Indirect Relation Between Rises in Oxygen Consumption and Left Ventricular Output at Birth in Lambs

Joseph J. Smolich, Martin Soust, Philip J. Berger, and Adrian M. Walker

To examine the relation between increased newborn oxygen requirements and the postnatal rise in cardiac output, we measured left ventricular (LV) output, organ blood flows, and whole-body oxygen consumption using radioactive microspheres in late-gestation sheep fetuses and in the same animals 1 and 4 hours after cesarean section delivery. LV output rose from 264±23 ml·min⁻¹·kg body wt⁻¹ in fetuses to 444±33 ml·min⁻¹·kg body wt⁻¹ in lambs at 1 hour after delivery (p<0.005) and was unchanged at 4 hours after delivery. This rise in LV output was associated with a more than fourfold increase in the LV flow contribution to tissues situated distal to the ductus arteriosus (fetus, 51±9 ml·min⁻¹·kg body wt⁻¹; lamb, 226±22 ml·min⁻¹·kg body wt⁻¹; p<0.005), which were mainly perfused by the right ventricle in utero. However, average blood flow to body tissues was similar in fetuses (37±4 ml·min⁻¹·100 g tissue⁻¹), 1-hour lambs (39±4 ml·min⁻¹·100 g tissue⁻¹), and 4-hour lambs (40±5 ml·min⁻¹·100 g tissue⁻¹). Oxygen consumption increased by 58%, from 7.84±0.43 ml·min⁻¹·kg body wt⁻¹ in fetuses to 12.38±2.4 ml·min⁻¹·kg body wt⁻¹ in 1-hour lambs (p<0.01), and was unchanged in 4-hour lambs. Although systemic blood flow did not change after birth, the arteriovenous oxygen content difference increased by 54%, from 1.98±0.16 ml/dl in fetuses to 3.05±0.19 ml/dl in 1-hour lambs (p<0.005), and was unaltered in 4-hour lambs. We conclude that 1) an increased LV output after birth results from the LV taking over the perfusion of tissues supplied by the right ventricle in utero, 2) the perinatal rise in LV output maintains overall systemic perfusion, 3) an increased newborn oxygen consumption is achieved through a rise in arteriovenous oxygen extraction, and 4) rises in oxygen consumption and LV output at birth are not directly related to one another. (Circulation Research 1992;71:443–450)

Key Words • fetus • newborn • cardiac output • oxygen consumption • radioactive microspheres

Left ventricular (LV) output and whole-body oxygen consumption both increase substantially with birth. It is tempting to assume that these changes are closely related to one another, especially in view of the parallel reductions in oxygen consumption and LV output that occur during subsequent postnatal growth. This assumption, however, overlooks the complexity of the circulatory events associated with birth. Specifically, an increased LV output after birth could result from three factors. First, LV output might increase because of a net postnatal rise in organ blood flows. Second, because systemic blood flow is derived from both ventricles in the fetus but only from the LV in the newborn, LV output might increase after birth to compensate for loss of the fetal right ventricular (RV) contribution to systemic perfusion. Third, left to right shunting across an incompletely constricted ductus arteriosus in the early postnatal period might also augment LV output.

An increase in oxygen consumption after birth could also occur through several mechanisms. Because oxygen consumption is the product of systemic blood flow and the arteriovenous oxygen content difference, elevated newborn oxygen requirements could be met by increased tissue perfusion. Alternatively, the augmented postnatal oxygen consumption might result from an increase in oxygen extraction by tissues. The latter, in turn, could be related either to the rise in arterial oxygenation associated with the onset of air breathing or to a greater fractional extraction of oxygen delivered to tissues.

To determine the relative contribution of these various factors to birth-related changes in LV output and whole-body oxygen consumption, we performed blood flow and blood gas measurements in chronically instrumented sheep fetuses and in the same animals 1 and 4 hours after delivery by cesarean section.

Materials and Methods

Ten fetuses with known breeding dates were chronically instrumented at 133 or 134 days of gestation (term, 147 days). Anesthesia was induced in fasted Border-Leicester cross ewes with intravenous thiopentone sodium (30 mg/kg) and maintained by ventilation with a mixture of 1–3% halothane, 30% nitrous oxide, and 67–69% oxygen. Under strict aseptic conditions, the
pregnant horn of the uterus was exposed through a lower abdominal midline incision and incised over the fetal hind limbs. Polyvinyl catheters (1 mm i.d. and 1.5 mm o.d.) were inserted into a pedal artery and vein and advanced into the distal descending aorta and inferior vena cava, respectively. In eight of the 10 fetuses, a polyvinyl catheter was also passed into a large umbilical vein from a peripheral tributary. The uterine incision was then closed.

