Effect of Fetal or Adult Red Cells on Tissue Oxygenation and Myocardial Function in Normoxemic Newborn Lambs

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Summary

Twelve newborn lambs less than 48 hr old had their high oxygen affinity blood exchanged for low-affinity fresh adult blood. Tissue oxygenation, hemodynamic status, blood gases, and myocardial function were compared before and after the exchange transfusion. The P_{50} was increased from 18 to 29 mm Hg after exchange transfusion; pH and hemoglobin levels remained constant; and there was no change in myocardial function, arteriovenous O_2 content difference, O_2 consumption, or cardiac output. However, mixed venous PO_2 was significantly increased with low affinity red cells (33 versus 23 mm Hg).

Speculation

This study suggests that in the immediate neonatal period adequate a lowering of red cell oxygen affinity under normoxemic conditions can result in a increase in tissue PO_2 .

Early preterm newborn infants have blood with high oxygen affinity (2). Does this leftward displacement of the oxygen hemoglobin dissociation curve limit the delivery of oxygen to the tissues? Although improvement in tissue oxygenation has been suggested after exchange transfusion using adult blood (6, 8), the reason remains unclear. Most publications have compared various biologic parameters using adult red cells whose O_2 affinity has been modified (3, 9, 10, 11, 15, 17, 20). However, none of these studies would be directly related to the normal human preterm infant under normoxemic conditions. It was deemed important to evaluate, using an appropriate newborn animal model, whether the lowering of high oxygen affinity could have any advantage, as far as delivery of oxygen to the tissues was concerned, during the immediate neonatal period in normoxemic conditions.

The present study was undertaken to compare tissue oxygenation, hemodynamic status, blood gas changes, and myocardial performance of newborn lambs whose high oxygen affinity blood was exchanged for low oxygen affinity adult blood. The newborn lamb has during the first 48 hr of life a P_{50} (18 to 20 mm Hg) (1) which is similar to that of an early preterm newborn infant (2). The P_{50} range of the adult sheep (35 to 40 mm Hg) is considerably higher (14).

MATERIALS AND METHODS

Twelve newborn lambs less than 48 hr old were included in the study. The animals were prepared in conformance with the guiding principles in the care and use of animals as recommended by the Declaration of Helsinki. They were sedated enough to be kept asleep with repeated subcutaneous injections of Diazepam (0.3 mg/kg every 20 to 30 min). To eliminate sensibility to pain during

catheter positioning, lidocaine hydrochloride (2%) was used as a local anesthetic. To ensure comparable constant metabolic conditions, they all received an intravenous injection of curare (0.3 mg/kg). A quarter of this initial dose was then repeated every 30 min. They were all mechanically ventilated with ambient air to maintain an arterial PCO_2 of 35 mm Hg $\pm$ 5. Temperature was kept constant at 38°C $\pm$ 0.5.

Polyethylene catheters were positioned in the right atrium and the descending aorta along with a Swan-Ganz 5F flow-dependent balloon catheter in the pulmonary artery using both of the femoral veins and one of the femoral arteries. Systemic and pulmonary artery pressures were recorded continuously on a Grass model 7 recorder. Two micromanometer tipped catheters (Millar, Mikro-tip, No. 7-F, model PC-470; Millar Instruments, Houston, TX) were also placed, one from the carotid artery into the left ventricle (LV) and the other from the remaining femoral artery just above the aortic valve. Oxygen content was measured in samples taken from aorta and pulmonary artery using a Lex O_2 con (Lexington Instrument Corporation, Waltham, MA). Throughout the study, the difference between the O_2 content of the pulmonary artery and the right atrium was never greater than 2%, indicating that there was no left-to-right shunt through the ductus arteriosus.

Samples obtained from descending aorta were used to determine pH, PaO_2 , PCO_2 , Hb concentration, and oxygen saturation; oxygen saturations were also determined in right atrium and pulmonary artery. The mixed venous PO_2 was determined on samples obtained from the pulmonary artery. All analysis were done using an IL Instrument Laboratory from Instrumentation Laboratory Inc. Lexington, MA (213 blood gas analyser tonometer, 208 gas mixing system, and 182 co-oximeter).

