THE CARDIOVASCULAR changes that occur immediately after birth have been studied extensively. These changes are concerned with adaptation from fetal to extrauterine life and include elimination of the umbilical-placental circulation, establishment of an adequate pulmonary blood flow and closure of the ductus arteriosus. The subsequent changes associated with postnatal development have not been examined in detail. It is well known that the pulmonary vascular resistance continues to decrease for several weeks after birth and that pulmonary arterial pressure progressively falls. Cross et al. 1 reported that cardiac output falls after birth in the lamb, but their studies were performed on anesthetized animals and anesthesia may have affected the circulation profoundly. Woods et al. 2 reported a progressive fall in heart rate in the first few weeks and a rapid increase in systemic arterial pressure to adult levels immediately after birth in lambs. However, sequential changes in heart rate, systemic arterial pressure, and cardiac output have not been studied carefully. We have measured several cardiovascular variables in three groups of unanesthetized newborn lambs with mean ages of 1, 4, and 6 weeks. The influence of the autonomic nervous system on cardiovascular function in the resting state was assessed by administration of selective parasympathetic and a-adrenergic blocking agents. Also, the response of the circulation to volume loading by rapid infusion of saline was studied in the lambs at various ages.

SUMMARY We examined postnatal circulatory changes in three groups of lambs at 1, 4, and 6 weeks after birth. Five lambs in each group were instrumented chronically with electromagnetic flow transducers on the ascending aorta and catheters in the aorta, left ventricle, left atrium, and superior vena cava. After recovery for 2 days, measurements were made daily at rest and during intravenous infusion of 0.9% NaCl solution (25 ml/kg per min) for 2 minutes into the superior vena cava to increase mean left atrial pressure to about 25 mm Hg. Resting heart rate fell progressively, from 210 ± 27/min (mean ± sD) at 1 week to 141 ± 26 at 6 weeks, whereas arterial pressure increased from 71 ± 8 mm Hg during the 4th week to 80 ± 10 at 6 weeks. Aortic flow per kilogram body weight fell from the high level of 425 ± 86 ml during the 1st week to 147 ± 28 ml by the 6th week. This reduction in cardiac output probably is associated with alterations of oxygen consumption per kilogram body weight in the neonatal period. During infusion of saline, left ventricular output increased by a modest 35% over control levels in the 1-week-old lambs, but rose more (58%) in the other two groups. The maximal cardiac output achieved during saline infusion was greater during isoproterenol and less after propranolol administration in each group. We, therefore, suggest that since the neonatal lamb has a high resting cardiac output it has less capacity to respond to volume loading than does the older lamb.

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Methods

We studied 15 lambs, born to Western Hampshire ewes; the date of birth was documented. Three groups, comprising five lambs each, were prepared for study at 0-3 days (group I), 18-24 days (group II), and 38-42 days (group III) after birth. Throughout the study period, the lambs remained with their mothers and fed well.

