STATE OF THE CIRCULATION AND OXYGEN SUPPLY TO THE BODY AFTER TOTAL BLOOD REPLACEMENT BY PERFLUOROTRIBUTYLAMINE EMULSION

Academician N. A. Fedorov,* V. S. Yarochkin, I. R. Kolonina, and N. I. Afonin

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Their low viscosity and low surface tension, combined with the high solubility of oxygen and carbon dioxide in them have attracted the attention of scientists in several countries to the possibility of using emulsions of perfluoro-compounds as blood substitutes and oxygen carriers.

The possibility of using total exchange transfusion with an emulsion of a perfluoro-compound, in principle, was studied in animals for the first time in the USSR in the Laboratory of Pathological Physiology of the Central Research Institute of Hematology and Blood Transfusion, directed by Academician of the Academy of Medical Sciences of the USSR N. A. Fedorov. An emulsion of perfluorotributylamine (PFTBA) was prepared and supplied for physiological study on animals by the Laboratory of Biologically Active Emulsions (Head, Candidate of Medical Sciences N. I. Afonin).

The writers studied the possibility of using an emulsion of a perfluoro-compound as oxygen carrier, in principle, as long ago as in 1975, when a 12% PFTBA emulsion was tested in experiments on the isolated rabbit heart. The results showed that living tissue (myocardium) can utilize oxygen from a circulating emulsion of a fluorocarbon, as reflected in the arteriovenous oxygen difference.

The results served as the basis for subsequent experiments *in vivo* on the intact animal.

EXPERIMENTAL METHOD

Experiments were carried out on 14 cats (eight experimental and six control animals). Under pentobarbital anesthesia (30 mg/kg) the animals were intubated and breathed pure oxygen at ordinary barometric pressure. Normovolemic exchange blood transfusion was carried out on the animals so that total blood replacement took place without a fall of arterial pressure or change in circulating blood volume. The blood of the experimental animals was replaced by a 12% emulsion of PFTBA. A 7% solution of a Soviet copolymer of ethylene oxide and propylene oxide was used as the emulsifier. Immediately before injection of the emulsion into the animal a solution of electrolytes and rheopolyglucin was added to it in the ratio of 1:4 in accordance with Geyer's formula. The resulting emulsion was filtered through a "Millipore" disk with a pore size of 0.22 μ. Its viscosity was 3.0 cP.

In the animals of the control group (six experiments) blood was replaced by the aqueous phase of the emulsion, which consisted of rheopolyglucin (20%) and water (80%) with the essential set of electrolytes.

The blood pressure (BP) in the femoral artery, central venous pressure (CVP) at the mouth of the inferior vena cava, the total oxygen consumption (OC), the partial pressures of oxygen and carbon dioxide (pO_2 and pCO_2), the oxygen concentration in mixed blood and separately, i.e., in the emulsion and in hemoglobin contained in erythrocytes, the hemoglobin concentration (Hb), and the hemaocrit index (Hct) were determined in the experiments. The

*Academy of Medical Sciences of the USSR.

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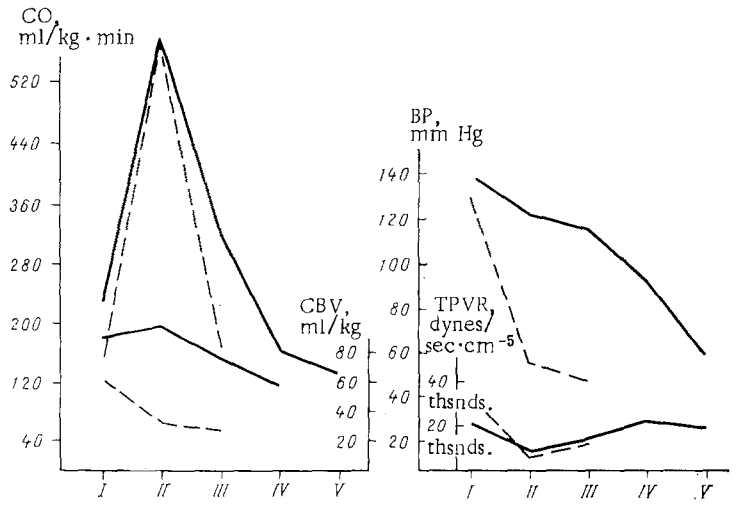

Fig. 1. Changes in basic parameters of the hemodynamics after exchange blood transfusion with PFTBA and its aqueous phase. Here and in Fig. 2, abscissa: I) initial data, II) immediately after exchange transfusion, III) 1 h, IV) 2 h, and V) 4 h after transfusion; continuous line represents experimental animals, broken line control animals.

