Cardiovascular response of the neonatal lamb to hypoxia and hypercapnia

M. STAHLMAN, J. GRAY, W. C. YOUNG, AND F. M. SHEPARD
Laboratory of Newborn Physiology, Vanderbilt University School of Medicine, Nashville, Tennessee

The profound circulatory effects of asphyxia or respiratory failure in the newborn infant are well recognized; there is a striking increase in resistance to blood flow in the pulmonary vascular bed which results in the shunting of blood away from the lungs through the persistent fetal pathways, the foramen ovale and the ductus arteriosus. A similar response is seen in the newborn lamb. Since asphyxia or respiratory failure is accompanied by hypoxia, hypercapnia, and acidosis, an attempt was made to evaluate the individual roles of two of the stimuli, hypoxia and hypercapnia, in the normal unanesthetized newborn lamb under steady-state conditions, allowing each animal to serve as its own control. The hemodynamic changes in pulmonary and systemic circulation were correlated with the changes in acid-base state and in oxygenation.

METHODS

Thirty-one normal unanesthetized lambs were studied on 44 occasions from 4 hr to 10 days of age and ranging in weight from 1.8 to 7.6 kg. Only lambs without demonstrable shunting through the ductus arteriosus, either right-to-left or left-to-right, were included in this study, so that evaluation of pulmonary blood flow and pulmonary vascular resistance would be possible. The lambs were immobilized and kept quiet by the use of pacifiers. Electrocardiogram and rectal temperatures were constantly monitored, and intermittent recording of respiratory rate and changes in intrathoracic pressure were made from a saline-filled esophageal catheter and Statham transducer. Under local lidocaine (Xylocaine) anesthesia, no. 5 polyvinyl feeding-tube catheters were inserted in the femoral artery, the left atrium via the femoral vein, and the main pulmonary artery via the jugular vein. Catheter positions were determined by pressure contour, oxygen tension, and fluoroscopy. Indicator-dilution curves were performed from pulmonary arterial and left atrial injection sites with femoral arterial pullout using 0.2 - 0.3 ml of indocyanine green dye (12.5 mg/ml). Blood was withdrawn by a constant-speed Harvard pump at approximately 6 ml/min past a cuvette densitometer placed 20 cm from the catheter tip with a sampling site to densitometer dead space of approximately 0.20 ml (12, 13). Blood loss per cardiac output determination was approximately 3.0 ml.
Right atrial, pulmonary arterial, left atrial, and femoral arterial pressures were measured intermittently using Statham P23Db transducers and a Sanborn recorder. Arterial blood determinations for pH, PaO₂, PaCO₂ and hematocrit were made during each experimental condition by previously described methods (12, 13). Systemic and pulmonary vascular resistances were calculated by standard formulas when possible and expressed as dynes-second centimeters⁻⁵.

Base-line pressures, cardiac output determinations, and arterial pH, PaO₂, and PaCO₂ values were obtained first with the lamb quietly breathing room air. Subsequently, on 26 occasions, lambs were given 8 % O₂-92 % N₂ by face mask for 20-60 min and the studies were repeated. Eight lambs included in the hypoxic experiments were then used in the study of the effects of acetylcholine to be reported elsewhere. After a 30- to 60-min recovery period during which pressures and pH, PaO₂, and PaCO₂ determinations were observed to return to base-line levels, 8 % CO₂-21 % O₂-71 % N₂ was administered via face mask and the sequence of studies was repeated on 13 occasions. Also, on 13 occasions, 100 % O₂ was administered to lambs studied as above. On 17 occasions, indicator-dilution curves were done from inferior vena caval injection sites at the onset of the study, and in each case there was either no, or a very small (<5 %), right-to-left shunt through the foramen ovale demonstrable. In eight lambs these injections were repeated during 8 % O₂ inhalation and none showed any shunt.

In most instances, at the conclusion of a study, the catheters were removed and the lambs were given intramuscular penicillin, streptomycin, and iron and returned to their mothers for repeat study at a later age.