The fetal head, forelimbs, and upper thorax were carefully delivered through a second uterine incision. The diaphragm was exposed via the 10th left costal interspace, and an electromyogram electrode was inserted into its costal portion to monitor respiratory activity as part of another study. The thoracotomy was closed, and a second thoracotomy was performed in the third left interspace. The pericardium was incised over the pulmonary trunk, sparing the phrenic and vагus nerves passing over the ducatus arteriosus. By using a modification of the technique described by Iwamoto and Rudolph,14 two Teflon cannulas were inserted through adventitial purse-string sutures into the pulmonary trunk and connected to polyvinyl catheters. The tip of one cannula faced the RV and was situated approximately 2 cm distal to the pulmonary valve. The tip of the other cannula was directed into the proximal part of the left main pulmonary artery. A polyvinyl catheter was also inserted into the left atrial cavity. The pericardium was closed, and after ensuring that adequate hemostasis was present, the ribs were reapproximated and overlying muscle layers repaired. A Teflon cannula was inserted nonocclusively into the left carotid artery in the neck, and the attached polyvinyl catheter was exteriorized through the chest incision, which was then closed. Last, a wide-bore catheter was sutured to the anterior chest wall for measuring amniotic fluid pressure. The fetus was returned to the uterus, and all incisions were closed. The vascular catheters were filled with heparin sodium solution (1,000 IU/ml) and sealed. All catheters and the electromyogram wires were tunneled subcutaneously to the ewe’s right flank and secured with elastic netting. Postoperatively, the vascular catheters were flushed every second day and refilled with heparin sodium. Antibiotics (500 mg streptomycin and 5×10⁶ units penicillin) were instilled into the amniotic cavity at the time of surgery and then administered daily, either as an intramuscular injection to the ewe or directly into the amniotic cavity when catheters were flushed.

Experimental Protocol

Experiments were performed 7 days after surgery, i.e., at a gestation of 140 or 141 days. The ewes stood unrestrained in a mobile laboratory cart and were allowed free access to food and water. Environmental temperature was controlled at 23±1°C. All animal experiments were performed in accordance with guidelines set by the National Health and Medical Research Council of Australia.

The first part of the protocol was performed in fetuses. After systemic and pulmonary arterial pressures and heart rate were recorded, fetal LV and RV outputs and organ flows were measured with radioactive microspheres in duplicate (n=9) or triplicate (n=1). Immediately after each microsphere injection, blood samples were collected aerothetically from the carotid artery, descending aorta, pulmonary trunk, and umbilical vein for hemoglobin and blood gas analysis.

In the second part of the protocol, low spinal anesthesia was induced in the ewe with 5 ml of 0.5% bupivacaine. In one ewe this was supplemented with intravenous Diprivan (propofol, 5 mg/kg, ICI, Australia). The abdominal incision was reopened, the fetus was quickly delivered, and the umbilical cord was clamped and cut. The ewe was then killed with an intravenous overdose of sodium pentobarbitone. The newborn lamb was held at the level of the uterus, suctioned, dried, and then placed on a heated table. All lambs breathed spontaneously. One animal required short-term (<20-minute) supportive ventilation because adequate respiration was not maintained after delivery. The other lambs immediately progressed to a regular, rhythmic breathing pattern. A single radioactive microsphere measurement of LV output and organ flows was performed 1 hour after cord clamping. Lambs were then fed with either ewe’s milk or a milk formula. LV output and organ flows were remeasured in duplicate 4 hours after cord clamping. Postnatal microsphere injections were performed with the lamb either in a quiet sleep or quiet awake state. Hemodynamics were recorded before each microsphere injection; blood samples were collected from the carotid artery, descending aorta, pulmonary trunk, and left pulmonary artery after each microsphere injection for hemoglobin and blood gas analysis.

Physiological Measurements

Aortic, pulmonary arterial, and amniotic fluid pressures were monitored with strain-gauge pressure transducers (model 1280B, Hewlett-Packard Co., Waltham, Mass.), which were calibrated against a water manometer before each experiment. Vascular pressures in fetuses were referenced to amniotic fluid pressure; those in newborn lambs were referenced to atmospheric pressure at the mid-chest position. Mean vascular pressures were obtained electronically. Heart rate was measured with a tachometer triggered by either a systemic or pulmonary arterial pulse. The electromyogram signal was processed with an AC amplifier (model NT114, Neomedix Systems, Sydney, Australia) and filter (model NT123, Neomedix Systems). All signals were displayed on an eight-channel paper recorder (model 7758A, Hewlett-Packard, or model 800Z, Neomedix Systems).

Blood pH, Po₂, PaCO₂, and base excess were measured with a blood analyzer (model 168, Corning Medical, Halstead, England). Blood gas and pH determinations were corrected to 39°C in fetuses and to the measured rectal temperature in lambs. Blood hemoglobin content and oxygen saturation were measured photometrically with a hemoximeter (model OSM2, Radiometer, Copenhagen, Denmark).

