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The Effect of High or Low Oxygen Affinity Red Cells on Tissue Oxygenation and Myocardial Function in Hypoxic Newborn Lambs with or without Hypercapnia

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Summary

In order to compare high and low oxygen affinity blood under conditions of severe respiratory failure, the effects of a high or low P_{50} were evaluated in two groups of newborn lambs (P_{50}, 20 mmHg *versus* 30 mmHg), under conditions of hypoxic hypoxia (FiO_2, 10%) and hypercapnic hypoxia (FiO_2, 10% and $FiCO_2$, 10%). Data on cardiovascular function, blood gas parameters, and tissue oxygenation were collected under normoxic conditions and during severe hypoxia. During hypoxic hypoxia, a higher arterial oxygen content was noted in the high affinity group throughout the experiment; however, there were no significant differences detected in the remainder of the parameters studied. During hypercapnic hypoxia, the position of the oxygen dissociation curve did not cause any significant differences. When, however, hypercapnic hypoxia was compared to hypoxic hypoxia, there was a significant increase in cardiac output and myocardial contraction during hypercapnia.

Abbreviations

HbO_2, hemoglobin oxygen saturation
LV, left ventricle
LVET, left ventricular ejection time
PEP, pre-ejection period
ODC, oxygen dissociation curve
$P\bar{v}O_2$, venous oxygen tension

Recent studies in our laboratory have shown that a lower mixed venous oxygen tension ($P\bar{v}O_2$) in presence of high O_2 affinity red cells occurs in normoxemic newborn lambs and that severe anemic hypoxia is better tolerated in lambs with low affinity blood compared to high affinity blood (13, 26). A shift of the ODC to the right is believed to be advantageous at normoxia (13), anemia (26), and mild hypoxia (1, 12, 14, 18); however, it may be maladaptive under conditions of severe hypoxia (11). Early preterm newborn infants who have a high oxygen affinity blood (P_{50}, 18–19 mmHg) (3) frequently suffer from repiratory failure due to hyaline membrane disease. When the disease is severe they are often intubated and mechanically ventilated. Because hyperbilirubinemia is frequent in these infants, many of them are exchange transfused with adult blood (P_{50}, 27–28 mmHg).

In order to evaluate whether the manipulation of oxygen affinity could result in observable differences in cardiovascular function and tissue oxygenation during severe hypoxia, a study was planned to simulate severe respiratory failure in the neonatal period. Newborn lambs were chosen as an experimental model during the first 48 h after birth when their blood P_{50} is similar to that of early preterm newborn infants (18 mmHg) whereas the adult animal's P_{50} ranges between 32–40 mmHg (2, 3). The newborn lamb, after an exchange transfusion with adult sheep blood, would have its P_{50} increased so that it is in the range of adult human blood (27 mmHg).

MATERIALS AND METHODS

Twenty-six mixed breed newborn lambs less than 48 h old were included in this study. Intramuscular diazepam was used as sedation (0.2 mg/kg as a loading dose, 0.1 mg/kg repeated at hourly intervals). Infiltration of lidocaine 2% provided local anesthesia at catheterization site. In an attempt to maintain constant metabolic demands, the animals were curarized with *d*-tubocurarine (0.2 mg/kg intravenously), half of this dose being repeated if necessary. They were intubated and mechanically ventilated. Rectal temperature was constantly controlled at 38.5 ± 0.2°C.

Polyethylene catheters were positioned in descending aorta and right atrium. A Swan-ganz balloon catheter 5F was also placed in the pulmonary artery as described previously (13, 26). Statham P23Dc transducers provided pressure curves which were registered on a Grass model 7 paper recorder, giving heart rate, systolic, diastolic, and mean pressure values of both systemic and pulmonary circulations. The position of the catheters was determined by the morphology of the pressure curve. For the right atrium the catheter was advanced until the appearance of atrial extrasystoles. At the end of the experiment the position of all catheters were confirmed at autopsy. The lambs were divided in four groups, two of which had their high affinity red blood cells exchanged for low affinity red blood cells (Fig. 1). This was achieved by a two volume exchange transfusion (160 ml/kg) of fresh heparinized adult sheep blood. The first series of 12 experiments were carried out to compare the high and low oxygen affinity groups (six animals in each group, 1A and 1B) when being ventilated with a gas mixture of 10% O_2 and 90% N_2. Then another series of similar experiments were carried out with 14 animals (seven animal in each group, 2A and 2B) using a gas mixture of 10% O_2, 10% CO_2, and 80% N_2.

