GAS EXCHANGE AND HEMODYNAMICS AFTER TOTAL BLOOD REPLACEMENT BY A SOLUTION OF PURIFIED HEMOGLOBIN

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UDC 615.384:547.963.4].015.45:612.1/.2

Complete exchange replacement of the blood (to a hematocrit index of 1-3%) by a 7-8% solution of human hemoglobin, purified completely from stroma and procoagulant activity, was carried out in cats. The Hb solution is able to transport O_2 and can support life of the completely exsanguinated animal for a certain length of time (up to 2-6 h). It readily takes up O_2 in the lungs and gives up O_2 in the tissues, but to a much lesser degree than Hb incorporated in erythrocytes. The Hb solution can also maintain the basic indices of the hemodynamics for a certain time.

KEY WORDS: *hemoglobin solution; oxygen transport by the blood.*

Intensive research into the use of a concentrated solution of native hemoglobin (Hb) as a hemodynamic blood substitute which, at the same time, can transport O_2, is currently in progress in various countries (the USSR, USA, West Germany, etc.). The main reason for this trend is the development of ways of obtaining a solution of Hb free from stroma and from coagulant activity [4], and also the publication of research in which such solutions were found to have no harmful effect on kidney function [2, 4, 5, 6].

The object of the investigation described below was to study the possibility of O_2 transport by a solution of native Hb after total replacement of the blood, and also to examine its ability to maintain the basic indices of the hemodynamics at a physiological level.

EXPERIMENTAL METHODS

Experiments were carried out on 10 cats anesthetized with pentobarbital (30 mg/kg), in which a three-stage exchange of the blood by a 7-8% solution of Hb freshly prepared from human erythrocytes was carried out in portions of 10 ml to a hematocrit index of 1-3%. Normovolemic hemodilution in this way rules out the possibility of hypovolemia and enables the animal's blood to be almost completely freed from erythrocytes without lowering the blood pressure. The cats were intubated and they breathed atmospheric air.

The Hb solution was obtained by Rozenberg et al. [1]. This solution corresponds in its spectral characteristics and molecular weight to native Hb and is completely free from erythrocyte stromas and from procoagulant activity.

The blood pressure (BP) in the femoral artery and the central venous pressure (CVP) at the mouth of the inferior vena cava, the total gas exchange and the blood gases, the partial pressures of oxygen (pO_2) and carbon dioxide (pCO_2), the pH of the arterial and mixed venous blood, the Hb concentration, and the hematocrit index were determined in these experiments and the number of erythrocytes remaining in the blood stream was counted. The minute volume of the circulation (MVC) was calculated by Fick's method, and the arteriovenous difference (AVD) for oxygen and the total peripheral resistance (TPR) also were calculated.

The indices to be studied were determined before exchange blood replacement (initial data), and 10-15 min and 1, 1.5, and 3 h after replacement. The animals were divided into two groups in 1 h after isovolemic hemodilution. In group 1 (6 cats) the animals remained under observation without any additional infusions. In group 2, 1 h after blood replacement,

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Laboratory of Pathological Physiology, Central Institute of Hematology and Blood Transfusion, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 84, No. 10, pp. 402-405, October, 1977. Original article submitted May 24, 1977.

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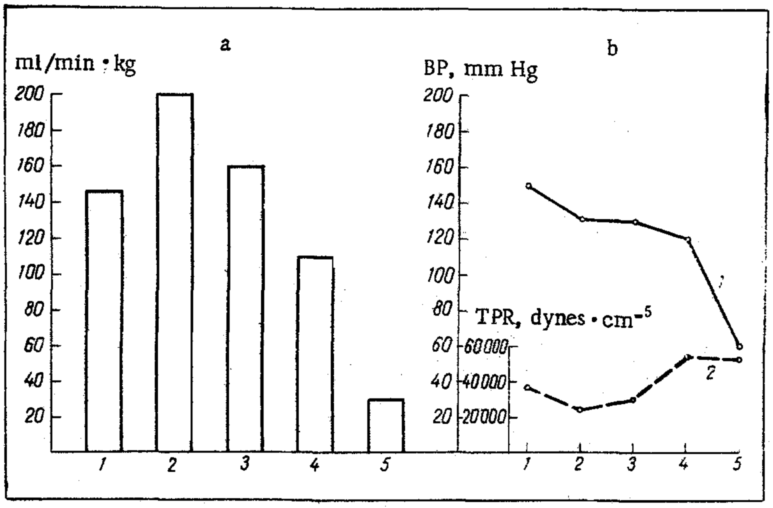

