magnitude higher than that for water. During circulation of OPFC corpuscles in the plasma, gas flows from erythrocytes to tissues and *vice versa* increase due to increasing summary coefficient of mass transfer. Hence, PF emulsion in the bloodstream can be regarded as a two-channel stimulator of gas flow. OPFC corpuscles maintain a higher level of Po_2 in arterial blood. The rates of erythrocyte oxygenation and deoxygenation increase in the presence of OPFC emulsion. PF emulsion changes blood rheology. Low viscosity of the blood/emulsion system improves delivery and facilitates diffusion of blood gases.

The efficacy of PF in blood loss, shock, cerebral circulation disorders, intoxications, microcirculatory disorders, and other pathological processes has been proven. PF (about 800 ml) was used in the treatment of 46 patients with combined injuries to pelvic organs and massive blood loss [38]. Therapeutic effect is manifested by increased volume of circulating blood (VCB), linear and volume velocities of blood flow, and oxygen capacity of the blood; the incidence of complications and mortality is much lower.

PF was used in surgical treatment of peptic ulcer with severe and very severe hemorrhages [54,60]. Fifteen-twenty minutes after infusion of PF, hemodynamic parameters improved, systolic and diastolic pressure increased, heart rate decreased, while VCB, minute and stroke cardiac output, and central venous pressure increased. Oxygen capacity of the blood increased 1.5-2 times. After 2-4 h of PF infusion, venous blood Po_2 and Po_2 increased, indicating a decrease of tissue hypoxia. The arteriovenous difference for oxygen was 60% higher than in the control group treated traditionally. Postoperative mortality was decreased by 50%. It was sufficient to maintain O_2 in inhaled air at the level of 20% and in only some patients at the level of 40%. Blood pH increased significantly: to 7.38-7.4, and so did the content of bicarbonates. The content of lipid peroxides decreased, and antioxidant activity increased. Use of PF emulsion decreased 2-fold the volume of donor blood required. The postoperative period was uneventful.

PF in a dose of 900-1800 ml had a stable therapeutic effect in patients with severe blood loss [5]. PF increased oxygen capacity of the blood 1.5-2 times and eliminated tissue hypoxia. During the first day after intravenous infusion of 800 ml PF to 14 patients with severe combined injuries, the respiratory index increased, pulmonary microcirculation improved, and minute heart output increased [6]. Good clinical results were obtained during the use of PF in patients with combined battle injuries [63]. PF was infused in doses of 5-18 ml/kg (sometimes 24 ml/kg) by fractions every 3 days, up to 4 infusions were made. PF promoted a more rapid and effective stabilization of vital functions, reduced the formation of pathophysiological factors of traumatic disease, and prevented cardiovascular and respiratory failure, disorders in brain function, and hypoxia.

PF was effective in the treatment of radiation injuries. The effect of PF as part of multiple-modality treatment was assessed in 22 patients with radiation injuries. PF improved the tolerance to radiotherapy: pancytopenia, blood hyperviscosity syndrome, and endogenous intoxication were less expressed. Antioxidant defense was activated and erythrocytic membranes stabilized. Protective effect of PF on pulmonary and hepatic components of the detoxication system has been established.

Experimental studies confirmed positive effect of PF in radiation exposure followed by blood loss [67]. Circulatory hypoxia was compensated at the expense of hemodynamic effect of the agent. PF in a dose of 30 ml/kg led to pronounced increase in arterial blood Po_2 and significant increment in arteriovenous difference for oxygen. Expressed compensatory potentialities of the gas transporting system manifested after 50% VCB had been substituted for PF. Contribution of PF to systemic O_2 transport reached 18-20%. Gas-transporting capacity of PF was stimulated by preoxygenation of the emulsion, maintaining the cardiorespiratory function at a stable level. The proportion of PF in total O_2 consumption was at least 30%.

PF stabilizes erythrocyte plasma membrane under conditions of acute hypoxia. During the use of polygluquin, the number of irreversible and hemolyzed erythrocytes is 79%, while with PF, only 26% [26]. Anti-ischemic activity of PF was demonstrated in experiments with clamping of the hepatoduodenal ligament. With PF, fatty and hyaline-droplet dystrophy of hepatocytes was less pronounced than with polygluquin. This effect of PF may be due to its stabilizing action on cell membranes.