When cardiac output determinations were satisfactory for both PA and LA injections during any one experimental condition, an average value was used for calculating pulmonary and systemic vascular resistance. Also for each cardiac output calculation, the transit time volume (MTTV) was calculated, and from the pulmonary artery injection curves, the slope volume was calculated by the formula of Newman et al. (7, 8). The latter volume is derived from the observation that the transit times of indicators through a vascular system are determined by the flow-to-volume ratios (F/V) in the various parts of the circuit. This family of transit times thus determines the shape of the downslope of the indicator-dilution curve, which approximates a single exponential for the pulmonary circulation. The slope of this exponential would be determined by the relationship between blood flow and the volume in which the indicator is mixed. Therefore, a change in the slope of the downslope of a curve with a constant flow represents a change in the physiological volume through which flow occurred (3, 7). Further, studies have shown that when flow occurs through several volumes in sequence, if one volume is considerably larger than the others (i.e., pulmonary blood volume as compared to right and left ventricular volumes), the slope of the indicator-dilution curve is determined by the largest volume involved, regardless of its sequence in the circuit (7). Thus from the equation S = F/V, knowing flow and slope, one can calculate a volume, which, in the case of the curve resulting from a pulmonary arterial injection with aortic withdrawal, would represent some physiological volume of blood in the pulmonary vascular bed. Therefore, if flow through the pulmonary circulation remains constant, any decrease in the slope time of the indicator-dilution curve must be the result of a decrease in the volume of blood in which the indicator was mixed during the passage through the lungs, and vice versa. For the sake of brevity

### TABLE 1. Changes in pH, PaO₂, PaCO₂

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>PaO₂</th>
<th>PaCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>7.43±.008 (42)</td>
<td>65±2.26 (42)</td>
<td>37.2±0.91 (42)</td>
</tr>
<tr>
<td>8% O₂, 92% N₂</td>
<td>7.50±0.018 (25)</td>
<td>23±1.33 (27)</td>
<td>27.6±0.66 (25)</td>
</tr>
<tr>
<td>8% CO₂, 21% O₂</td>
<td>7.27±0.015 (15)</td>
<td>79±1.20 (15)</td>
<td>49.5±1.50 (15)</td>
</tr>
<tr>
<td>100% O₂</td>
<td>7.40±0.016 (14)</td>
<td>300±1.16 (14)</td>
<td>35.2±1.40 (14)</td>
</tr>
</tbody>
</table>

Arterial blood values are expressed as means ± SE. Numbers in parentheses = no. of observations.
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P. A. MEAN PRESSURE PULMONARY VASCULAR CARDIAC OUTPUT

901

mmHg dyne set cm⁻¹ ml/kg/min

50-

20-

MEAN = MEAN = MEAN

19

19

ROOM AIR

8% O₂

FIG. 2. Changes in pulmonary arterial mean pressure, pulmonary vascular resistance, and cardiac output in 21 normal unanesthetized lambs subjected to inhalation of 8% oxygen in 92% nitrogen.

MEAN = MEAN = MEAN = MEAN

69.4 69.4 44.5 44.5

MEAN = MEAN = MEAN

107.6 49.9

ROOM 8% O₂, ROOM 8% O₂

FIG. 3. Changes in aortic mean pressure, systemic vascular resistance, and cardiac output in 21 normal unanesthetized lambs subjected to inhalation of 8% oxygen in 92% nitrogen.

this calculated volume will be referred to as the pulmonary slope volume.

RESULTS

The base-line values on lambs breathing room air agreed well with previous results in this laboratory (12, 13). The values for pH, PaO₂, and PaCO₂ are shown in Table 1. The cardiac output of the quietly resting lamb ranged from 0.908 to 4.250 liters/min or 205—778 ml/kg per min, with a mean value of 455 ml/kg per min. The values for systolic pulmonary arterial and aortic pressures show a moderate spread when viewed as a group; however, when compared by age of the lamb at the time of measurement, the marked increase in systemic pressure and the gradual fall in pulmonary arterial pressure during the first 10 days after birth are apparent as shown in Fig. 1.

Effect of hypoxia. The response of all lambs given 8% oxygen was that of prompt increase in rate and depth of respiration; however, mean intrathoracic pressure and right and left atrial pressures did not change significantly. This hyperventilation is reflected in the fall in PaCO₂ and development of moderate respiratory alkalosis as shown in Table 1. Adequate data were obtained from 21 of the 26 hypoxic experiments to permit calculation of cardiac output and pulmonary and systemic vascular resistances. These data are shown in Figs. 2 and 3. There was no consistent change in cardiac output during hypoxic stress, the mean value for room air being 435 ml/kg per min and that during 8% oxygen inhalation being 315 ml/kg per min.

However, the pulmonary arterial pressure, both mean and systolic values, rose consistently. In general, the more marked increase in pulmonary arterial pressure occurred in the younger lambs. Calculated pulmonary vascular resistance increased from 780 dynes-sec cm⁻¹ on room air to 1,420 dynes-sec cm⁻¹ on 8% oxygen (Fig. 2).