Fig. 1. Change in minute volume of blood (A), blood pressure (1), and total peripheral resistance (2) (B) after exchange blood replacement by hemlglobin solution. Abscissa (here and in Figs. 2 and 3), stages of experiment: 1) initial value, 2) immediately after blood replacement, 3) 1 h, 4) 1.5-2 h, 5) 3 h after replacement. Ordinate: A) minute volume (ml/min•kg) and total peripheral resistance (in dynes•cm^{-5}); B) blood pressure (in mm Hg).

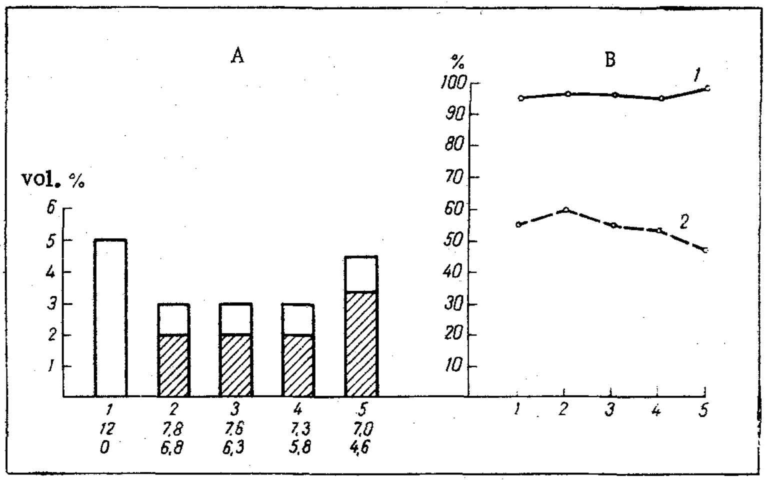

Fig. 2. Arteriovenous difference (A) and oxygen saturation of arterial (1) and mixed venous (2) blood (B) following exchange replacement of blood by Hb solution. Abscissa, stages of experiment; ordinate: A) arteriovenous difference (in vols. %), B) percentages. Shaded part of columns represents hemoglobin dissolved in plasma. Numbers beneath columns: top) total Hb, bottom) Hb dissolved in plasma.

autologous blood was transfused in a dose of 10-12 ml/kg. The results were subjected to statistical analysis by the difference method.

EXPERIMENTAL RESULTS

After exchange normovolemic hemodilution the hematocrit index fell from 34 to 2%. The total Hb concentration under these circumstances was 8 g%. Dissolved Hb accounted for 7 g% of this total.

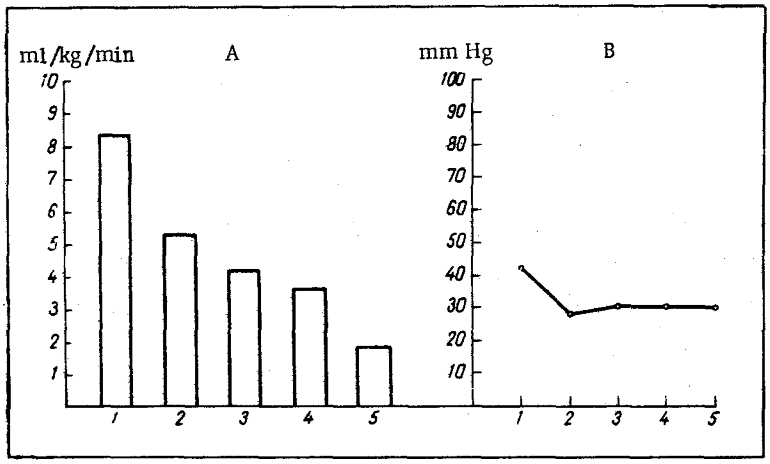

Fig. 3. Total oxygen consumption (A) and partial pressure of oxygen in mixed venous blood (B). Abscissa, stages of experiment; ordinate: A) O_2 consumption (in ml/kg/min). B) partial pressure of O_2 (in mm Hg).