Oxygen content was measured in aorta, right atrium, and pulmonary artery samples 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 and pulmonary artery were used to determine pH, Po_2, Pco_2, hemoglobin concentration and HbO_2 using instruments from Instrumentation Laboratory Inc. Lexington, MA (213 blood gas analyser tonometer, 208 gas mixing system, 182 co-oximeter). The expired gas was collected in a spirometer and its O_2 concentration was measured with an O_2 analyser apparatus S3A (Applied electrochemistry Inc. Sunnyvale, CA). Oxygen consumption per minute ($\dot{V}O_2$) could thus be determined. Cardiac output ($\dot{Q}$) was calculated applying the Fick principle and was reported to animal weight ($ml \cdot kg^{-1} \cdot min^{-1}$). Total pulmonary and

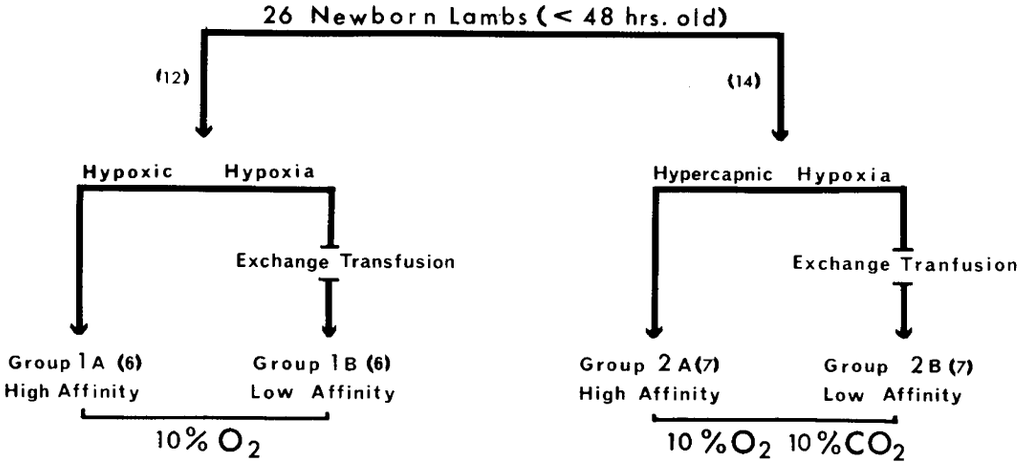

Fig. 1. Schematic representation of the experimental protocol.

systemic resistances (dynes·sec·cm^{-5}) were obtained by dividing the mean pulmonary or aortic pressure with the cardiac output.

During twelve experiments in the hypoxic-hypercapnic groups (six with high and six with low affinity RBCs) and seven experiments in the hypoxic groups (four with high and 3 with low affinity RBC's), the left carotid artery was catheterized with a Millar Mikrotip pressure transducer catheter, which was positioned above the aortic valve. This aortic pressure tracing and an ECG with a well identified Q wave were recorded on photographic paper at a speed of 200 mm/sec using a Electronics for Medicine apparatus Model DR_{12} (Electronics for Medicine White Plains, NY). From five consecutive complexes, the PEP and the LVET were measured as well as the ratio PEP/LVET, which is an accepted index of myocardial contractility. The Mikrotip catheter was also positioned in the LV and the LV pressure signal was processed through a pre-calibrated differentiator model RC-1 giving the dp/dt in mmHg/sec as another assessment of LV contractility. At each experimental phase the Mikrotip catheter was successively positioned above and under the aortic valve giving PEP/LVET than dp/dt.

Heart rate, cardiac output, blood pressures, and vascular resistances of both pulmonarty and systemic circulation, left ventricular PEP/LVET and dp/dt, Pa_{O_2}, $P\bar{v}_{O_2}$, P_{CO_2}, pH, O_2 content and P_{50} were measured twice at a basal state (room air), then after 20, 45, and 90 min of hypoxia. All data are expressed as a mean and standard deviation (S.D.). The statistical test used to compare the mean data obtained between the high and low affinity groups was the Student's two sample *t* test. But when the differences within the same group were compared (control and hypoxic values), a paired *t* test was used. In order to evaluate the variability of a given lamb, the same data were collected from two different animals for 12 h under normoxic conditions.

