GAS EXCHANGE AND STATE OF THE CIRCULATION IN DOGS AFTER REPLACEMENT OF ACUTE BLOOD LOSS BY A PERFLUORO COMPOUND EMULSION

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UDC 616-005.1-092.9-085.384:547.221

KEY WORDS: Acute blood loss; replacement transfusion; emulsion of perfluoro compounds, hemodynamics, gas exchange.

Investigations of normovolemic exchange replacement of blood by emulsions of perfluoro compounds (PFC) have recently been undertaken [1, 4-6]. These studies showed that the further study of PFC emulsions as the basis for creation of a blood substitute with gas-transport function is worthwhile and promising.

This paper describes the results of an evaluation of the state of the hemodynamics and gas exchange after infusion of the emulsion into lethally exsanguinated dogs.

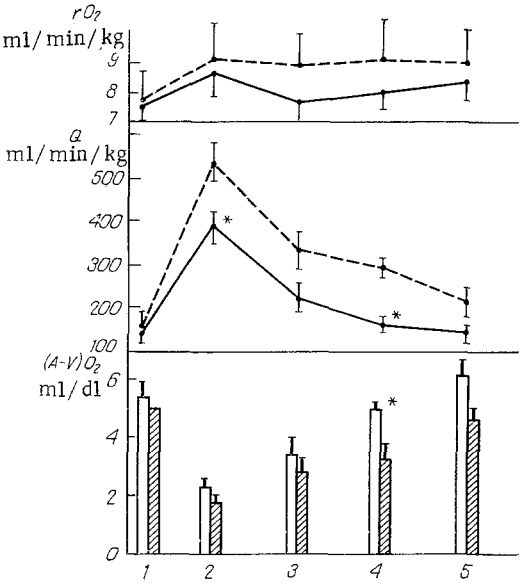

Fig. 1. Values of rO_2, Q, and $(A - V)O_2$ before and after replacement of lost blood by PFC emulsions (n = 5) and PSS (n = 5). 1) Initial data, 2, 3, 4, 5) 10-15 min and 1, 2, and 4 h respectively after replacement of lost blood. Broken line and shaded columns denote PSS, continuous line and unshaded columns — PFC emulsion. Asterisk indicates results differing significantly from corresponding values in control group.

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 0007-4888/83/9609-1212$07.50

TABLE 1. Mean Blood Pressure, Heart Rate, and CBV before and after Replacement of Lost Blood by PFC Emulsions (n = 7) and PSS (n = 5) (M ± m)

Parameter	Blood substitute	Initial data	At end of blood loss	After replacement of lost blood			
				10—15 min	1 h	2 h	4 h
P_a, mm Hg	PFC	150±8	0—5	145±13	142±8	145±6	141±6
	PSS	159±9	0—5	134±8	147±9	154±7	159±7
f, beats/min	PFC	182±13	72±14	153±16	159±17	157±15	169±17
	PSS	185±16	88±10	150±16	177±17	172±25	176±21
CBV, ml/kg	PFC	101±7	—	—	103±7	—	88±7

Legend. No differences significant according to t test ($P < 0.05$).

TABLE 2. Some Parameters of Gas Exchange before and after Replacement of Lost Blood by PFC Emulsion (n = 7) and PSS (n = 5) (M ± m)

Parameter	Blood substitute	Initial data	After replacement of lost blood			
			10—15 min	1 h	2 h	4 h
Hb, g %	PFC	17,4±0,9	7,8±0,9	7,6±0,6	8,0±0,7	8,5±0,8
	PSS	17,3±0,4	8,0±0,6	8,6±0,4	8,3±0,3	9,4±0,4
c_aO_2, ml/dl	PFC	22,6±1,2	11,6±0,7*	12,1±0,8*	12,7±0,9*	13,3±0,9*
	PSS	22,4±0,7	9,6±0,4	10,1±0,4	10,0±0,6	10,6±0,4
P_aO_2, mm Hg	PFC	112,7±7,9	545±24,2*	557±15,3*	553±16,6*	534±19,8*
	PSS	105,2±5,5	431±16,7	456±43,3	424±9,8	443±26,8
p_vO_2, mm Hg	PFC	44,0±2,4	197±34,3*	121±33,3*	68,4±12,3*	48,9±7,1*
	PSS	39,2±7,6	52,6±8,2	38,7±3,6	37,4±7,0	29,0±3,8

*Data differing significantly from corresponding values in control group ($P < 0.05$).