The systemic vascular response to hypoxia is shown in Fig. 3. There was a consistent fall in both systolic and mean aortic pressure. The change in systemic vascular
resistance was more variable, although the mean value fell from 3,900 to 3,280 dynes-sec cm\(^{-5}\) during hypoxia. The magnitude of response to hypoxia in one lamb at 24 hr of age was such that the pulmonary arterial systolic pressure was 66 mm Hg while the aortic systolic pressure fell to 68 mm Hg. Indicator-dilution curves showed no evidence of shunting through the ductus arteriosus at that time.

The marked increase in pulmonary vascular resistance and pulmonary arterial pressure suggests an active vasoconstriction of the pulmonary vascular bed. This is supported by the changes observed in the slope volume of the indicator-dilution curve from the pulmonary arterial injection site. As shown in Fig. 4, 14 of 18 lambs in which pulmonary slope volumes could be calculated on both room air and on 8% oxygen inhalation showed a definite decrease in pulmonary slope volume with hypoxia, the mean volumes falling from a control of 69.4 to 44.5 ml during hypoxia. Since MTTV represents the volume of blood in which the indicator is distributed from injection site to withdrawal site, the MTTV calculated from left atrial injection was subtracted from the MTTV calculated from pulmonary arterial injection, both during room air inhalation and during hypoxia. The values obtained in six of seven lambs from this subtraction decreased during hypoxia (Fig. 1), again suggesting a contraction of the pulmonary vascular bed.

**Effect of hypercapnia.** The administration of 8% CO\(_2\) in 20% O\(_2\)-72% N\(_2\) by face mask also caused a marked increase in the rate and depth of respiration and an increase in pulse rate. The administration of 8% CO\(_2\) resulted in a mean arterial Pco\(_2\) of 49.5 mm Hg, with a moderate fall in arterial PH to 7.27 (Table 1).

The most striking circulatory response to hypercapnia in newborn lambs was the increase in cardiac output from 515 ml/kg per min to 780 ml/kg per min on 8% CO\(_2\), an increase of 45% (Fig. 5). At the same time there was a fall in systemic vascular resistance from 3,575 to 2,250 dynes-sec cm\(^{-5}\) as seen in Fig. 5. The aortic systolic pressure remained unchanged, the average values for both room air and hypercapnic animals being 111 mm Hg, while aortic mean pressure fell slightly from 86 to 81 mm Hg. The increase in cardiac output was reflected in the pulmonary circulation by a moderate fall in pulmonary vascular resistance without a change in pulmonary arterial mean pressure as shown in Fig. 6. It is interesting to note that the fall in pulmonary vascular resistance occurred in the face of the moderate acidosis accompanying this degree of acute hypercapnia. Also, hypercapnia resulted in an increase in pulmonary slope volume in six out of seven lambs (Fig. 7), suggesting that the vasodilatory effect of increased CO\(_2\) tension occurs in both systemic and pulmonary vascular beds.

**Effect of hyperoxygenation.** The administration of 100% oxygen at 1-atm pressure via face mask with an increase of arterial Pao\(_2\) to a mean value of 300 mm Hg had little effect on the circulatory dynamics of the normal newborn lamb. Satisfactory data were available on eight lambs which showed little or no change in cardiac output, pulmonary or systemic pressures, and pulmonary or systemic vascular resistance from the room air values. In those animals studied immediately after being hypoxic, there was a prompt lowering of pulmonary arterial pressure and pulmonary vascular resistance (Fig. 8), but these values were not significantly lower than the base-line room air determination.

**DISCUSSION**

The effect of hypoxia on the circulatory dynamics of the newborn lamb, particularly the increase in pulmonary arterial pressure, has been documented by a number of investigators (2, 10); however, such studies
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Fig. 7. Changes in pulmonary slope volume in 6 normal unanesthetized lambs subjected to inhalation of 8% CO₂ in 21% oxygen and 71% nitrogen.

in the past have usually involved extensive surgical manipulation and sedation of the animal. The techniques used in the present study made it possible to evaluate the effect of hypoxia, hypercapnia, and high oxygen inhalation without the superimposed effects of general anesthesia, barbiturates, surgery, or prior metabolic acidosis resulting from them. The major disadvantage of this technique is that calculation of pulmonary vascular resistance is not possible when shunting, either left to right or right to left, exists at the ductus arteriosus. Unfortunately, this eliminated from this study most lambs less than 24 hr old. Although the absence of right to left shunts through the foramen ovale was not ascertained in every instance during hypoxia, if such shunting had occurred, this would not invalidate the increase in pulmonary vascular resistance. In fact, with the presence of right to left shunting at the atrial level, pulmonary blood flow would be overestimated since shunt flow would enter the circulation between the injection site and the site of sampling. Overestimation of pulmonary blood flow during hypoxia would underestimate the calculated pulmonary vascular resistance. Therefore, the actual increase in pulmonary vascular resistance during hypoxia might be considerably greater than that observed in these experiments if unrecognized, right to left atrial shunts had developed during hypoxia.