The hemoglobin values (mg/100 ml) in the high affinity groups (nonexchange transfused) and the low affinity groups (exchange transfused) were not significantly different. They were 12.1 ± 1.3 *versus* 10.8 ± 0.7 and 11.8 ± 1.4 *versus* 10.4 ± 0.6 in the hypoxic hypoxia and hypercapnic hypoxia groups respectively.

RESULTS

Hypoxic hypoxia. The mean P_{50} increased significantly from 20.4 ± 2.1 to 30.3 ± 1.9 mmHg after exchange transfusion and remained stable until the end of the experiments. In the untransfused lambs the P_{50} remained stable at 21.8 ± 2.6 mmHg. The P_{CO_2} was maintained at 35 ± 3 mmHg during the experiments. Throughout the hypoxia, the Pa_{O_2} decreased significantly but the pH remained stable (7.49 ± 0.04 for high affinity and 7.47 ± 0.04 for low affinity). The $P\bar{v}_{O_2}$ at basal state was significantly lower with high affinity blood in the circulation ($P < 0.001$). During hypoxia, $P\bar{v}_{O_2}$ decreased with low (18 ± 3 mmHg) and high (20 ± 9 mmHg) affinity RBCs and the difference was no longer significant. There was a rapid decrease in arterial and venous O_2 content during hypoxia with a significantly greater arterial O_2 content in the high affinity groups, as shown in Figure 2 ($P < 0.005$ for high affinity, $P < 0.001$ for low affinity).

The arteriovenous difference in O_2 content (CaO_2–$C\bar{v}O_2$), the $\dot{V}O_2$ and the $\dot{Q}$ of each animal are presented in Figure 3 under normoxic condition and after 20 min of hypoxia. No significant changes were found between the mean value at 20, 45, and 90 min of hypoxia. The $\dot{V}O_2$ decreased significantly for high and low affinity but CaO_2–$C\bar{v}O_2$ and $\dot{Q}$ remained stable.

Pulmonary pressure increased significantly for both groups 34 ± 8 to 55 ± 10 mmHg for high affinity and 32 ± 7 to 59 ± 4 mmHg for the low affinity ($P < 0.001$). The mean pulmonary resistance increased from 2342 ± 507 to 3349 ± 891 dynes·sec·cm^{-5} for the high affinity group ($P < 0.01$) and from 2267 ± 560 to 3696 ± 1640 dynes·sec·cm^{-5} for the low affinity group ($P < 0.05$). Systemic pressure did not change (80 mmHg ± 20) during hypoxia as did systemic resistance (5500 ± 1400 dynes·sec·cm^{-5}). Heart rate did not change significantly and remains at 200 ± 30 for both groups.

During hypoxic hypoxia the left ventricular mean dp/dt did not vary significantly changing from 3786 ± 667 to 4000 ± 1143 mmHg/sec with high affinity RBCs and from 3162.5 ± 787 to 3637 ± 862 mmHg/sec with low affinity RBCs group. The PEP/LVET changed from 0.294 ± 0.035 to 0.330 ± 0.034 for high affinity group and from 0.284 ± 0.124 to 0.240 ± 0.028 for low affinity RBCs. These changes were not significant. There were no statistical differences in myocardial function between the high and low affinity groups.

Hypercapnic hypoxia. The mean P_{50} increased significantly from 18.3 ± 3.2 to 29.1 ± 2.9 mmHg after exchange transfusion and remained stable until the end of the experiment. In the nonexchanged transfused lambs the P_{50} remained stable at 21.4 ± 2.2 mmHg. The P_{CO_2} was increased significantly from 35 ± 3 to 70 ± 5 mmHg ($P < 0.001$). The severe hypercapnic hypoxia induced severe acidosis (7.47 ± 0.07 to 7.1 ± 0.07 for the high affinity group and 7.48 ± 0.07 to 7.1 ± 0.04 for the low affinity). Figure 4 shows that the $P\bar{v}_{O_2}$ was lower with high affinity RBCs at the basal state ($P < 0.05$) and decreased significantly to similar levels during hypercapnic hypoxia (17 ± 2 for high affinity, 20 ± 4 for low affinity). When comparing high affinity to low affinity blood during hypoxic states the PaO_2 was significantly higher with low affinity blood ($P < 0.02$). Arterial and venous O_2 content decreased significantly ($P < 0.001$) but there was no differences between the low and high affinity groups. Figure 5 illustrates the changes in CaO_2–$C\bar{v}O_2$, $\dot{V}O_2$ and $\dot{Q}$, which occurred after 20 min of hypercapnic hypoxia. No significant changes were found