Surgical Procedure

Each lamb was anesthetized with Fluothane and then intubated with a cuffed endotracheal tube and ventilated by intermittent positive pressure with a Harvard respirator pump. We used sterile techniques and performed a left thoracotomy; polyvinyl catheters (i.d. 1.0 mm, o.d. 1.8 mm) were passed through the internal thoracic artery to the brachiocephalic trunk and through the internal thoracic vein into a large central vein. The pericardium was incised widely from the base to the apex and similar catheters were inserted through pursestring sutures into the left atrium and the left ventricle through the apex. A precalibrated electromagnetic flow transducer was applied around the ascending aorta just above the coronary arteries. The diameter of the aorta was measured with a divider, and transducers with lumens of 8 to 15 mm were selected to fit snugly without producing more than 5-10% constriction. The ductus arteriosus was examined to confirm that it was closed; in the younger animals it was ligated. A chest drainage tube (polyvinyl, i.d. 2.0 mm, o.d. 25 mm, with multiple side openings) was placed in the left pleural cavity. No attempt was made to close the pericardium. All catheters and the flow transducer cable were protected by a nylon cloth pouch sewn to the skin. The catheters were led to the skin on the left flank, where they were incised widely from the base to the apex and similar catheters were inserted through pursestring sutures into the left atrium and the left ventricle through the apex. A precalibrated electromagnetic flow transducer was applied around the ascending aorta just above the coronary arteries. The diameter of the aorta was measured with a divider, and transducers with lumens of 8 to 15 mm were selected to fit snugly without producing more than 5-10% constriction. The ductus arteriosus was examined to confirm that it was closed; in the younger animals it was ligated. A chest drainage tube (polyvinyl, i.d. 2.0 mm, o.d. 25 mm, with multiple side openings) was placed in the left pleural cavity. No attempt was made to close the pericardium. All catheters and the flow transducer cable were led to the skin on the left flank, where they were protected by a nylon cloth pouch sewn to the skin. The chest was closed and fluid and air were withdrawn. Through a small incision in the neck a polyvinyl catheter (o.d. 4 mm) was passed through the external jugular vein to the superior vena cava. The pericardium was incised widely from the base to the apex and similar catheters were inserted through pursestring sutures into the left atrium and the left ventricle through the apex. A precalibrated electromagnetic flow transducer was applied around the ascending aorta just above the coronary arteries. The diameter of the aorta was measured with a divider, and transducers with lumens of 8 to 15 mm were selected to fit snugly without producing more than 5-10% constriction. The ductus arteriosus was examined to confirm that it was closed; in the younger animals it was ligated. A chest drainage tube (polyvinyl, i.d. 2.0 mm, o.d. 25 mm, with multiple side openings) was placed in the left pleural cavity. No attempt was made to close the pericardium. All catheters and the flow transducer cable were led to the skin on the left flank, where they were protected by a nylon cloth pouch sewn to the skin. The chest was closed and fluid and air were withdrawn. Through a small incision in the neck a polyvinyl catheter (o.d. 4 mm) was passed through the external jugular vein to the superior vena cava. All catheters were filled with heparinized saline solution and plugged.

The lambs recovered rapidly and were returned to their mothers soon after surgery. No fluid or air could be withdrawn from the chest after the second day. Studies were started on the 3rd day after surgery, counting the day of surgery as the 1st day.

Measurements

Each lamb was weighed and arterial blood gases, pH, and hematocrit were measured daily. The lamb was placed in a straw-filled box, the left atrial and ventricular and systemic arterial catheters were connected to Statham P23Db pressure transducers, and the flow transducer was connected to a Statham SP 2202 flowmeter. After a variable period, the lambs relaxed and lay down in the box. Pressures and aortic blood flow were recorded continuously for at least 5 and up to 30 minutes while lambs rested quietly, or slept. The electromagnetic flow transducer and flowmeter system had a frequency response of 100 Hz, a reproducibility of ±2%, and a percent error of 5%. The pressures and flows were recorded on a Beckman Dynograph multiple-channel oscillographic recorder.

Infusion Studies

In preliminary observations, we noted spontaneous changes in heart rate and aortic blood flow. These changes were very marked when infusions of saline were given to the lambs. In order to reduce this marked variability of heart rate, atropine (0.2 mg/kg) was given into a venous catheter and, after heart rate, pressures, and flows had been constant for about 5 minutes, 0.9% NaCl, warmed to 40°C, was infused at a rate of 25 ml/kg of body weight per minute for a period of 2 minutes with a continuous infusion pump (Monostat Varistaltic Pump). Systemic arterial pH, P02, and PCO2 were measured before and within 1 minute after the saline infusion.

The responses of the three groups of lambs to isoproterenol were studied both during a control period and during saline infusion. After baseline measurements had been obtained for the resting lamb, isoproterenol was infused intravenously at a rate of 0.1 μg/kg per min into the internal thoracic venous catheter. After all cardiovascular measurements were stable, atropine was given and 0.9% NaCl was infused as described above. The isoproterenol infusion was continued throughout the entire period.

The effects of administration of propranolol also were examined. Cardiovascular variables were measured in the resting lamb before and after intravenous injection of propranolol, 1 mg/kg. The effectiveness of this dose of propranolol in producing β-adrenergic blockade had been demonstrated previously by showing complete blockade of response to isoproterenol infusion at a rate of 0.1 μg/kg per min. After recording the responses to propranolol alone, we gave atropine and started the infusion of saline.