To measure oxygen consumption, expired air was collected, and minute-volume was measured in a spirometer. The O_2 concentration in the expired air was determined with an O_2 analyser apparatus S.3A (Applied Electrochemistry Inc., Sunnyvale CA). Cardiac output was calculated applying the Fick principle. The percentage of O_2 tissue extraction was obtained according to the formula: arterial O_2 content - venous O_2 content/arterial O_2 content $\times$ 100. From the cardiac output and the mean pressures, it was possible to calculate the total resistance in the pulmonary and systemic circulations (12).

In five animals, throughout the experiment, the myocardial function data, which included the LV and aortic pressures obtained from the micromanometer tipped catheters, an electrocardiogram with a well identified Q wave, and an endocavity phonocardiogram obtained from the LV catheter, were all stored in a four-channel FM tape recorder (Hewlett-Packard, model 3960A, Palo Alto CA). The tape was later processed through an Electronics for Medicine recorder model DR 12, (Electronics for Medicine, White Plains, NY) allowing photographic recording of the tracings at a paper speed of 200 mm/sec. On the aortic pressure tracing,

the pre-ejection period (PEP), isometric contraction time, and left ventricular ejection time (ET) were measured as well as the ratio PEP/ET as described by Weissler *et al.* (18). The ratio PEP/ET and isometric contraction time are not influenced by change of heart rate and are well-known indices of myocardial function (18). The left ventricular pressure signal was processed through a precalibrated differentiator model RC-1 giving a continuous assessment of the contractility of this cavity expressed as the dp/dt in mm Hg/sec (13). The results of the systolic time intervals and the dp/dt studies represent an average of five consecutive complexes.

After obtaining these data, all newborn animals had an exchange transfusion with freshly drawn maternal blood under sterile conditions. The blood was collected in 500 ml blood sacs (Blood-Packs; Fenwal Laboratories, Deerfield IL). The amount used corresponded to approximately twice the blood volume (160 cc per kg) of the newborn animal. After a recovery period of 30 min the same studies as previously described were repeated.

The P_{50} was determined by gas mixing tonometry pre- and postexchange transfusion and expressed in mm Hg at a pH 7.4, PCO_2 of 40 mm Hg, and 37°C. All data were expressed as a mean and S.D.

RESULTS

The hemoglobin affinity for oxygen expressed as the P_{50} increased from 18 mm Hg $\pm$ 3.1 before to 29 mm Hg $\pm$ 2.8 after the exchange transfusion (which indicated that approximately 80% of the fetal red cells had been exchanged). This increase is highly significant ($P < 0.01$). The following parameters were not modified pre- and postexchange transfusion: pH (pre, 7.44 $\pm$ 0.06; post, 7.45 $\pm$ 0.06) and hemoglobin (pre, 12.2 g % ml $\pm$ 1.8; post, 11.9 $\pm$ 1.2 g %).

No significant change in arteriovenous oxygen content difference occurred despite the marked change in P_{50} (pre-exchange, 4.7 ml/100 ml $\pm$ 1.2; postexchange, 4.9 $\pm$ 1.0). The percentage of O_2 extraction was: pre-exchange, 31.8 $\pm$ 8.2, and postexchange, 37.7 $\pm$ 6.7. The cardiac output also remained stable being 265.4 ml/min/kg $\pm$ 35.4 before and 285.6 ml/min/kg $\pm$ 78.9 after exchange; finally, the O_2 consumption also stayed constant with an average value of 12.1 ml/kg $\pm$ 2.2 before exchange and 13.5 ml/kg $\pm$ 2.3 after exchange. These findings are shown in Figure 1.

Figure 2 shows the arterial and mixed venous PO_2 as well as the arterial and venous hemoglobin saturations before and after exchange transfusion. Mixed venous PO_2 increased significantly in the presence of low-affinity adult red cells. The increase was from 23.8 $\pm$ 5.2 to 33.2 $\pm$ 3.3 mm Hg ($P < 0.01$). There was no difference in the mean values obtained for arterial and venous hemoglobin saturations.

The myocardial function studies showed that heart rate, systolic time intervals, and dp/dt of the left ventricle did not change during the study. The findings are illustrated on Table 1. The mean systemic and pulmonary arterial pressures and resistances before and after exchange transfusion were similar; however, there were large variations in the resistances between individual animals. The values for the mean systemic and pulmonary arterial pressures in mm Hg were 82 $\pm$ 10 versus 83 $\pm$ 13 and 32 $\pm$ 6 versus 32 $\pm$ 6, respectively. The mean values for the systemic and pulmonary arterial resistances in dynes $\cdot$ sec $\cdot$ cm $^{-5}$, were 5908 $\pm$ 1523 versus 5703 $\pm$ 1539 and 2344 $\pm$ 664 versus 2170 $\pm$ 602, respectively.