Radioactive Microsphere Technique

Ventricular outputs and organ flows were measured with radioactive microspheres by the reference sample method.15 The microspheres, 15 μm in diameter and labeled with one of six gamma-emitting isotopes (¹⁴C, ⁵⁷Cr, ¹¹⁵Sn, ⁸⁵Sr, ⁹⁵Nb, or ⁸²Sc; New England Nuclear, Boston), were ultrasonicated for 10–15 minutes before injection and then injected over 30–45 seconds with 10 ml isotonic saline. In the fetuses, approximately 1×10⁶
microspheres were injected through the leg vein catheter while reference samples were drawn simultaneously from the pulmonary trunk, carotid artery, and descending aorta. In the newborn lambs, approximately 0.5 × 10^6 microspheres were injected into the left atrium, and reference samples were obtained from the carotid artery and the descending aorta. The reference samples were drawn at a rate of 4.11 ml/min with a mechanical pump (model 901A, Harvard Apparatus, South Natick, Mass.). Reference sample collection was begun 5–10 seconds before injection and continued for an additional 75 seconds after the end of injection. In fetuses, the blood withdrawn in the reference samples was simultaneously replaced with a plasma substitute (Haemaccel, Behring, Marburg, FRG). In lambs, reference sample blood was replaced either with fetal blood collected from the umbilical cord at delivery or with maternal blood if adequate amounts of fetal blood were not available. The reference samples were immediately transferred into plastic counting vials and hemolyzed.

After completion of the protocol, the lambs were killed with an intravenous overdose of sodium pentobarbital. At autopsy, the position of all catheters was carefully checked. The lamb and the placenta, which had been previously removed from the uterus by gentle traction, were placed in formalin fixative for 7–10 days. After removal of the lungs, the lamb carcass was divided into cephalic (upper body) and caudal (lower body) portions at the level of the third intercostal space and dissected as follows. The brain, thyroid, heart, and representative samples of forelimb muscles (biceps brachii and triceps brachii) and skin were removed from the upper body. The liver, spleen, gastrointestinal tract, kidneys, and representative portions of hind limb muscles (quadratus femoris, biceps femoris, semitendinosus, and semimembranosus) and skin were removed from the lower body. After removal of gut contents and drainage of body fluids, the individual organs, the upper and lower body remnants, and the placenta were weighed, placed in aluminum pans, and incinerated at a temperature of 300°C in a vented box furnace. The carbonized tissues were then ground into a coarse powder in a fume hood and packed into plastic counting vials to a height of ≤2 cm.

The radioactivity of the blood reference samples and the tissue vials was counted in a through-hole gamma counter (model 5260, Packard Instrument Co., Inc., Meriden, Conn.) at the appropriate window settings. The photo peaks of the isotopes were separated by an on-line computer program (COMPUSPHERE, Packard Instrument) using the matrix inversion technique. Tissue flows were calculated using the following relation:

\[ Q(\text{tissue}) = Q(\text{reference}) \cdot R(\text{tissue}) / R(\text{reference}) \]  

(1)

where \( Q \) is flow (ml/min) and \( R \) is radioactivity.

LV output in lambs was calculated as the sum of the flows to the upper body, lower body, and lungs. Fetal LV and RV outputs were calculated with equations similar to those previously published. Fetal LV output was calculated as follows:

\[ \text{Fetal LV output} = Q_{UB} + Q_{LB} + Q_{LV} \left( \frac{R_{DA} - R_{PT}}{R_{CA} - R_{PT}} \right) \]  

(2)

where \( Q_{UB} \) is total upper body flow (ml/min), \( Q_{LB} \) is the sum of total lower body and placental flows, and \( R_{CA}, R_{PT}, \) and \( R_{DA} \) represent radioactivity (counts/min) in the carotid, pulmonary trunk, and descending aorta reference samples, respectively. Fetal RV output was calculated as follows:

\[ \text{Fetal RV output} = Q_{L} + Q_{LB} + Q_{LV} \left( \frac{R_{DA} - R_{PT}}{R_{CA} - R_{PT}} \right) \]  

(3)

where \( Q_{L} \) is lung flow (ml/min).

In some cases, aberrant radioactivity counts in fetal reference samples were corrected with a simple proportionality equation derived from the measured oxygen contents in the carotid artery, descending aorta, and pulmonary trunk. Corrections were required when a reference sample withdrawal was interrupted by a catheter blockage (five of 63 withdrawals) or when the descending aortic reference counts were not intermediate between the carotid arterial and pulmonary trunk reference counts (two of 21 injections). In the latter instance, the radioactivity count in the pulmonary trunk reference sample was corrected, on the assumption that this was the most likely site of poor mixing of microspheres.