Extensive clinical studies of PF have been carried out at the Burdenko hospital [37,47]. PF was used in 472 patients aged 19-87 years to control acute and chronic hypovolemia (blood loss and shock), disorders of microcirculation, tissue gas exchange, and metabolism of different origin, for the treatment of osteomyelitis under conditions of regional perfusion of the leg, for lavage of the lungs in pneumonia and respiratory distress syndrome. Tissue Po_2 increased by 20-40% and the levels of creatinine and urea nitrogen in the blood decreased, indicating improvement

of renal microcirculation; decreased level of transaminases indicated a decrease of tissue hypoxia, while cytochrome P-450 production increased. As an adsorbent with active surface of 600 m^2/100 ml emulsion, PF stimulates epithelialization of trophic ulcers, prevents brain edema and lipid embolism, stimulates tracheobronchial mucosal secretion, improves lung drainage, and prevents lung edema. Hemodynamic and antishock effects of PF are stronger than those of polygluquin. PF are decreased subsequent blood transfusion by 40-60%. Unlike dextrans, PF causes no coagulopathic disorders. It decreases blood viscosity, decreases erythrocyte aggregation index, and induces hemodilution. Improving the integral parameters, PF normalizes the index of oxygen extraction by tissues.

Positive therapeutic effects were observed when PF was used in the treatment of patients with craniocerebral injuries, brain edema, and in neurosurgical operations. In animals with craniocerebral injuries, PF normalized arterial pressure 15 min after infusion [57]. Stable spontaneous respiration, pupil, corneal, and oculomotor reflexes, and bioelectrical activity of the cerebral cortex were restored in all animals. PF promoted a decrease in the activity of the stress-realizing agent noradrenalin; platelet hemostasis normalized, and blood rheology improved [58,59].

Intracerebral hematomas were induced in rabbits by intravenous or intrathecal injection of 2 ml autoblood into the left parietal lobe [52]. Intravenous infusion of PF markedly (by 59.5%) increased cerebral blood flow. Vascular reactivity increased to the initial values, and Po_2 was higher than in intact brain. Intrathecal injection of PF increased cerebral blood flow by 218.8%. A stable positive effect was attained by intravenous infusion of PF in 10 out of 17 patients: consciousness was regained and psychomotor excitation and hypoxic hypoxia were liquidated. A temporary clinical effect was observed in 7 patients with irreversible changes in the brain, probably because the dose of PF was insufficient. No complications were observed in any of the patients. Positive effect of PF is explained by appreciable increase of tissue Po_2 (by 30-40%). Submicron corpuscles of PF penetrate (in contrast to erythrocytes) in zones with impaired microcirculation to deliver oxygen and remove carbon dioxide.

PF action was studied in experiments on rats with monolateral involvement of the spine [35]. The agent was infused 1 h after the injury. Spinal function was restored more often and completely in comparison with the control, and the contralateral side was less often involved. Destructive changes in the neurofilament were less expressed and sooner regenerated. Astrocyte expression is delayed during PF treatment, this affecting the development of astrocytic gliosis (glial cicatrix).

PF was used in intensive care of 112 patients with acute traumatic, vascular, and inflammatory diseases of the brain [64]. The drug was infused intravenously during the early periods (up to 8 h) of disease. Mortality was decreased by 7%, severity of brain symptoms decreased, terms and depth of neurological disorders decreased, blood supply to the brain and gas exchange improved, and lactate concentration decreased.

Recently PF was used with good effect in intoxications. PF infusion to animals 30 min after metaphos poisoning (LD_{50}) improved the erythrocyte plasma membrane resistance to the damaging action of the toxin [10]. Oxidative destruction of proteins decreased and the levels of ATP, 2,3-diphosphoglycerate, glucose-6-phosphate dehydrogenase, and total numbers of SH- and SS-groups in erythrocytes normalized.

Morphological analysis of internal organs in experimental and clinical cases with hydrogen sulfide, carbon tetrachloride, and acetic acid poisoning showed that a single infusion of PF preventes severe dystrophic changes and necrosis in the liver, myocardium, and kidneys [7]. No dystelectasias, hemorrhages, or desquamation bronchitis developed in the lungs. PF prevented the formation of erythrocyte aggregations. Patients' status improved during 24 h after PF infusion, which was confirmed by laboratory data.