The sequence of the saline infusion experiments was as follows: on the 3rd, 6th, and 9th postoperative days, response to saline infusion alone was studied; on the 4th and 7th postoperative days, responses during isoproterenol infusion; and on the 5th and 6th postoperative days, responses after propranolol administration were examined.

The unpaired Student's t-test was used to compare corresponding populations from different age groups. Each lamb received three infusions of saline during control periods, two infusions while receiving isoproterenol and two infusions after propranolol administration. To compare the effects of these various studies within each group, the data from similar experiments in a single lamb were pooled and the paired Student's t-test was used. There were no statistically significant differences in the resting cardiac output measured on each day, nor were there significant differences in the responses to saline infusion alone, or to infusion after administration of drugs on different days. Therefore, all data from similar types of studies in each age group were pooled.

Results

The lambs recovered rapidly from the surgical procedure and all showed normal weight gain. The weights for each group were: group I, 4.7 (±0.65) (mean ± SD) kg; group II, 8.67 (±1.32) kg; and group III, 11.5 (±1.73) kg. Resting systemic arterial blood gases and pH were...
similar to those observed in lambs of the same age, not subjected to thoracotomy, that we have studied in our laboratory. The group I lambs had a pH of 7.42 (±0.04), a Po2 of 71 (±9.6) torr, and a Pco2 of 41 (±4.8) torr. Corresponding values in group II were: pH 7.46 (±0.05), Po2, 80 (±7.4) torr; Pco2, 39 (±5.6) torr; and in group III: pH 7.45 (±0.04), Po2, 81 (±9.7) torr; and Pco2, 37 (±3.0) torr. There was a significantly higher pH and Po2, and a lower Pco2 in the group II and III as compared with the group I lambs, but no significant difference in those values between groups II and III. Resting hematocrit was 28 (±2.4) in the group I lambs and it was slightly but significantly higher in group II (31 ± 2.8) and group III (32 ± 3.7).

Following the administration of the various drugs there were no significant changes in blood gases, pH, or hematocrit, and following the infusion blood gases and pH were not changed.

The effects of the infusion on the hematocrit were not studied in all the lambs. We did measure the decrease in hematocrit at the end of infusion in two lambs in each age group; values fell to levels of about 20 at the end of the infusion from resting levels of about 30. This represents a 33% decrease that was similar in all age groups. Measurement of hematocrit 2–5 minutes after infusion also showed that the three groups responded in similar manner. In three lambs in each group the levels 2–5 minutes after infusion were: group I: before infusion 28 ± 2.4, after infusion 25 ± 2.3; group II: before infusion 31 ± 2.8, after infusion 27 ± 2, and group III: before infusion 32 ± 3.7, after infusion 27 ± 2.8. The changes were not significantly different between the groups. There were no changes in resting hematocrit in any individual lamb in which it was measured over the 7-day study period.

**Hemodynamic Measurements at Rest and after Atropine**

Resting values for heart rate showed a progressive decrease with increasing age (Table 1). Mean systemic arterial pressure did not change in the first 4 weeks, but rose significantly between 4 and 6 weeks after birth. Mean left atrial pressure did not change in the first 4 weeks, but decreased by 6 weeks. The ascending aortic blood flow increased from 2000 ml/min in the first week to 3030 ml/min by 4 weeks, but then fell dramatically to 1650 ml/min by the 6th week. When expressed in relation to body weight, aortic blood flow showed a progressive decrease with advancing age from 425 ml/kg per min in the 1st week to 355 ml/kg per min by the 4th week and 147 ml/kg per min by the 6th week. Left ventricular stroke volume related to body weight did not change between 1 and 4 weeks, but decreased by 6 weeks.

Following administration of atropine, there was a significant increase in heart rate in all three groups (Table 2), but the percentage increase was considerably greater in groups II and III (Fig. 1). Aortic flow also increased in all groups, but there was a progressively greater percentage increase over resting levels with advancing age. Stroke volume fell in all groups, but the fall was more marked in groups II and III. Mean arterial blood pressure did not change significantly in any group after atropine administration.