DISCUSSION

The transport of oxygen from the lungs to the tissues is influenced by the pulmonary gas exchange, the blood-carrying capacity, the cardiac output, and the hemoglobin oxygen affinity (7). In this series of experiments, an attempt was made to isolate oxygen-hemoglobin affinity as a variable and to elucidate its influence on tissue oxygen delivery and myocardial function. This was achieved successfully by maintaining a stable and constant metabolic activity as well as O_2 consumption by sedating, curarizing, and mechanically ventilating the newborn lambs. The O_2 consumption of the animal used in this study as well as the cardiac output was in the same range as has been reported by others using anesthetized newborn lambs (4, 5, 19). The experiments were always carried out at less than 48 hr of age because oxygen consumption (5) and P_{50} (2) can change dramatically in newborn lambs during the first wk of life.

Despite the marked change in P_{50} obtained by the exchange transfusion, the O_2 delivered to the tissues remained unaltered. However, a significant increase in the arteriovenous oxygen tension differences was found when fetal red cells were in circulation. This was due to a more substantial decrease in the mixed venous

Fig. 1. Arteriovenous O_2 content differences, O_2 consumption, cardiac output, and O_2 extraction in 12 newborn lambs with high-affinity red cells (●) and low-affinity cells (□). The values for individual animals are connected by lines. Bars and vertical line, mean $\pm$ S.D.

Fig. 2. Arterial and venous PO_2 and hemoglobin saturations in 12 newborn lambs with high-affinity red cells (□) and low-affinity red cells (●). The values for individual animals are connected by lines. Bars and vertical line, mean $\pm$ S.D.

Table 1. Heart rate (in beats/min), systolic time intervals (in msec) and dp/dt (in mm Hg/sec) of the left ventricle of newborn lambs with fetal and adult red cells

	Heart rate	PEP	ET	PEP/ET	ICT ¹	dp/dt
Fetal	244 ± 29	39 ± 7	120 ± 11	0.32 ± 0.03	15 ± 5	4075 ± 1616
Adult	242 ± 26	37 ± 3	118 ± 9	0.31 ± 0.02	14 ± 6	3998 ± 1016

¹ ICT, isometric contraction time.

PO_2 in the high O_2 affinity group. The level of mixed venous blood tension is considered a reliable index of peripheral capillary and tissue oxygen tension (16). The rate of transfer of oxygen from the blood to the tissues depends mainly upon the pressure gradient between the two components, therefore, a lowering of mixed venous PO_2 without evidence of decreased O_2 consumption indicated that the mixed venous oxygen tension compensated for the high O_2 affinity of the fetal red cells, and adequate O_2 was available for tissue requirements under normoxic conditions.

Some investigators in animal studies have suggested that variations in blood oxygen affinity results in changes in both venous PO_2 as well as cardiac output so that O_2 consumption remains stable (11). These authors postulated that a left-sided shift in the oxygen-hemoglobin dissociation curve could result in a falling venous PO_2 or and an increase in cardiac output. In the present study, only mixed venous PO_2 changed. Myocardial function as well as cardiac output and arteriovenous O_2 content differences remained constant, irrespective of the type of red cells in the circulation.

The findings in our study could reflect the consequences of a rapid decrease of red cell oxygen affinity during the immediate neonatal period, and they suggest that the position of the oxygen-hemoglobin dissociation curve has little or no significance in the newborn lamb under stable metabolic conditions with a normal arterial oxygenation. However, the exchange of high-affinity blood for low-affinity blood causes an increase in mixed venous PO_2 (Fig. 3). Although one cannot extrapolate the results of these experiments directly to the human newborn infant, the relationship between venous PO_2 and mean tissue PO_2 is considered a good approximation under stable conditions (16). A decrease in red blood cell oxygen affinity could result in an increase in mean tissue PO_2 during the neonatal period.

Effect of leftward shift of the ODC

Fig. 3. The effect of the shift of the oxygen-hemoglobin dissociation curve on oxygen transport. The fetal curve lowers $P\bar{v}O_2$ and does not limit the transfer of oxygen.

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