Although the most striking effect of hypoxia in the newborn lamb is the marked pulmonary vasoconstriction and increased pulmonary arterial pressure, a moderate fall in aortic pressure in all lambs and a fall in systemic vascular resistance in many lambs were observed. The simultaneous increase in pulmonary arterial pressure and the fall in systemic arterial pressure was often of such magnitude that marked shunting of blood right to left through the patent ductus arteriosus might occur if it were still patent, as has been demonstrated both in distressed newborn lambs and newborn infants. (12, 13)

The mechanism through which the pulmonary vasoconstrictive response to hypoxia occurs is not known. The predominant factor would seem to be a local response of either pre or postcapillary vessels (4), since Reeves and co-workers have shown that hypoxemia produced by the shunting of venous blood from inferior vena cava to left atrium did not result in pulmonary hypertension in the calf (9). Others have shown that marked pulmonary vasoconstriction occurs in the excised or denervated lung (1). It has been suggested that high pulmonary vascular resistance in the fetus and newborn is produced by the chronic low oxygen tension of the fetal blood in utero, increased Pco₂ and low pH. However, since the administration of high concentrations of oxygen does not lower the pulmonary vascular resistance below control values and since Pco₂ and pH values in utero in unstressed lamb fetuses are not abnormal (6), one must postulate that other factors are also important in the control of basal pulmonary vascular tone in the newborn animal. Whether the decline in pulmonary artery pressure with age as shown in Fig. 1 could be accelerated by prolonged exposure to high oxygen concentrations remains to be studied.

Although right to left shunting through the foramen ovale may be either produced or increased by hypoxia as has been demonstrated in both newborn infants and animals, the decrease in slope volume measurement and MTTV difference calculations would not be invalidated by the production of such shunts since right to left shunting at the atrial level would lead to overestimation of pulmonary blood flow and pulmonary slope volume with hypoxia. The demonstration of a decrease in pulmonary blood volume in response to hypoxia is consistent
with the results of Sackner et al. in adult human using radiologic techniques (11).

There is little information available in the literature concerning the effect of increased CO₂ tension on the circulatory system of the newborn. It is well known that high CO₂ tensions will cause increased blood flow and systemic vasodilatation in the adult, and the present study shows that a similar response of the systemic circulation exists in the newborn lamb. The changes in pulmonary vascular resistance and in pulmonary slope volume during hypercapnia were somewhat unexpected, for acidosis, either metabolic or respiratory, has been shown to cause a marked increase in pulmonary vascular resistance (3, 10). Therefore, one might speculate that hypercapnia, in a situation in which arterial pH were kept constant at 7.40 by the infusion of a buffer such as tris (hydroxymethyl) amino methane (THAM), might indeed result in more marked pulmonary vasodilatation.

Pulmonary hypertension and increased pulmonary vascular resistance resulted from the inhalation of 8% oxygen for up to 1 hr without accompanying acidosis, in contrast to the results of others (10). Indeed, the occurrence of increased pulmonary vascular resistance and pulmonary hypertension was repeatedly observed in the face of mild respiratory alkalosis in the normal unanesthetized lamb. In addition, the mild acidosis accompanying 8% CO₂ inhalation was accompanied by a fall in pulmonary vascular resistance in six out of eight lambs without an increase in pulmonary arterial mean pressure. These findings would suggest that factors other than a change in H⁺ ion concentration were primarily responsible for the changes in pulmonary arterial pressure and pulmonary vascular resistance in these lambs.

The pronounced effects of hypoxia in the fetus or newborn with the simultaneous elevation of pulmonary arterial pressure, lowering of systemic pressure, and dilatation of the ductus arteriosus can readily result in the shunting of large amounts of blood away from the lungs and inadequate pulmonary perfusion. Furthermore, the presence of hypercapnia associated with hypoxia might potentiate this by decreasing systemic vascular resistance. Thus, in the newborn with either intrinsic pulmonary disease or ventilatory failure due to central nervous system depression, hypoxia leads to right-to-left shunting of blood through the ductus arterious and/or the foramen ovale, further increasing the degree of hypoxemia. This, if not corrected by prompt oxygenation and ventilation, could lead to progressive metabolic acidosis and rapid deterioration of the infant. Such prompt correction would seem advisable.

REFERENCES