**Effects of Isoproterenol and Atropine**

Isoproterenol infusion produced a significant increase in heart rate, with a small but not significant decrease in arterial pressure in all three groups. Cardiac output increased significantly in each group. The cardiac output per kilogram body weight during isoproterenol infusion was not significantly different between groups I and II but was significantly lower in group III. Infusion of isoproterenol in the same amount in relation to body weight resulted in a 29% increase in cardiac output in the lambs in group I, a 45% increase in group II, and a 62% increase in group III animals (Fig. 2).

**Effects of Propranolol and Atropine**

Propranolol alone produced a significant decrease in heart rate in all three groups of lambs, but there was no significant difference in the percentage change from controls. Aortic flow also fell but the percentage change was not significantly different in the three groups. In atropinized lambs, propranolol produced a small decrease in heart rate in all groups, but had no consistent effect on arterial pressure. The decrease in heart rate was statistically significant only in group I. Aortic flow per kilogram decreased slightly in all three groups, but the fall was significant only in the youngest animals in which it fell by an average of 11% (Fig. 2).

**Effects of Infusion on Cardiac Output**

During the infusion, heart rate did not increase significantly above the levels present just prior to infusion in any of the three groups, either in the lambs that received atropine alone, or during isoproterenol infusion, or fol-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Resting Values for Cardiovascular Variables (mean ± SD) in the Three Groups of Lambs Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (n = 35)</td>
</tr>
<tr>
<td>Heart rate (per min)</td>
<td>210 ± 27</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>69 ± 6.2</td>
</tr>
<tr>
<td>Mean left atrial pressure (min Hg)</td>
<td>6.4 ± 3.1</td>
</tr>
<tr>
<td>Aortic flow (ml/min)</td>
<td>2000 ± 488</td>
</tr>
<tr>
<td>Aortic flow (ml/kg per min)</td>
<td>425 ± 86.3</td>
</tr>
<tr>
<td>Stroke volume (ml/kg)</td>
<td>2.1 ± 0.54</td>
</tr>
</tbody>
</table>

Differences between the groups are designated as statistically significant (S, P < 0.05) or not significant (N).
TABLE 2  Response of Cardiovascular Variables to Drugs and Saline Infusion in Lambs

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aortic flow (ml/kg per min)</td>
<td>Heart rate (beats/min)</td>
<td>Aortic mean pressure (mm Hg)</td>
</tr>
<tr>
<td>Before atropine</td>
<td>425±86.3</td>
<td>210±27</td>
<td>68±4.0</td>
</tr>
<tr>
<td>Atropine alone</td>
<td>430±83.8</td>
<td>226±21</td>
<td>69±6.2</td>
</tr>
<tr>
<td>(n = 35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before propranolol</td>
<td>413±93</td>
<td>206±36</td>
<td>71±7.9</td>
</tr>
<tr>
<td>Propranolol alone</td>
<td>351±74</td>
<td>181±33</td>
<td>67±8.4</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine and isoproterenol (n = 10)</td>
<td>553±90.3</td>
<td>286±16</td>
<td>67±8.0</td>
</tr>
<tr>
<td>Atropine and propranolol (n = 10)</td>
<td>391±78.7</td>
<td>191±25</td>
<td>69±8.2</td>
</tr>
<tr>
<td>With infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine alone</td>
<td>577±135</td>
<td>234±26</td>
<td>81±10.5</td>
</tr>
<tr>
<td>(n = 15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine and isoproterenol (n = 10)</td>
<td>670±156</td>
<td>279±35</td>
<td>78±11.7</td>
</tr>
<tr>
<td>Atropine and propranolol (n = 10)</td>
<td>428±99.9</td>
<td>195±21</td>
<td>73±9.6</td>
</tr>
</tbody>
</table>

The aortic blood flows per kilogram body weight, heart rates, and aortic mean blood pressures (mean ± SD) in each group of lambs are shown at rest and after administration of drugs. Also, the peak levels of flow achieved with infusion of saline with each drug or combination of drugs are presented.

The percentage changes in heart rate, mean systemic arterial pressure, and aortic flow per kilogram resulting from administration of atropine are shown in each group of animals (mean and standard error of mean).