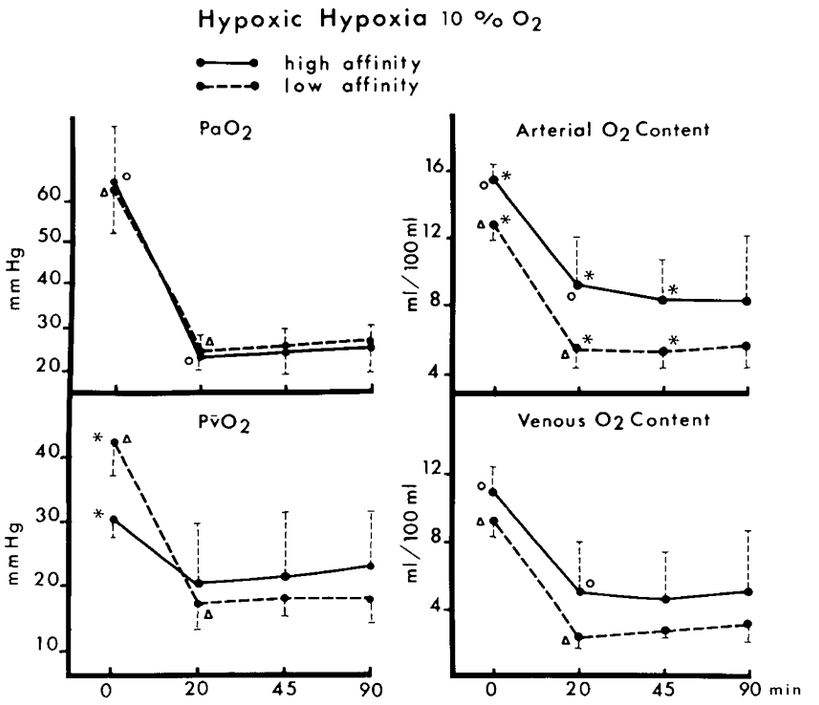

Fig. 2. The Pa_{O_2}, mixed venous O_2 pressure ($P\bar{v}O_2$), arterial and venous O_2 content are represented at normoxia and after 20, 45, and 90 min of hypoxic hypoxia. The lines join the mean and ± standard deviation (S.D.) of the newborn lambs with either high or low affinity blood. The notations ○ and △ represent significant differences between control and hypoxia values, whereas * indicates a significant difference between high and low affinity blood groups.