TABLE 3. Oxygen Concentration in Arterial Blood after Replacement of Lost Blood by PFC Emulsion (n = 7) and PSS (n = 5) before and after Disconnecting Oxygen (M ± m)

Parameter	Blood substitute	After 2 h			After 4 h		
		$+O_2$	$-O_2$	Δ	$+O_2$	$-O_2$	Δ
C_aO_2, ml/dl	PFC	12,7±0,9*	9,3±0,7	3,4±0,6*	13,3±0,9*	9,4±0,9	3,9±0,4*
P_aO_2 mm Hg		553±17*	106±14	447±14*	534±20*	109±6	425±13*
c_aO_2, ml/dl	PSS	10,0±0,6	9,0±0,7	1,0±0,3	10,6±0,3	9,8±0,5	0,9±0,3
P_aO_2, mm Hg		424±10	102±13	322±12	443±27	109±6	334±16

Legend. Δ) Difference in oxygen concentration in arterial blood and pO_2 before and after disconnection of oxygen. *Data differing significantly from corresponding values in control group ($P < 0.05$).

EXPERIMENTAL METHODS

Experiments were carried out on twelve mongrel dogs weighing 7-12 kg, anesthetized with pentobarbital (30-35 mg/kg, intravenously). The intubated animals were artificially ventilated at a preassigned constant volume and frequency. In the initial state the animals breathed atmospheric air, but after replacement of the blood loss they breathed 85% medical oxygen. Blood loss in a volume of 50 ± 5 ml/kg body weight was carried out by the method described previously by Koziner and Fedorov [3]. To replace the lost blood, in the experimental group of dogs (7) an emulsion of perfluorodecaline and perfluorotripropylamine (20 vol. %), in the ratio of 7:3, was used. Proxanol P-268 was used as emulsifier. To create the necessary colloid-osmotic gradient, immediately before injection a protein-salt solution (PSS) containing an isotonic solution of electrolytes and albumin from blood donors, was added to the preparation up to a final concentration of 5%. In control experimemts (5 dogs) PSS alone was used to replace the lost blood.

The following parameters were measured in the experimental animals: mean arterial pressure (P_a); heart rate (f); Hb — by the hemoglobin cyanide method; the O_2 concentration in

arterial (C_aO_2) and mixed venous (C_vO_2) blood and in samples of inspired and expired air — on the LEKS-O_2-KOH instrument; pO_2 — on the AVL-940 instrument. Arterial blood for analysis was taken from the femoral artery, and mixed venous blood by catheter from the right ventricle. The circulating blood volume (CBV) was measured by the use of [^{131}I]albumin. The total oxygen consumption (rO_2) was determined and the arteriovenous O_2 difference $(A - V)O_2$ and cardiac output (Q), by the Fick method, were calculated.

The individual contribution of the PFC emulsion and PSS to the total O_2 concentration in the arterial blood during oxygen breathing was estimated by the difference in C_aO_2 after transferring the animal from O_2 to atmospheric air.

The animals were kept under observation for 4 h after replacement of the lost blood.

All the numerical data were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

After replacement of the lost blood the values of P_a and f returned in animals of both groups close to their initial levels, and they remained there until the end of the experiment. CBV in the experimental animals 1 h after replacement of the lost blood remained at its initial level, but 4 h later it was down to 88% of the initial value (Table 1).

As a result of blood loss and hemodilution, due to infusion of PFC emulsion and PSS, the Hb concentration in the control and experimental dogs fell by more than half. There was a corrsponding decrease in the oxygen capacity of the blood. It is important to emphasize, however, that C_aO_2 was higher in the blood of dogs of the experimental group after replacement of the lost blood at all stages of the investigation than in the control animals (on average by 2.0-2.7 ml/dl). Under these circumstances p_aO_2 in these animals rose sharply immediately after turning on the O_2 supply and was higher than p_aO_2 in the control animals by more than 100 mm Hg during the 4 h of observation (Table 2).

In the course of the experiment rO_2 of dogs of both groups was about equal, but this was evidently achieved in different ways. For instance, the value of Q after replacement of the lost blood in the experimental animals was increased by 2.5 times, but in the controls it was increased by 3.5 times, and the normalization of this parameter took place much faster after infusion of the PFC emulsion (Fig. 1). The value of $(A - V)O_2$ was higher in the experimental dogs at all stages of the investigation.