![Figure 1](http://circres.ahajournals.org/)

**Figure 1**  The percentage changes in heart rate, mean systemic arterial pressure, and aortic flow per kilogram resulting from administration of atropine are shown in each group of animals (mean and standard error of mean).

**Figure 2**  The percentage changes in aortic flow per kilogram body weight from the level after atropine administration are shown after administration of isoproterenol (Iso) or propranolol (Prop) alone, with saline infusion (Inf), and with saline infusion during isoproterenol or propranolol. The two columns on the right represent the percentage increase of flow resulting from infusion, using the level after administration of the respective drugs as the baseline (mean and standard deviation).
There was a curvilinear relationship between the increase in aortic flow and mean left atrial pressure in all three groups of lambs, after atropine alone, as well as during isoproterenol infusion and after propranolol administration (Fig. 3). The increases in mean left atrial pressure were similar in all three groups. Although the pressures were slightly lower during isoproterenol infusion and slightly higher after propranolol, none of these differences was significant except between the infusion of saline alone (24.2 mm Hg) and the infusion of saline during isoproterenol (20.1 mm Hg) in group III. In all three groups, the aortic flow was higher following saline infusion during isoproterenol administration, and lower with saline infusion after propranolol, than during infusion of saline after atropine alone had been given (Table 2, Fig. 2). As shown in Figure 3, this relationship was noted at any specific left atrial pressure in each group of animals.

In addition to the different levels of aortic flow per kilogram body weight noted during infusion and with β-adrenergic receptor stimulation and blockade, we observed striking differences in the percentage changes of flow as compared with resting levels (Fig. 2). Infusion of saline in lambs that had received atropine alone resulted in a 34 ± 4.7% increase in aortic flow in group I lambs, but a 60 ± 5.9% increase in group II and a 58 ± 8.2% increase in group III. The response in group I differed significantly from that in groups II and III. With saline infusion during isoproterenol administration, aortic flow compared after atropine alone was 49% higher in group II, and 152% higher in group III; the increase was significantly lower in group I than in groups II and III. We also calculated the further increase in aortic flow occurring with saline infusion over that resulting from isoproterenol alone; in group I there was a 20% increase, a rise which was significantly lower than that occurring in group II (51%) or group III (56%).

Infusion of saline after atropine and propranolol administration resulted in a small decrease in the aortic flow per kilogram as compared with levels in group I atropinized lambs, and a small increase in groups II and III. In each group of lambs that had received atropine and propranolol, infusion of saline resulted in a significant increase in aortic flow, but the percentage increase was greater in groups II and III than in group I.

In one or two animals in each group, left ventricular and aortic pressures measured 8-10 days after surgery showed no systolic pressure differences across the region of the aortic flow transducer at rest.

**Discussion**

The patterns of change of heart rate, blood pressure, and cardiac output have not been described in detail for unanesthetized animals or human infants over the first few weeks after birth. Woods et al., noted that systemic arterial pressure increased rapidly after birth to adult levels and that heart rate dropped markedly within a few weeks. Sequential changes in cardiac output in the postnatal period have not been described. Cross et al. and Downing et al. reported cardiac outputs of 300-325 ml/kg per min in anesthetized newborn lambs. Also, Kirkpatrick et al. estimated left ventricular output at 1950 ± 89 ml/min in 7 unanesthetized newborn lambs, but weights were not reported.

We used electromagnetic flowmeters to measure cardiac output so that we could examine the responses to rapid infusion of fluid. Bishop et al. and Stone et al. showed that the maximal level of cardiac output reached at the late phase during rapid infusion of fluid was a measure of cardiac performance.

The possibility that the lambs had not recovered when we started our studies was considered, since Carlson et al. and Kirkpatrick et al. suggested that an interval of several weeks may be required for recovery of cardiac function after surgery. However, our procedures were much less traumatic. In support of the fact that the animals had recovered was the observation that there were no differences in the resting values or responses to infusion, of heart rate, blood pressure, and cardiac output in the three control periods done every 3rd day. Furthermore, the values for cardiac output ms in the resting lambs were similar to those reported by Lister et al. for lambs that had not been subjected to thoracotomy.