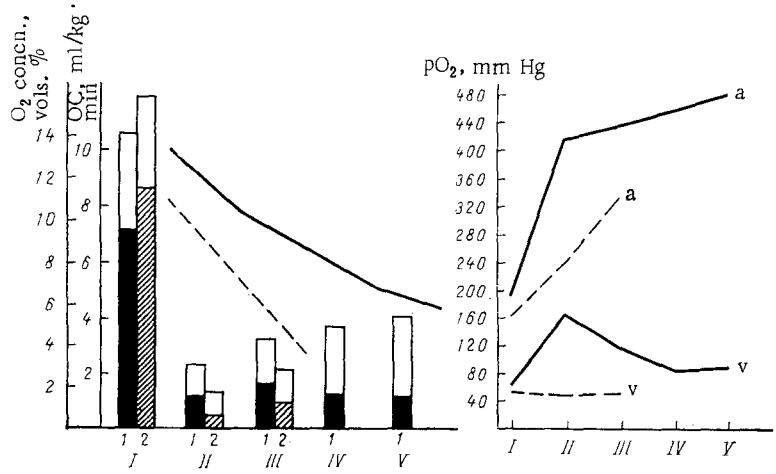

Fig. 2. Changes in blood gas composition during exchange blood transfusion with PFTBA emulsion and with its aqueous phase. 1) Oxygen concentration in arterial (unshaded part of column) and venous blood (black part of column) of experimental animal; 2) the same in control animals (unshaded part of column represents arterial blood, obliquely shaded part represents venous blood). a) Arterial blood, v) venous blood.

following parameters were calculated: the cardiac output (CO) by the Fick principle, the total peripheral vascular resistance (TPVR), and the arteriovenous oxygen difference ($a\text{-}vO_2$). The parameters studied were determined before the experiment and 10-15 min and 1, 2, and 4 h after exchange transfusion.

EXPERIMENTAL RESULTS

After replacement of blood by the PFTBA emulsion Hct fell from its initial level of 33% to 3% and the blood oxygen concentration fell by about four-fifths.

The oxygen supply to the body is functionally closely dependent on the state of the circulation. Changes in its basic parameters are shown in Fig. 1. It will be seen that BP fell progressively to reach 42% of its initial value after 4 h. The CVP rose sharply (by 8 mm Hg) immediately after exchange transfusion and returned to normal at the subsequent stages of observation. In response to infusion of the emulsion TPVR fell by about two-thirds. At that time BP was maintained entirely by an increased CO, the value of which was 2.5 times higher than initially. After 2 h BP was maintained at the lower limit of normal purely as a result of compensatory vasoconstriction, as shown by the values of TPVR. After 4 h the compensatory-defensive mechanisms of the body showed signs of collapse. The cause of this phenomenon was a fall in the circulating blood volume (CBV), the value of which after 2 h was 63% of the initial value.

The total period of survival of the experimental animals was 3-5 h. Animals of the control group died not later than 60-90 min after exchange transfusion.

It will be clear from Fig. 1 that the general direction of the changes in the basic parameters of the hemodynamics (BP, CO, TPVR) in animals of the control group was exactly the same as that in the experimental group. However, the changes were more sharply defined. The only exception was CBV, the value of which fell significantly actually in the course of normovolemic blood replacement, and it is not surprising that immediately after the end of the exchange transfusion CBV was down to 50% of its initial value.

Consequently a decrease in CBV, or in other words hypovolemia, is the primary cause of the circulatory disturbance and rapid death of the animals in both the control and the experimental groups.

Immediately after blood replacement by PFTBA emulsion and its aqueous phase, only the first signs of impairment of the circulation were found under conditions of severe anemia. Analysis of the gas exchange under conditions preceding disturbance of the circulation is therefore of special interest. Changes in the blood gas composition are illustrated in Fig. 2. In the course of the experiment OC of the animals of both control and experimental groups fell progressively, primarily on account of the catastrophic fall in CO.

A criterion of oxygen consumption by the tissues is the level of $a\text{-}vO_2$. Immediately after exchange blood transfusion it fell in the control group from an initial level of 4.4 vols. % to 1.1 vols. % and in the experimental animals to 1.6 vols. %, as a result of a decrease in the oxygen capacity of the "blood." The oxygen concentration in the arterial blood of animals of the experiment and control groups in fact fell approximately from 15 to 3.1 vols. % and 1.7 vols. % respectively. In the experimental animals, moreover, of the total quantity of oxygen in the arterial "blood," the PFTBA emulsion accounted for 2.0 vols. % and the erythrocytes remaining in the blood stream carried 1.1 vols. %. This difference in the oxygen concentration in the arterial blood of the animals of the two groups was accounted for by the fact that pO_2 in the emulsion was significantly higher than in the aqueous phase and, in addition, by the fact that the PFTBA emulsion is a good solvent for oxygen.