In other words, the compensatory mechanisms developing in response to the changes in homeostasis arising after blood loss took place mainly along the path of an increase in Q in dogs of the control group, but along the path of increased utilization of O_2 in dogs of the experimental group. Along with other factors, this could be facilitated by the higher values of c_aO_2 and p_aO_2 in the experimental animals.

The effect of an increase of p_vO_2 after replacement of the lost blood in the experimental animals compared with the controls deserves attention. This phenomenon, described prevously [5, 7, 8], is not found in the case of transfusion with blood substitutes with no O_2 transport function. In the present case, for instance, immediately after replacement of the lost blood p_vO_2 in the experimental animals was 197 mm Hg, after 1 h it was 121 mm Hg, but in the controls it was only 53 and 39 mm Hg respectively. However, with these values of p_vO_2 in the experimental dogs the O_2 of the erythrocytes could not be utilized, for at these pO_2 values Hb is not converted from the oxy-form into the deoxy-form, and O_2 is supplied to the tissues of the body on account of O_2 transported by the PFC emulsion. In our view this can be explained as follows. After replacement of the lost blood by any blood substitute restoring CBV, Q rises and $(A - V)O_2$ falls [2]. In the present case, therefore $(A - V)O_2$ fell after replacement of the lost blood by PSS from 5.0 to 1.6 ml/dl, but after replacement of the lost blood by PFC emulsion it fell from 5.4 to 2.3 ml/dl. After disconnection of O_2 and transfer of the animals to breathing atmospheric air, when p_aO_2 fell to 102-109 mm Hg the PFC emulsion gave up 3.4-3.9 ml/dl, whereas PSS gave up only 0.9-1.0 ml/dl (Table 3).

The oxygen supply to the tissues of the body after infusion of PSS thus cannot be completely provided by oxygen dissolved in the plasma, whereas after infusion of PFC emulsion into the blood stream the tissues can extract the required quantity of O_2 from it. This accounts for the high values of p_vO_2 in the experimental group. Later, when Q falls and $(A - V)O_2$ rises to exceed the value of O_2 dissolved physically in the emulsion, the erythrocytes begin to function and oxygen begins to be supplied by O_2 of both emulsion and erythrocytes.

The suggested preparation thus restores the basic parameters of the hemodynamics and gas exchange well, when disturbed after blood loss, and it can be recommended as the basis for a combined plasma expander and oxygen carrier.

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TOXIC ACTION OF DITHIZONE ON INSULIN-PRODUCING CELLS

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UDC 616.379-002.4-092.9-02: 615.916:546.3].015.25

KEY WORDS: Islets of Langerhans; zinc; chelating agents; dithizone; structural damage.

Interest in the toxic action of chelating agents on cells is due not only to advances in the fundamental sciences, but also to purely practical problems. These agents are being increasingly used in agriculture, in various branches of industry, and in medicine [6, 7, 9]. It has been shown that administration of the powerful chelating agent dithizone to rabbits causes necrosis of the B-cells of the pancreatic islets and the development of permanent diabetes [4, 8, 9]. The mechanism of these changes has been studied [5].

The object of this investigation was to compare the toxic action of dithizone on insulin-producing cells in animals at different levels of evolutionary development.

EXPERIMENTAL METHODS

Altogether 320 animals of different species were used (fishes, frogs, pigeons, mice, guinea pigs, golden hamsters, rats, rabbits, cats, and dogs).

Dithizone was injected intravenously and intra-arterially (fishes) in doses of 50-100 mg/kg as a 1% solution in 0.5% ammonia solution. The animals were killed from 3 min to 5 days after the injection. Frozen sections were cut from pieces of pancreas and fixed in Bouin's fluid, in acetone, and by Timm's method.

For the morphological investigation paraffin sections were stained with hematoxylin and phloxine by Gomori's method. The specific granules of the insulin-producing cells were revealed by means of aldehyde fuchsin. Zinc was detected by staining sections with dithizone and with 8-(p-tosylamino)quinoline (8-TQ) [1, 2]. Sections also were fluorochromed with chlorotetracycline (to detect calcium bound with hydrophobic sites in the cells) and with acridine orange (for the metachromatic reaction) [3]. To excite luminescence UFS-3 and FS-1 filters were used, in conjunction with ZhS-3 and ZhS-18 filters for protection.

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 9, pp. 23-25, September, 1983. Original article submitted December 21, 1982.