In preliminary experiments, we found that implantation of flow transducers around the ascending aorta in newborn lambs caused constriction within about 2 weeks, as manifested by development of a systolic pressure difference between the left ventricle and the aorta. We therefore prepared three groups of animals at different periods after birth and studied them before there was any significant aortic outflow obstruction.

The resting heart rate was quite high (210/min) in the 1-week-old lambs, even during sleep. We confirmed the observation of Woods et al. that there was no difference in the percentage fall in heart rate after propranolol administration in the younger as compared with the older lambs, suggesting there was no greater resting sympathetic or circulating catecholamine effect on the heart. The reason for the rapid fall in resting heart rate from 210 to 141/min over the 6-week period after birth is not appar-
ent. We did confirm, however, the observations of Woods et al.\textsuperscript{2} that it was not entirely due to a high level of sympathetic-adrenal stimulation in the younger animals, since propranolol did not reduce the heart rate to similar levels in the three groups. In contrast to the data of Woods et al., we noted no significant increase in mean systemic arterial pressure from the 1st to the 3rd week, but a significant rise occurred by the 6th week. We cannot explain this difference, nor the finding that blood pressure increased after the 3rd week.

The flow transducer recorded left ventricular output minus coronary blood flow because we had applied it on the ascending aorta above the coronary arteries. Thus the cardiac output measurements we report are about 4\% less than actual cardiac output. Cross et al.\textsuperscript{1} and Kirkpatrick et al.\textsuperscript{1} showed there was an increase in cardiac output after birth. In our studies, total left ventricular output increased significantly in the 3-week-old lambs but were significantly lower in the oldest group than in either of the two younger groups.

When related to body weight, left ventricular output was highest in the youngest group; it fell modestly by 4 weeks and then dramatically by 6 weeks. From our studies of chronically instrumented fetal lambs in utero, using radioactive labeled microspheres,\textsuperscript{6,11} we calculated that combined ventricular output in the fetal lambs is about 500 ml/kg per min. In the 1-week-old lamb, the cardiac output is 425 ml/kg per min. Since in the postnatal circulation blood flows in series through the pulmonary and systemic circulations, the combined output of the two ventricles is 850 ml/kg per min, a level about 70\% higher than that in the fetus. In the fetus, left ventricular output is about 33\% of combined ventricular output,\textsuperscript{10} or about 170 ml/kg per min, as compared with the newborn left ventricular output of 425 ml/kg per min; this represents an increase of at least 2.5-fold after birth.

Although resting heart rate falls dramatically after birth, this is not entirely responsible for the fall in cardiac output. Stroke volume of the left ventricle in the fetal lamb is about 1 ml/kg (heart rate 180/min, left ventricular output 170 ml/kg per min). In the first postnatal week it doubles, and does not change significantly up to the 4th week, but falls to about 1 ml/kg by the 6th week.

The reasons for the dramatic increase in cardiac output and stroke volume after birth, and the rapid fall over the first 6 weeks are not apparent. Although \( \beta \)-adrenergic blockade caused a somewhat larger reduction in resting cardiac output per kilogram in the youngest group of lambs, sympathetico-adrenal stimulation was not entirely responsible for the higher output. After propranolol, resting cardiac output per kilogram was still much higher in the youngest lambs. Factors that may be responsible include changes in blood tissue oxygen requirements, type of hemoglobin, oxygen dissociation, and metabolic pathways.