PF effects were studied in patients with neurotropic poisoning (barbiturates, carbophos, and azaleptin) [2]. PF was infused in a single dose of 400 ml on the first day of hospitalization. Immediately after infusion, the content of low- and medium-molecular-weight substances (LMMWS) significantly decreased, while the content of malonic dialdehyde and recovered glutathione in blood plasma increased. Leukocyte count increased by 25%. The levels of lipids and cationic proteins and activity of neutrophil myeloperoxidase normalized by day 5. These results indicate that PF reduces endogenic poisoning due to adsorption of LMMWS. This modifies blood cells and endothelial cell surface, decreases their adhesive activity, and normalizes microcirculation. The activity of cholinesterase in the blood, brain cortex, and liver was studied in experimental poisoning with carbophos [49]. After poisoning, the activity of cholinesterase dropped by 51-91%. PF exerted therapeutic effect both alone and in combination with the antidote complex during the early period of poisoning (3 h). Cholinesterase activity increased by 72-85%. Antidotes alone did not lead to such results. In later periods (24 h) the therapeutic effect of PF was null.

Apparently, PF alters the conditions of the toxin absorption and distribution.

Infusion of PF to patients with severe acute poisonings of different origin on day 1 increased Po_2 because of decreased pulmonary shunting. The concentration of erythrocyte-bound LMMWS decreased [53]. Oxygen consumption increased significantly in the group of survivors, and the proportion of dead space decreased. By removing LMMWS from the blood and endothelial cell surface, PF may decrease cell adhesion and normalize microcirculation.

Experimental and clinical data on the use of PF helped define the indications for its administration to toxicological patients [55], specifically, for preventing and treating exogenous shock, decreasing the rate of "lethal production" of lipophilic toxins, increasing the efficacy of traditional antidotes, preventing and treating toxic coma, encephalopathy, disseminated intravascular blood coagulation, decreasing the severity of endotoxicosis, improving the efficacy of extracorporeal detoxication methods, and accelerating rehabilitation during the postintoxication period.

The effects observed experimentally and clinically in intoxications are explained by the fact that OPFC, the basic component of PF, due to their chemical inertness are pseudosubstrates of microsomal monooxygenases, and do not undergo oxidative transformations. By the intensity of inductive action OPFC are superior to traditional agents. They induce production of cytochrome P-450, a key enzyme of the monooxygenase system. The toxicity of lipophilic toxins can be modified by OPFC [56].

Positive characteristics of PF are used to prepare the spleen to extracorporeal detoxication. Drainage of splenic vessels by PF reduces the number of nonviable cells to 4.3% *vs.* 18% in the control.

The effect of PF on distribution of diisopropyl fluorophosphate, a potent organophosphorus toxin, has been investigated. Infusion of PF modified its distribution in the organism, promoting its accumulation in the organs active in xenobiotic biotransformation (lungs, blood, serum, liver, and kidneys) and decreasing its accumulation in the cerebral cortex and medulla oblongata [46].

Experimental and clinical studies demonstrated the effectiveness of PF in infections. In patients with viral hepatitis PF decreased bilirubin level and transaminase activities [36].

Intraperitoneal administration of PF to rats with diffuse peritonitis repaired the function of the liver monoxygenase system, intensified xenobiotic transformation, increased the detoxifying function of the liver, and decreased the severity of intoxication and mortality [48].

Blood substitution with PF (24% VCB) in rabbits challenged with staphylococcus (strain P-209, 2×10^9 bacterial corpuscles) after PF infusion showed 60% perfluorophages to phagocytize staphylococci. Complete phagocytosis was observed almost in all perfluorophages [50]. Dressings with PF in patients with suppurative surgical infections of soft tissues (50 cases) effectively cleansed the wounds during the first 8-10 h. Intense epithelialization was observed along the entire perimeter of the wound in 2 weeks [62].