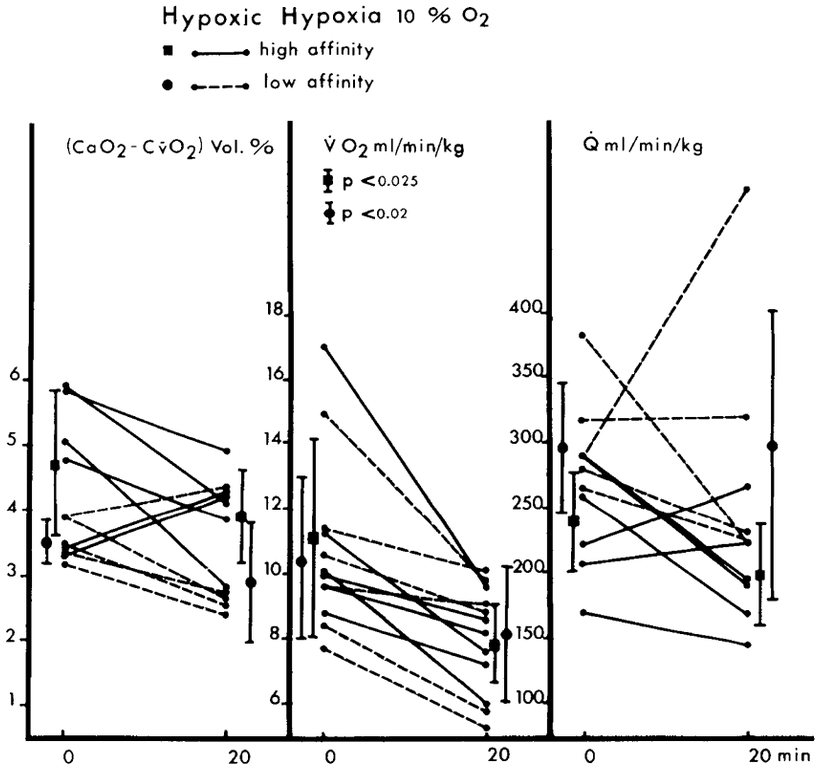

Fig. 3. The CaO_2–$C\bar{v}O_2$, $\dot{V}O_2$ and $\dot{Q}$ are represented for each animal at normoxia and after 20 min of hypoxic hypoxia. The notations ● and ■ represent the mean ± standard deviation (S.D.).

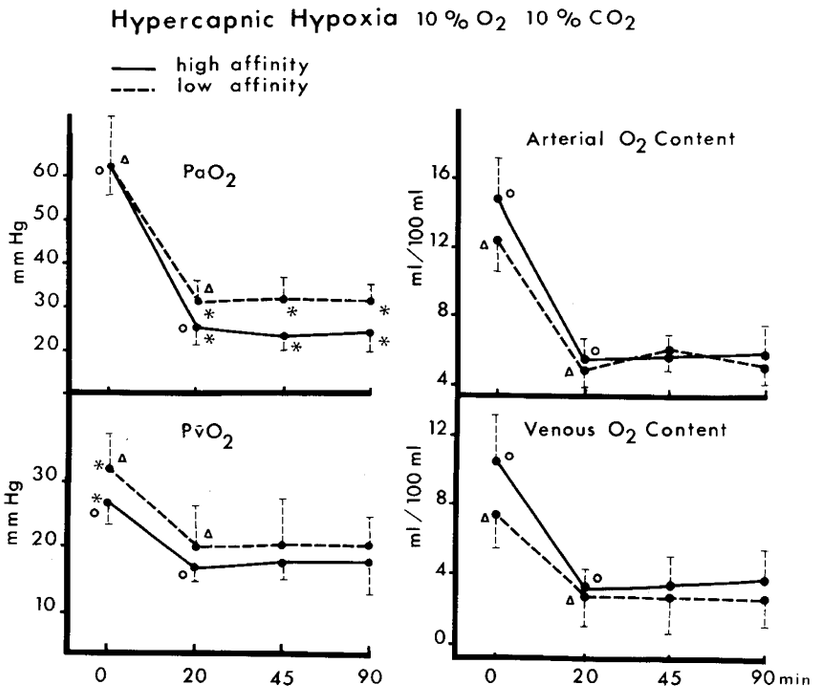

Fig. 4. The Pa_{O_2}, mixed venous O_2 pressure ($P\bar{v}O_2$), arterial and venous O_2 content are represented at normoxia and after 20, 45, and 90 min of hypercapnic hypoxia. The lines join the mean and ± standard deviation (S.D.) of the newborn lambs with either high or low affinity blood. The notations ○ and △ represent significant differences between control and hypoxia values, whereas the * indicates a significant difference between high and low affinity groups.