**Calculation of Fetal Ventricular Flow Distribution**

A logical extension of equations for calculating fetal univentricular outputs allows precise quantitation of the distribution of these outputs. The contribution of the fetal LV and RV outputs to lower body and placental perfusion can be calculated from knowledge of the aortic isthmus flow \( Q_{AI} \), lower body flow \( Q_{LB} \), and placental flow \( Q_{PL} \). From Equation 2

\[ Q_{AI} = Q_{LB} + Q_{LV} \left( \frac{R_{DA} - R_{PT}}{R_{CA} - R_{PT}} \right) \]  

(4)

It has been demonstrated experimentally that microspheres from the aortic isthmus and ductus arteriosus are well mixed in the descending aorta and that there is no streaming of flow in fetal systemic arteries. Thus, of that portion of LV output crossing the aortic isthmus, \( Q_{LB} \) \( Q_{AI} - Q_{PL} \) will be distributed to the fetal lower body and \( Q_{PL} \) \( Q_{AI} - Q_{PL} \) will be distributed to the placenta. The lower body and placental flows originating from the RV will therefore equal \( Q_{LB} \) \( Q_{AI} - Q_{PL} \) and \( Q_{PL} \) \( Q_{AI} - Q_{PL} \).

**Blood Gas Calculations**

The oxygen content (\( CO_2 \)) of arterial or venous blood (ml \( O_2 \)/dl blood) was calculated as \( 1.36 \cdot HbS \cdot Hb / 100 + (0.003 \cdot PO_2) \), where \( HbS \) is hemoglobin oxygen saturation (%), \( Hb \) is hemoglobin level (g/dl), and \( PO_2 \) is oxygen tension (mm Hg).

Systemic flow to the fetal body comprises \( Q_{UB} + Q_{LB} + Q_{LV} \), i.e., the sum of the flows to the upper body, lower body, and lungs. Total oxygen delivery to the fetal body is therefore equal to \( Q_{UB} \cdot Cao_2 \) \( + (Q_{LB} \cdot Cdo_2) + (Q_{LV} \cdot Cpt02) \), where \( Cao_2 \), \( Cdo_2 \), and \( Cpt02 \) are the oxygen contents in the carotid artery, descending aorta, and pulmonary trunk, respectively. In those fetuses with an umbilical venous catheter, whole-body oxygen consumption was calculated according to the Fick principle as \( Q_{p} \cdot (Cvo_2 \ - Cdo_2) \), where \( Cvo_2 \) is umbilical venous oxygen content. Because this calculation excludes oxygen consumption by the placenta,
it enables direct comparison of whole-body oxygen consumption of the fetus and newborn. Four variables were calculated in fetuses for perinatal comparison of oxygenation status. Average arterial oxygen content was calculated as fetal body oxygen delivery divided by fetal body flow; arteriovenous oxygen extraction (i.e., the arteriovenous oxygen content difference) was calculated as whole-body oxygen consumption divided by fetal body flow, mixed venous oxygen content as average arterial oxygen content minus the arteriovenous oxygen content difference, and the oxygen extraction coefficient as whole-body oxygen consumption divided by fetal body oxygen delivery.

After the circulatory changes at birth, systemic flow in lambs was equal to $Q_{SB} + Q_{LB}$ average arterial oxygen content to (CcaO$_2$ + CdaO$_2$)/2, and mixed venous oxygen content to CptoO$_2$. Total-body oxygen delivery in lambs was calculated as $(Q_{SB} + Q_{LB}) \cdot [(CcaO_2 + CdaO_2)/2 - Cpto_2]$, and oxygen consumption as $(Q_{SB} + Q_{LB}) \cdot [(CcaO_2 + CdaO_2)/2 - Cpto_2]$. The oxygen extraction coefficient was given by $[(CcaO_2 + CdaO_2)/2 - Cpto_2]/[(CcaO_2 + CdaO_2)/2]$.

**Statistics**

In line with convention,4–9 ventricular outputs, large region flows (upper and lower bodies, lungs, and placenta), and oxygen consumption data were indexed to body weight. Organ flows were indexed to 100 g wet tissue weight. Results were analyzed with standard statistical methods.22 Changes in hemodynamics, blood gas parameters, tissue blood flow, and ventricular outputs were analyzed with two-way analysis of variance. When the F statistic exceeded the critical level, the sums of squares were orthogonally partitioned into individual degrees of freedom, and the significance of changes between the fetal and 1-hour newborn and between 1-hour and 4-hour newborn intervals was evaluated using the Bonferroni procedure for multiple tests.23 Results are reported as mean±SEM, and $p<0.05$ was considered significant.

**Results**

The combined weight of the dissected organs and carcass remnants was 3.33±0.19 kg (range, 2.28–4.25 kg). The transition from the fetal to newborn period was associated with falls in carotid arterial pH and hemoglobin content, the emergence of a base deficit, and rises in oxygen saturation and tension. Between 1 and 4 hours after birth, blood pH returned toward normal, the base deficit was reduced, and arterial oxygen saturation and tension rose further (Table 1). Mean pulmonary arterial pressure fell, and heart rate rose significantly after birth. Mean systemic blood pressure rose in seven but fell in three lambs after birth so that overall there was no significant postnatal rise in this variable (Table 1).