The basic changes in the hemodynamics in the experiments with total replacement of blood by Hb solution are shown in Fig. 1. Immediately after replacement BP fell a little, though it remained within physiological limits. The level of BP is the resultant of two variables: the MVC and the resistance of the vessels to the blood flow. Analysis of TPR showed that the vessel walls relax in response to infusion of the Hb solution, TPR fell statistically significantly, and BP was maintained during this period entirely by an increase in MVC ($P < 0.01$). However, MVC fell to its initial level after 1 h and continued to fall thereafter. To maintain BP within physiological limits, the animal responded by a progressive and substantial increase in the TPR, and this naturally placed an increased load on the heart muscle. After 3 h the compensatory mechanisms collapsed, MVC fell sharply, and the increasing TPR was insufficient to maintain BP. In those animals which were given additional blood, the indices of the hemodynamics were more stable.

As the results in Fig. 2 show, the oxygen saturation of the Hb solution in the lungs was perfectly satisfactory. The O_2 saturation of the venous blood fell a little, indicating increased O_2 utilization by the tissues. Immediately after exchange hemodilution, the AVD for oxygen fell from 5 vol.% initially to 3 vol.% ($P < 0.001$) and it was maintained at that level at all stages of investigation, with only a small increase at the 3rd hour. A decrease in AVD is the natural result of a decrease in the oxygen capacity of the blood.

It is interesting to note that of the total value of AVD, dissolved Hb (shaded part of the columns, Hb = 7 g%) accounted for 2 vol.%, i.e., for two-thirds, whereas the 500,000 erythrocytes (hematocrit index 2%) remaining in the animal's blood stream transported 1 vol.%, i.e., one-third of the oxygen. Whereas immediately after exchange replacement the decrease in the total AVD was connected with an increase in MVC, during the 2 h after hemodilution, despite a progressive fall in MVC, AVD was maintained at its previous low level. This indicates that the basic compensatory mechanism — an increase in the extraction of O_2 by the tissues from the blood flowing through them, while the velocity of the blood flow was reduced — was not working, evidently because of the increased affinity of the Hb solution for oxygen, i.e., a shift of the oxygen dissociation curve to the left.

The O_2 consumption of each individual animal under standard conditions was relatively constant. It will be clear from Fig. 3 that the total O_2 consumption by the animals was reduced by 50% ($P < 0.01$) 1 h after blood replacement and by 75% after 3 h. At the same time, pO_2 in the venous blood fell. The fall in the O_2 consumption could be the result either of a decrease in the oxygen demand of the tissues, or, which is more likely, the development of uncompensated hypoxia.

Whereas MVC was reduced 2 h after replacement of the blood by pure Hb solution, after additional blood transfusion it remained at its initial level. Additional transfusion of autologous blood led to a sharp change in AVD between the Hb in the erythrocytes and that dissolved in the plasma. For instance, after injection of blood AVD of the free Hb fell from 2 to 0.8 vols. % ($P < 0.001$), and to 0.6 vol.%, i.e., more than threefold, by the end of the experiment. Hence, in the presence of erythrocytic Hb the ability of the dissolved Hb to satisfy the body's O_2 requirements was considerably reduced, whereas its ability to transport O_2 remained at its previous level, as shown by the O_2 concentration in the mixed venous blood and the degree of its oxygenation.

The experimental animals whose blood was replaced by Hb solution survived for between 2 and 6 h.

In experiments on baboons [3] similar results were obtained to those described above. The authors cited mentioned as a great achievement the fact that the mean lifespan of the baboons was actually as much as 3 h.

The present experiments showed that Hb solution can transport O_2 and, for several hours, maintain life in the totally exsanguinated animal. The Hb solution is well saturated with O_2 in the lungs and gives up O_2 in the tissues, but by a much lesser degree than Hb contained in erythrocytes. The Hb solution also maintains the basic indices of the hemodynamics for a certain time.

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