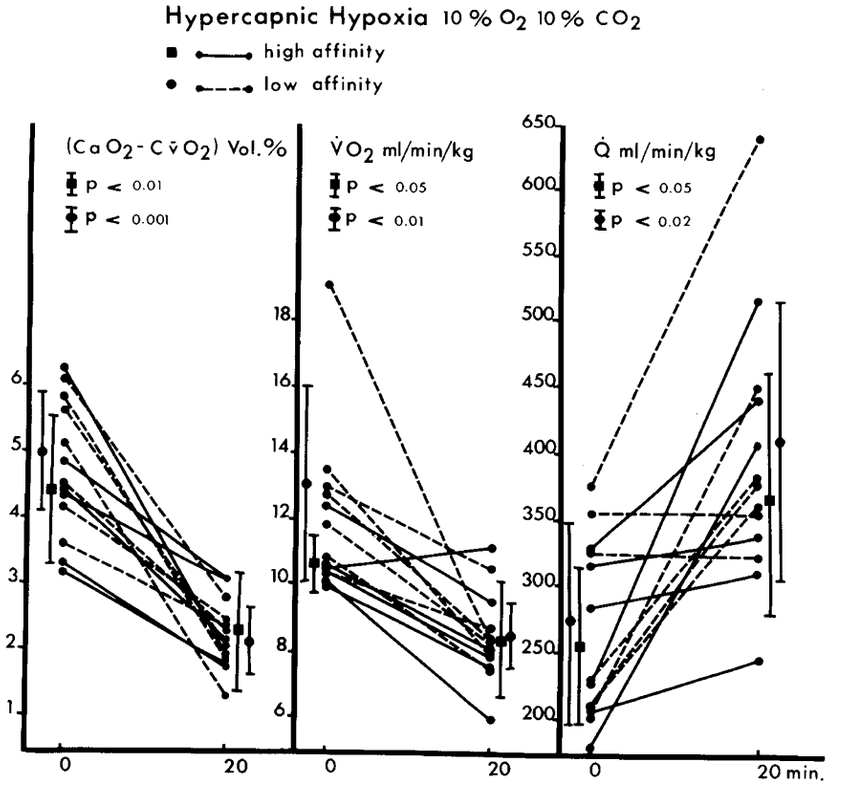

Fig. 5. The CaO_2–$C\bar{v}O_2$, $\dot{V}O_2$ and $\dot{Q}$ are represented for each animal at normoxia and after 20 min of hypercapnic hypoxia. The notations ● and ■ represent the mean ± standard deviation (S.D.).

between the mean values at 20, 45, and 90 min of hypercapnic hypoxia. The $\dot{V}O_2$ and CaO_2–$C\bar{v}O_2$ decreased significantly and $\dot{Q}$ increased significantly.

The mean heart rate increased from 197 ± 37 to 238 ± 18 ($P < 0.025$) for the high affinity blood and from 219 ± 34 to 243 ± 23 for the low affinity blood (nonsignificant). The pulmonary pressure increased markedly (from 30 ± 4 to 60 ± 8 mmHg, $P < 0.001$) whereas pulmonary resistance increases slightly (2300 ± 500 to 2800 ± 700 dynes·sec·cm^{-5}, nonsignificant) in both affinity groups. The mean systemic pressure changed little, increasing from 75 to 85 mmHg. Systemic resistance decreased significantly ($P < 0.05$) for the high affinity group (6092 ± 1126 to 4096 ± 1109 dynes·sec·cm^{-5}) and nonsignificantly for the low affinity group (5073 ± 1366 to 3897 ± 826 dynes·sec·cm^{-5}). But when comparing high and low affinity groups there were no significant differences.

In hypercapnic hypoxia left ventricular dp/dt increased significantly from 3693 ± 1075 mmHg/sec to 5410 ± 433 with high affinity RBCs and from 4482 ± 1580 to 5805 ± 1445 with low affinity RBCs ($P < 0.05$). The left PEP/ET remained stable, 0.257 ± 0.054 to 0.261 ± 0.037 and 0.280 ± 0.059 to 0.308 ± 0.058 with high and low affinity blood respectively. There were no difference between the high and low affinity blood groups.

The stability of the preparation used in this study was controlled by measurements taken over a 12-h period in two normoxic animals. The S.D. of serial measurements taken every hour over this period was 4% of the mean for $\dot{V}O_2$, 10.5% of the mean for $\dot{Q}$ and 8% of the mean for CaO_2–$C\bar{v}O_2$, the variation of the other parameters remains under 5% of the mean. As shown by greater S.D., the variability between our experimental animals during normoxia was more important. The S.D. was 23% of the mean for $\dot{V}O_2$, 23% for $\dot{Q}$ and 24% for CaO_2–$C\bar{v}O_2$ and variations of the other parameters remained between 15–20%.

DISCUSSION

This study provides information on the influence of the position of the ODC upon the oxygenation of the newborn lamb under severe hypoxic hypoxia and severe hypercapnic hypoxia. The animals were lightly sedated, ventilated and curarized in an attempt to maintain constant metabolic demands. The use of sedated and ventilated newborn lambs certainly had its limitations. Cross *et al.* (5) reported that $\dot{V}O_2$ in nonshivering, nonpanting lambs less than 1-day-old was 12–15 ml·kg^{-1}·min^{-1} under normoxic conditions and that it decreases to 6 ml·kg^{-1}·min^{-1} under hypoxic conditions (FiO_2, 10–12%). Those values were similar to the $\dot{V}O_2$ found in this study. Also cardiac output values, as in this study, did not change under hypoxic conditions (5, 6). In other studies carried out with unsedated lambs during the first day of life, the reported $\dot{V}O_2$ and $\dot{Q}$ were either similar (28) or slightly higher than the data reported in this study (4, 19). The differences are likely due to the lowered oxygen requirements of the mechanically ventilated newborn lambs reported in this study.