Before birth, the fetus is in a temperature environment of the mother’s body. After birth, when exposed to air, energy requirements are increased to maintain body temperature. Cross et al.\textsuperscript{1} have reported a 2- to 3-fold increase in oxygen consumption after birth in lambs, and it is possible that this accounts for the increase in cardiac output. The decrease in cardiac output per kilogram in the first 6 weeks after birth is associated with a parallel decrease in oxygen consumption per kilogram body weight.\textsuperscript{4} However, changes in oxygen requirements alone cannot account for the changes in cardiac output. We have calculated the flow to the body required to provide the amount of oxygen consumed in resting animals (Fig. 4). In the fetal lamb, combined ventricular output is about 500 ml/kg per min, and since about 40\% of combined ventricular output is distributed to the placenta, the fetal body receives about 300 ml/kg per min. Thus, with a fetal oxygen consumption (excluding the placenta) of about 8 ml/kg per min,\textsuperscript{12} 37.5 ml of blood flow provide 1 ml of oxygen. After birth, although both oxygen consumption and cardiac output increase, the systemic blood flow associated with 1 ml of oxygen to the tissues is reduced to about 28.5 ml. By 6 weeks, the level falls further to 19 ml flow/ml oxygen which is similar to that calculated from data for adult sheep, reported by Stowe and Good.\textsuperscript{13} This interesting change in the relationship between tissue flow and oxygen consumption could be related to changes in hemoglobin from the fetal to the adult type, and to the postnatal fall in hemoglobin level. Since fetal hemoglobin has a greater capacity for binding oxygen than the adult type, release to the tissues would be slower, and a greater flow would be required to provide the same amount of oxygen. This is modified to some extent by the higher organic phosphate levels present in the red cells of newborn lambs.\textsuperscript{14} Another factor that could account for the higher flow per milliliter oxygen consumption in the fetus is a possible difference in the metabolic pathways used for energy production. If alternate pathways were used to a greater extent in the fetus, the oxygen consumption might be lower and thus the ratio of flow to oxygen utilization would be greater. Furthermore, since the flow-oxygen consumption rate is an average for the whole body, it is

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Changes in systemic blood flow per kilogram body weight (CO), oxygen consumption/kg (VO\textsubscript{2}), and the ratio of the volume of flow per ml of oxygen consumed (CO/VO\textsubscript{2}) from the fetus to the adult have been calculated. There is a progressive decrease in the flow associated with a specific level of oxygen consumption.}
\end{figure}
possible that changes in relative weights and metabolic activity in different organs could account for the changes.

The differences in the response of cardiac output to saline infusion at varying times after birth is of great interest, particularly in regard to the ability of the neonate to tolerate volume loads, which occur with systemic-pulmonary communications. The restricted ability of the younger lambs to increase left ventricular output during saline infusion possibly could be explained by a lesser capacity of the myocardium to develop force. Friedman et al.15 noted that isolated fetal myocardial strips showed a lesser extent of shortening, velocity of shortening, and development of isometric force than similar preparations obtained from adult sheep. A second possible explanation is that the sympathetic innervation of the ventricular myocardium is not fully developed at birth and is complete only several weeks after birth.15, 16 Neither of these is likely; the left ventricular output rises dramatically after birth, demonstrating the capability of the left ventricle to achieve a considerable increase in output. In our studies with propranolol, we showed that there was a somewhat greater resting sympatho-adrenal action on the heart in the youngest group of animals, so that whether this was provided by direct sympathetic innervation or by circulating catecholamines, there was no lack of myocardial stimulation. Also, propranolol reduced the percentage increase in left ventricular output achieved by saline infusion to a similar extent in the three groups of lambs.

We demonstrated that saline infusion resulted in similar peak left atrial mean pressures in all three groups of lambs, so that it is unlikely that significant differences in left ventricular end-diastolic pressure could account for the variability in response. However, we have not excluded differences in left ventricular compliance as a possible reason for the lesser ability to raise its output, but Romero et al.17 have suggested, from studies in freshly excised hearts, that the compliance of the newborn lamb heart is less than that of adult sheep. An additional factor to be considered is that the left ventricles of late gestation fetal lambs did not increase their extent of shortening or stroke volume beyond end-diastolic pressures of 10-12 mm Hg.18 It is possible that a rapid progressive change in the pressure-volume characteristics of the left ventricle after birth could account for the differences in response to volume loading in the lamb in the first 6 postnatal weeks.

The most likely explanation for our findings is that the resting cardiac output of the 1-week-old lamb is very high to provide an adequate tissue flow for the high level of oxygen requirement, and there is thus a limited capacity for further increases in response to volume loading. This may be of serious concern in newborn infants with congenital cardiac lesions with left-to-right shunts. Since elevation of left atrial mean pressures by 10 mm Hg results in only a 34% increase in left ventricular output in the 1-week-old lambs, a shunt larger than this would result in a decrease in systemic blood flow, and other compensatory mechanisms for providing adequate tissue oxygen supply would have to be used. A delay of only a few weeks after birth before a large volume load is introduced would permit the infant to accommodate to the stress more readily.

References

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