**Table 1. Hemodynamic, Hemoglobin, and Blood Gas Values in the Carotid Artery Before and After Birth**

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>1 HR NB</th>
<th>4 HR NB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.2±0.4*</td>
<td>9.3±0.4</td>
<td>8.8±0.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.297±0.008*</td>
<td>7.137±0.029*</td>
<td>7.239±0.011</td>
</tr>
<tr>
<td>O$_2$ saturation (%)</td>
<td>48.0±3.0*</td>
<td>76.2±2.8*</td>
<td>87.7±1.6</td>
</tr>
<tr>
<td>PCO$_2$ (mm Hg)</td>
<td>22.9±1.1*</td>
<td>43.7±3.2*</td>
<td>61.5±3.1</td>
</tr>
<tr>
<td>PO$_2$ (mm Hg)</td>
<td>48.2±0.9</td>
<td>50.9±2.4</td>
<td>50.8±1.4</td>
</tr>
<tr>
<td>Base excess (mmol/l)</td>
<td>-2.4±0.5*</td>
<td>-11.4±1.4*</td>
<td>-5.2±0.6</td>
</tr>
<tr>
<td>MSABP (mm Hg)</td>
<td>51±1</td>
<td>59±4</td>
<td>54±3</td>
</tr>
<tr>
<td>MPABP (mm Hg)</td>
<td>52±1</td>
<td>48±4</td>
<td>37±2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>155±6*</td>
<td>206±11</td>
<td>204±8</td>
</tr>
</tbody>
</table>

**Ductal Shunting and Tissue Flows**

Oxygen content in the left pulmonary artery tended to be higher than in the pulmonary trunk 1 hour after birth (0.1>p>0.05) but was the same 4 hours after birth (Table 2). Lung blood flow, which comprises the summation of bronchial flow, flow from any left to right transuductal shunting, and microshares that have passed through the systemic circulation, was identical at both newborn periods, constituting 15.6±2.9% and 15.5±3.2% of the microshares injected into the left atrium at 1 and 4 hours, respectively.

Birth had a variable effect on organ blood flows (Table 3). Heart, thyroid, upper body muscle, splenic, and hepatic arterial–derived liver flows were not significantly different in fetuses and lambs. Brain and skin flows decreased with birth and did not change subsequently between 1 and 4 hours. Renal blood flow initially fell with birth but then rose between 1 and 4 hours. Gastrointestinal flow was similar in fetuses and 1-hour lambs but increased between 1 and 4 hours after birth. Blood flow to lower body muscle increased between fetuses and 1-hour lambs and then fell between 1 and 4 hours after birth. Despite the differing patterns of organ flows, average flow to the combined upper and lower body tissues (excluding the lung) was similar in fetuses (37±4 ml·min$^{-1}·100$ g tissue$^{-1}$), 1-hour lambs (39±4 ml·min$^{-1}·100$ g tissue$^{-1}$), and 4-hour lambs (40±5 ml·min$^{-1}·100$ g tissue$^{-1}$).

**Table 2. Regional Oxygen Contents After Birth**

<table>
<thead>
<tr>
<th>Oxygen content (ml/dl)</th>
<th>1 HR NB</th>
<th>4 HR NB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CcaO$_2$</td>
<td>9.55±0.48</td>
<td>10.64±0.85</td>
</tr>
<tr>
<td>CdaO$_2$</td>
<td>9.61±0.58</td>
<td>10.64±0.86</td>
</tr>
<tr>
<td>CptoO$_2$</td>
<td>6.31±0.67</td>
<td>7.86±0.95</td>
</tr>
<tr>
<td>CpaO$_2$</td>
<td>6.74±0.78</td>
<td>7.89±0.98</td>
</tr>
</tbody>
</table>

1 HR NB, lambs 1 hour after delivery; 4 HR NB, lambs 4 hours after delivery; CcaO$_2$, CdaO$_2$, Cpto$_2$, and CpaO$_2$, oxygen content in the carotid artery, descending aorta, pulmonary trunk, and left pulmonary artery, respectively. Values are mean±SEM; n=9.
distributed to the placenta, and 16% was distributed to the lungs (Figure 1).

Between the fetal and 1-hour newborn periods, LV output increased by 68% to 444±33 ml · min⁻¹ · kg body wt⁻¹ (p<0.005). The fate of this greater newborn LV output was apparent on examination of the distribution of LV output before and after birth. The contribution of LV output to upper body flow did not change between fetuses and 1-hour lambs (Figure 2). Likewise, the LV

component of placental flow (50±8 ml · min⁻¹ · kg body wt⁻¹) in fetuses was similar to the LV-derived portion of lung flow in the 1-hour lambs (65±12 ml · min⁻¹ · kg body wt⁻¹). However, although total lower body flow itself did not change significantly between fetuses and 1-hour lambs, the contribution of LV output to lower body flow increased more than fourfold, from 51±9 ml · min⁻¹ · kg body wt⁻¹ in fetuses to 226±22 ml · min⁻¹ · kg body wt⁻¹ in 1-hour lambs (p<0.005).