The biologic importance of differences or changes in ODC have been observed between mother and fetus, at altitude, and during hypoxia. The high oxygen affinity of fetal blood suggests that it is designed to facilitate oxygen uptake across the placenta. The comparisons of oxygen transport between different O_2 affinity blood in mammals as well as across the pregnant uterus have been reported by Metcalfe and his group (20, 21). These authors showed that an evaluation of tissue oxygenation can be made between high and low affinity blood, when the total O_2 consumption, O_2 content difference between arterial and venous blood as well as the $P\bar{v}O_2$ are determined. The important variable when evaluating oxygen delivery to the tissues is mixed venous PO_2. The concept that the level of mixed venous blood tension is a reliable index of tissue oxygenation has been supported by others (25).

In situations of compromised oxygen availability, such as occur in severe red cell mass deficits or poor arterial blood perfusion, a lowered hemoglobin oxygen affinity is of benefit (9, 23, 26). The changes in oxygen hemoglobin affinity that have been described at moderate altitude remain controversial. It has been accepted by some that there is a decrease in erythrocyte O_2 affinity induced by altitude which facilitates oxygen unloading at the tissue level (1, 12, 14, 18). But Winslow *et al.* (27) concluded that this shift was offset by compensated respiratory alkalosis with the net results that the ODC position was similar to that of sea level humans. Yet, animals living at high altitude have a higher blood O_2 affinity than their lowland relatives (22). Also it has been shown that rat survival at high altitude (10,000 m) was increased with high affinity hemoglobin in circulation (11) and in a very recent report it was shown that humans having high affinity hemoglobin mutants were better adapted to moderate altitude (16). Thus under conditions of hypoxic hypoxia it may be of greater physiologic importance to have an increase in oxygen binding rather than an increased in oxygen unloading.

In this study, during hypoxic hypoxia, the significant differences noted between high and low affinity can be explained by the respective position of the oxygen dissociation curve. For the same amount of extraction the $P\bar{v}O_2$ in low affinity group is higher under normoxic conditions. At identical PaO_2, the O_2 contents of the high affinity groups are higher. But no physiologic differences could be demonstrated by these changes because cardiac output, $\dot{V}O_2$, and CaO_2–$C\bar{v}O_2$ between high and low affinity groups were not different. Also the absence of acidosis showed that the minimal O_2 requirements during hypoxic hypoxia were maintained irrespectively of the ODC position.

During hypercapnic hypoxia as expected, $\dot{V}O_2$ also decreased significantly; however, unlike the eucapnic group, cardiac output increased probably due to the highly stimulant effect of CO_2 on the autonomic nervous system (10, 17, 24). Therefore for the same decrease in $\dot{V}O_2$, CaO_2–$C\bar{v}O_2$ decreased significantly owing to the increased $\dot{Q}$. There is no clear explanation for the significantly high PaO_2 in the low affinity group seen during hypercapnic hypoxia. A similar phenomena had been observed by others in hypercapnic low birth weight newborn infants after exchange transfusion (15). A possible speculation is that this finding is the result of a difference in cardiac output as well as pulmonary perfusion.

Although there was a significant decrease in $\dot{V}O_2$ in all groups during severe hypoxia, myocardial function was not impaired as shown by the stable dp/dt in hypoxic hypoxia. In hypercapnic hypoxia the dp/dt increased in both high and low affinity groups. These findings go along well with the increase in $\dot{Q}$. It may well be that a mild hypercapnia by improving $\dot{Q}$ could have a beneficial effect on tissue oxygenation which has been masked by the severe acidosis created by the degree of hypercapnia in this study.

There are several reports and studies which showed that the use of exchange transfusions increased the survival rate of infants of very low birth weight with severe respiratory distress syndrome (7, 8, 15). The cause of this decrease in mortality remains unclear. The present study shows that from an O_2 delivery point of view and myocardial function, the manipulation of red cell oxygen affinity is of no advantage nor disadvantage during severe respiratory failure of the newborn lamb.

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