PF is characterized by immunomodulating action. Immunosuppression was induced by x-ray exposure of mice immunized with sheep erythrocytes, and 30 min after exposure, PF was injected intraperitoneally. PF doubled all immunological parameters (content of antibody-producing cells, T cells, titer of hemagglutinins, etc.) and increased survival rate [27]. The counts of blood karyocytes, phagocytes, and lymphocytes stabilized, and phagocytic activity of granulocytes and mononuclear phagocytes increased in animals subjected to blood loss followed by PF compensation of VCB [42]. In experiments with prolonged thermal ischemia of the liver, PF accelerated lymphotization of the spleen and sooner repaired the structure of the thymus than in the control [51].

Due to its cardiotropic properties, PF is used in cardiology and cardiosurgery. In patients with myocardial infarction it decreases fibrinogen content, the risk of thrombus formation, improves blood rheology, increases the stroke and minute heart volume and cardiac index. Total and specific peripheral resistance and central venous pressure are decreased. The ECG values improve on day 2 after PF infusion: *ST* segment, *T* and *P* waves, and *PQ* interval are normalized [1].

PF was used in aortocoronary bypass [65]. Infusion of PF decreased the dose of dopamine, and noradrenalin was not needed at all. The gradient of temperature difference was 4-5°C, which is very important for preventing reperfusion injury to the myocardium during the early postoperative period. Patient's stay in intensive care wards after the operation was shortened. In the control, polarization microscopy of myocardial biopsy specimens taken 15-20 min after reperfusion showed signs of ischemic contractures in 50% cardiomyocytes *vs.* only 2-3% with PF.

We studied the cardioprotective effect of PF under conditions of cardioplegia and coronary perfusion [25]. After 2 h of coronary perfusion with Tirode's solution, myocardial metabolism and structure were altered: glycogen content, phosphorylase and redox enzymes activities decreased, second-third degree contractures of cardiomyocytes were seen, perinuclear, interstitial, and perivascular edemas developed, and myofibrils disintegrated. Similar changes were observed after a 6-h perfusion of coronary ves-

sels with PF emulsion. Metabolic and structural changes were observed in the myocardium after 3 h of hyperpotassium cardioplegia. During this period of fluorocarbon cardioplegia with PF emulsion the changes are less expressed and reversible. Anti-ischemic protection of the myocardium was studied experimentally [34].

PF is effective in renal transplantation [66]. After traditional preparation to transplantation, oligoanuria was observed in 72% donors. Acute renal insufficiency requiring several hemoperfusion sessions was observed in 50% recipients after surgery. PF notably increased diuresis. PF-treated kidneys started to function at the operation table in 39 out of 42 cases. The content of nitrous residues in the blood of recipients decreased on days 2-4 after surgery, and water- and nitrogen-excreting function normalized 1-2 weeks after the operation without resorting to hemoperfusion. Incidence of acute renal failure decreased. Urination within an hour after transplantation was observed in 100% cases after PF pretreatment of the kidney *vs.* 55% in the control. Mortality decreased by half. Rehabilitation was sooner attained, and hospital stay decreased. Experiments demonstrated that after preservation with PF, the kidneys retained viability for 72 h *vs.* less than 24 h in the control [28].

In ophthalmology PF is used in the treatment of hemophthalmia, subretinal and retinal hemorrhages, operated detachment of the retina with low visual function [30] and uveitis [33]. Vision was restored and visual field was widened. Linear blood flow velocity in the ocular artery increased due to improvement of blood rheology. OPFC are used with good effect in interventions for detachment of the retina and removal of the lens [16,17].

PF stimulates liver regeneration, increases litholytic activity of hepatocytes [29], is used in the treatment of erosions of the cervix uteri, stimulates epithelialization [43] and accelerates cicatrization of gastroduodenal ulcers [61]. Due to its membrane-stabilizing properties, PF maintains the ability of the pancreas to insulin production for a long time [41].

Comparative analysis detected the advantages of PF in comparison with foreign analogs [12].

Therefore, Russian commercial PF, a plasma substitute with oxygen-transporting function, is characterized by numerous beneficial effects: it normalizes gas exchange and metabolism, transports oxygen and carbon dioxide, stabilizes cell membranes, improves blood rheology, corrects microcirculatory disorders, normalizes central hemodynamics, and possesses adsorption and diuretic properties. The agent is allowed for medical use and commercial manufacture by the Ministry of Health of the Russian Federation (February, 1996).

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