This was accompanied by a loss of the fetal RV perfusion of these tissues (151±20 ml · min⁻¹ · kg body wt⁻¹) (Figure 2).

At 4 hours after birth, both the LV output (460±42 ml · min⁻¹ · kg body wt⁻¹) and the proportion of LV output passing to the upper and lower body (Figure 2) and lungs (67±14 ml · min⁻¹ · kg body wt⁻¹) were similar to values obtained in the 1-hour lambs.

**Total-Body Oxygen Consumption**

Oxygen consumption in fetuses (7.84±0.43 ml · min⁻¹ · kg body wt⁻¹) comprised a systemic blood flow of 412±36 ml · min⁻¹ · kg body wt⁻¹ and an arteriovenous oxygen extraction of 1.98±0.16 ml/dl (Figure 3). With birth, oxygen consumption increased by 58%, to 12.38±2.4 ml · min⁻¹ · kg body wt⁻¹ in the 1-hour lambs (p<0.01). Systemic blood flow did not change in the transition from fetus to newborn, but the arteriovenous oxygen content difference increased by 54% to 3.05±0.19 ml/dl (p<0.005) (Figure 3). This greater oxygen extraction 1 hour after birth was accompanied by rises in the arterial oxygen content (54%), oxygen delivery (49%), and mixed venous oxygen content (54%), but there was no change in the oxygen extraction coefficient (Table 4). There was no significant difference in oxygen consumption, systemic blood flow, and oxygen extraction (Figure 3) or in arterial oxygen content,
Second, overall blood flow to body tissues does not change significantly between the fetal and newborn periods. Third, with the maintenance of perfusion to systemic tissues, an elevated whole-body oxygen consumption after birth is achieved solely through an increase in the arteriovenous oxygen content difference. Consequently, the increases in LV output and whole-body oxygen consumption occurring at birth are not directly related to one another.

An important consideration in assessing the general applicability of our findings is the quality of the experimental preparation. On the basis of heart rate, arterial pressure, and blood gases, the condition of the fetuses in our study was similar to that of chronically instrumented animals prepared by other investigators. The combined ventricular output (604 ml·min⁻¹·kg body wt⁻¹) was within the range of 375–658 ml·min⁻¹·kg body wt⁻¹ previously reported in chronically instrumented fetal sheep. Because fetal cardiac output is depressed by surgery, the high value in our study indicates that the fetuses had adequately recovered from the thoracotomy performed 1 week earlier. In agreement with others, a fetal RV dominance was evident: the LV contribution to the combined ventricular output in our study (44%) was close to the 40% reported by Anderson et al but greater than the 33% found by Rudolph and coworkers.11,17 The blood gas status of our newborn lambs was similar to that of animals not subjected to thoracic surgery and undergoing either cesarean or vaginal delivery, indicating that a thoracotomy performed in the fetus need not impair lung ventilation after birth. LV output in the lambs of our study was also within the range reported in the first week of life by other investigators. Moreover, in accord with previous studies, heart rate rose and pulmonary arterial pressure fell after birth. Mean systemic blood pressure increased in seven of 10 animals in our study within 1 hour of birth, but the group data did not reach significance. Other studies have reported that systemic arterial pressure may not rise in newborn lambs after either vaginal or cesarean delivery. We are uncertain about the precise mechanisms that determine the level of arterial pressure immediately after birth. However, on the basis of the similarity of oxygen contents in the pulmonary trunk and left pulmonary artery (Table 2), we discount a patent ductus arteriosus as the sole explanation for the failure of arterial pressure to rise at birth.

Two previous reports have alluded to difficulties in calculating fetal univentricular outputs with the microsphere technique. Anderson et al determined fetal biventricular output with radioactive microspheres but

---

**Figure 3.** Bar graphs showing oxygen consumption, systemic blood flow, and arteriovenous oxygen extraction in fetuses (F), lambs 1 hour after delivery (1 HR NB), and lambs 4 hours after delivery (4 HR NB). Oxygen consumption and systemic blood flow are indexed for body weight; n=8. Fetal oxygen consumption and oxygen extraction are significantly lower than the newborn values (p<0.005).

**Discussion**

This study, which provides the first observations of the changes in LV output and whole-body oxygen consumption occurring with birth, has produced three important new findings. First, a rise in LV output immediately after birth reflects the perfusion by the LV alone of tissues perfused by the LV and RV in utero. Second, overall blood flow to body tissues does not increase significantly between the fetal and newborn periods. Third, with the maintenance of perfusion to systemic tissues, an elevated whole-body oxygen consumption after birth is achieved solely through an increase in the arteriovenous oxygen content difference. Consequently, the increases in LV output and whole-body oxygen consumption occurring at birth are not directly related to one another.