Analysis of the oxygen concentration in mixed venous blood immediately after exchange blood transfusion is very interesting. In the experimental animals it was 1.5 vols. % and in the control 0.6 vol. %. The question naturally arises: Why, under conditions of severe anemia, was the oxygen concentration in mixed venous blood of the experimental animals 2.5 times higher than in the controls? Analysis showed that of the 1.5 vols. % of oxygen remaining in the venous blood flow of the experimental animals 0.5 vol. % was accounted for by the PFTBA emulsion and 1.0 vol. % by erythrocytes. The oxygen concentration in erythrocytes of arterial blood was found to be equal to its concentration in erythrocytes of the mixed blood. This means that the erythrocytes of the experimental animals, on passing through the tissue capillaries, continue to remain in the oxygenated form, i.e., they do not give up to the tissues the oxygen so necessary for them under conditions of anemia. The reason for this phenomenon is the high level of pO_2 in the mixed venous blood. Whereas pO_2 of venous blood of the control animals fluctuated around 50 mm Hg, in the experimental animals immediately after the end of exchange blood transfusion it rose to 165 mm Hg, after 1 h it fell to 117 mm Hg, and not until after 2 h of observation was it stabilized at 85 mm Hg.

The S-shape of the oxyhemoglobin dissociation curve is of great physiological importance. It shows that under these experimental conditions an increase in pO_2 in the mixed venous blood leads to cessation of the liberation of oxygen from hemoglobin and to complete cessation of the giving up of oxygen to the tissues, i.e., to the exclusion of hemoglobin carried by erythrocytes from active gas exchange.

It is known that PFTBA emulsion is not eliminated from the body but accumulates in the organs and tissues. Intensive research is accordingly now in progress with the aim of finding emulsions free from this disadvantage (perfluorodecalin, adamantan, perfluorotributylpropylene). Meanwhile the character of gas transport in all emulsions is the same, and their physiological study has enabled us to discover some of the particular features of gas transport characteristic of all known emulsions of perfluoro-compounds.

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EFFECT OF STIMULATION OF ANTINOCICEPTIVE BRAIN ZONES ON THE ANALGESIC EFFECT OF ELECTROACUPUNCTURE IN RATS

Yu. N. Vasil'ev, Yu. D. Ignatov, B. V. Andreev, A. T. Kachan, and N. N. Bogdanov

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The mechanisms of production of acupuncture analgesia have not been finally explained, but there is experimental evidence that acupuncture induces activation of inhibitory processes and disturbs the conduction of nociceptive information at different levels of the CNS [5, 7, 11, 13]. It has recently been suggested that so-called antinociceptive brain systems, electrical activation of which is accompanied by the development of analgesia in animals and man, may participate in the analgesic effect of acupuncture [6, 9].

The object of the investigation described below was accordingly to study the effect of activation of antinociceptive brain zones on the intensity of the analgesic effect of acupuncture in rats.

EXPERIMENTAL METHOD

Altogether 26 experiments were carried out on male rats weighing 250-300 g with monopolar nichrome electrodes implanted into the posterior zones of the lateral hypothalamus and the central gray matter of the mesencephalon in accordance with coordinates in the atlas [8]. Nociceptive stimulation of the base of the tail was applied as volleys of square pulses (1 msec, 100 Hz, 1 sec, 30-100 V) through bipolar electrodes in the tunica elastica. The complex nociceptive response arising to stimulation of gradually increasing intensity was assessed on a scale which took into account five groups of features: 1) twitching and contraction of the tail, 2) rotation of the head and trunk, stepping movements with the paws, 3) squeaking, single rotations around an axis, 4) intensive and repeated crying, 5) crying with running away, repeated rotations, and aggressiveness. The features of group 1 were assessed as the animal's response to perception of aversive stimulation and it appeared to stimulation with an intensity of 30.5 ± 2.6 V, which was taken as the threshold. The two next groups of features reflect the animal's response to intensive yet tolerable nociceptive stimulation. Features of groups 4 and 5 were interpreted as manifestations of the emotional and behavioral response to intensive nociceptive stimulation; they appeared to stimulation with a strength of 1.9-2.2 thresholds.

Department of Pharmacology, I. P. Pavlov First Leningrad Medical Institute. Course of Reflex Therapy, S. M. Kirov Postgraduate Medical Institute, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR, V. V. Zakusov.)

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