An important consideration in assessing the general applicability of our findings is the quality of the experimental preparation. On the basis of heart rate, arterial pressure, and blood gases, the condition of the fetuses in our study was similar to that of chronically instrumented animals prepared by other investigators. The combined ventricular output (604 ml·min⁻¹·kg body wt⁻¹) was within the range of 375–658 ml·min⁻¹·kg body wt⁻¹ previously reported in chronically instrumented fetal sheep. Because fetal cardiac output is depressed by surgery, the high value in our study indicates that the fetuses had adequately recovered from the thoracotomy performed 1 week earlier. In agreement with others, a fetal RV dominance was evident: the LV contribution to the combined ventricular output in our study (44%) was close to the 40% reported by Anderson et al but greater than the 33% found by Rudolph and coworkers. The blood gas status of our newborn lambs was similar to that of animals not subjected to thoracic surgery and undergoing either cesarean or vaginal delivery, indicating that a thoracotomy performed in the fetus need not impair lung ventilation after birth. LV output in the lambs of our study was also within the range reported in the first week of life by other investigators. Moreover, in accord with previous studies, heart rate rose and pulmonary arterial pressure fell after birth. Mean systemic blood pressure increased in seven of 10 animals in our study within 1 hour of birth, but the group data did not reach significance. Other studies have reported that systemic arterial pressure may not rise in newborn lambs after either vaginal or cesarean delivery. We are uncertain about the precise mechanisms that determine the level of arterial pressure immediately after birth. However, on the basis of the similarity of oxygen contents in the pulmonary trunk and left pulmonary artery (Table 2), we discount a patent ductus arteriosus as the sole explanation for the failure of arterial pressure to rise at birth.

Two previous reports have alluded to difficulties in calculating fetal univentricular outputs with the microsphere technique. Anderson et al determined fetal biventricular output with radioactive microspheres but

---

**Table 4. Changes in Arterial Oxygen Content, Oxygen Delivery, Mixed Venous Oxygen Content, and Oxygen Extraction Coefficient With Birth**

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>1 HR NB</th>
<th>4 HR NB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial O₂ content (ml/dl)</td>
<td>6.37±0.60*</td>
<td>9.83±0.53</td>
<td>10.78±0.88</td>
</tr>
<tr>
<td>Arterial O₂ delivery (ml·min⁻¹·kg body wt⁻¹)</td>
<td>25.3±2.1*</td>
<td>37.6±2.8</td>
<td>40.7±3.0</td>
</tr>
<tr>
<td>Mixed venous O₂ content (ml/dl)</td>
<td>4.39±0.57*</td>
<td>6.78±0.67</td>
<td>7.91±1.02</td>
</tr>
<tr>
<td>O₂ extraction coefficient</td>
<td>0.33±0.04</td>
<td>0.32±0.04</td>
<td>0.27±0.04</td>
</tr>
</tbody>
</table>

*F, fetuses; 1 HR NB, lambs 1 hour after delivery; 4 HR NB, lambs 4 hours after delivery. Values are mean ±SEM; n=8.

*p<0.005 and **p<0.01 vs. corresponding value for 1 HR NB.
obtained the univentricular outputs with an electromagnetic flow probe sited on either the pulmonary trunk or ascending aorta. Fishman et al.28 injected different microsphere labels into the superior and inferior venae cavae and drew reference samples from the carotid artery, descending aorta, and pulmonary trunk; however, they were able to calculate univentricular outputs in only 19 of 32 measurements. We presume that, as in our study, these difficulties were related either to a loss of catheter patency during reference sample withdrawal or to a pattern of radioactivity counts in the carotid artery, descending aortic, and pulmonary trunk samples, which was inconsistent with the notions that descending aortic flow is from cephalad to caudal and that it comprises the sum of the ductus arteriosus and aortic isthmus flows. This “nonphysiological” pattern of reference counts is most likely related to the variability inherent in the microsphere technique29 as well as the potential for inadequate mixing of microspheres and blood in the pulmonary reference sample because of the proximity of the sampling site to the pulmonary valve.17 In our study, these potential problems were overcome with an independent method, i.e., by correcting aberrant reference sample counts with a proportionality equation derived from measured oxygen contents in the carotid artery, descending aorta, and pulmonary trunk.19

Although it is well established that LV output rises substantially at birth,1,2 the fate of the increased LV output has never previously been examined. Our results indicate that the increment in LV output in the newborn is distributed to systemic tissues located distal to the ductus arteriosus and supplied predominantly by the RV in utero. Therefore, our findings point to an intimate relation between the postnatal rise in LV output and the change from an “in parallel” fetal to an “in series” postnatal circulation. Factors other than this reorganization of the circulation did not make a significant contribution to the increased LV output in the newborn. Thus, average blood flow to systemic tissues did not change significantly between fetal and newborn lambs, despite variable alterations in the flow to individual organs. Moreover, in agreement with Breall et al.27 our measurement of oxygen contents in the pulmonary trunk and left main pulmonary artery revealed, at most, only minor left to right transdual shunting at 1 hour after delivery and effective functional closure of the ductus arteriosus by 4 hours after birth. This indicates that, although a left to right transdual shunt may contribute to an increased LV output within the first hour of birth in the sheep, it plays no significant role in the ensuing elevation of LV output.

The heart of the fetal sheep is structurally immature,16,30 and at resting filling pressures, the LV has a near-maximal output with only a limited capacity to increase its output further in response to increases in heart rate or preload.5,31 The cardiac mechanisms that effect the substantial increase in LV output at birth have therefore received considerable attention. A number of cardiac factors have been implicated in the perinatal augmentation of LV output, including an elevation in heart rate, an increase in LV contractile state,22,33 probably related to the birth-related surge in circulating catecholamine levels,2,13,34 an increase in LV cavity dimensions,1,33 and a reduction in ventricular constraint after the onset of lung ventilation.35 Scant attention has been paid, however, to defining the circulatory factors responsible for bringing these cardiac mechanisms into play. A plausible interpretation of our results is that LV output increases in the newborn primarily to maintain the perfusion requirements of systemic tissues. This is in accord with the notion that, ultimately, individual organs regulate their blood flows by a metabolic feedback mechanism and that the cumulative effect of this process is the regulation of cardiac output.36 One possible link between changes in LV output and the perfusion of systemic organs is apparent from consideration of events occurring during the birth process. Thus, with the onset of pulmonary ventilation, LV output is diverted to the lungs as a result of a decrease in pulmonary vascular resistance. Because of the substantial contribution of RV flow to systemic perfusion in utero, it is likely that this diversion results in at least a transient systemic hypoperfusion, particularly of tissues situated distal to the ductus arteriosus. This proposition is supported by the in utero experiments of Teitel et al.9 who demonstrated that lung ventilation was accompanied by an increase in pulmonary blood flow but a decrease in lower body perfusion. The presence of a systemic hypoperfusion at birth is also consistent with the metabolic acidosis observed in newborn lambs after either vaginal11,13 or cesarean section10,12 delivery (Table 1). We speculate that a transient systemic hypoperfusion could act, presumably at least in part via release of catecholamines, as a factor stimulating an increase in LV output immediately after birth.

Whole-body oxygen consumption in fetuses and lambs in our study fell within the reported ranges of 6–9.4 ml · min⁻¹ · kg body wt⁻¹ 5,37 and 11–16 ml · min⁻¹ · kg body wt⁻¹, 4,6,27 respectively. The increase in oxygen consumption after birth reflects an augmented metabolic demand related to many factors, including the heat production required for body temperature regulation, the work of breathing, and a greater gastrointestinal function.4 Our analysis indicates that the postnatal rise in oxygen consumption is achieved through an increase in the arteriovenous oxygen content difference, without any change in overall blood flow to systemic tissues. Thus, this is in marked contrast to the phase of ongoing postnatal growth, when decreases in LV output (and therefore systemic blood flow) are closely related to a reduction in whole-body oxygen consumption.5,6 We did not measure the oxygen consumption of individual organs. Thus, it is possible that flow changes may be important in determining oxygen consumption in organs such as brain, skin, muscle, and gut, which undergo substantial flow alterations with birth (Table 3).

Interestingly, the greater arteriovenous oxygen content difference after birth occurred in the setting of a rise in both the arterial and mixed venous oxygen contents. Moreover, because the increases in arterial and mixed venous oxygen contents were proportionally similar, the oxygen extraction coefficient did not change with birth. The mechanism for augmenting arteriovenous oxygen extraction at birth is therefore quite distinct from the mechanism for maintaining oxygen extraction during stresses such as umbilical cord compression in fetuses37 or hypoxemia38 and reductions in cardiac output6 in lambs. These conditions, which are
associated with a decreased oxygen delivery, are accompanied by a fall in the venous oxygen content and a rise in the oxygen extraction coefficient.\textsuperscript{6,37,38} Accordingly, our findings imply that the reserve capacity for removal of oxygen from blood by fetal and newborn tissues is not used during the birth process. In summary, this study has examined the changes in LV output and whole-body oxygen consumption occurring with birth. Our results indicate that a postnatal augmentation of LV output serves to maintain systemic perfusion and does not itself contribute to an increase in oxygen consumption in the newborn. Instead, the postnatal rise in oxygen consumption is accomplished through an increased arteriovenous oxygen extraction, which is supported by a birth-related increase in arterial oxygenation.

Acknowledgments

We acknowledge the valuable technical assistance of Ann Oates, Nicole de Preu, and Voita Brodecky.

References

Indirect relation between rises in oxygen consumption and left ventricular output at birth in lambs.

J J Smolich, M Soust, P J Berger and A M Walker

Circ Res. 1992;71:443-450
doi: 10.1161/01.RES.71.2.443

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/71/2/443

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/