Left Ventricular Performance and Regional Blood Flows Before and After Ductus Arteriosus Occlusion in Premature Lambs Treated with Surfactant

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SUMMARY The hemodynamic consequences of patent ductus arteriosus (PDA) were studied during the first few hours of life (1.9 ± 0.7 hours) in 13 mechanically ventilated, surfactant-treated, preterm lambs (gestational age of 120–124 days). Cardiovascular pressures, left ventricular (LV) performance and regional blood flows were measured using cine left ventriculography and radionuclide-labeled microspheres before and after occlusion of the PDA with a catheter balloon. Before occlusion, the left-to-right shunt was 44 ± 13%; after occlusion the shunt was negligible (2%). Heart rate (164 ± 17 beats/min), LV end-diastolic pressure (5 ± 3 mm Hg), ejection fraction (74 ± 8%) and cardiac output (241 ± 13 ml·min⁻¹·kg⁻¹) were normal and did not change after ductus occlusion. However, “effective” systemic blood flow increased significantly after occlusion (130 ± 53 to 228 ± 93 ml·min⁻¹·kg⁻¹, p < 0.001), as did blood flow to organs such as the brain, myocardium and gastrointestinal tract. The reduction of systemic blood flow in the presence of a left-to-right PDA shunt may be responsible for many early pathologic manifestations of the PDA “syndrome” of prematurity even in the absence of overt LV dysfunction.

THE PRESENCE of a patent ductus arteriosus and a left-to-right shunt adversely affects the clinical status of premature infants with respiratory distress syndrome. It has been proposed that a large left-to-right shunt may disproportionately “volume load” the left ventricle of the immature infant and lead to impairment of left ventricular systolic and diastolic performance. Clinical and experimental studies using electromagnetic flowmeters, cineortography, Doppler methods, and echocardiography have demonstrated a diastolic flow reversal pattern or “steal” of blood flow to the pulmonary artery in subjects with a patent ductus arteriosus and a left-to-right shunt. It has been proposed that this abnormal blood flow distribution might lead to organ dysfunction. However, this proposal has not been confirmed in the critically ill, small, preterm infant.

The study of the cardiovascular physiology of the patent ductus arteriosus syndrome of prematurity has been greatly facilitated by the use of mechanical ventilatory support and the administration of natural sheep surfactant to premature lambs during the first hours of life. Such treatment interrupted the marked respiratory deterioration and acid-base imbalance that occur in such lambs soon after birth. We studied the influence of early left-to-right ductal shunting on left ventricular performance and distribution of organ blood flows before and after occlusion of the ductus arteriosus in premature lambs treated with natural surfactant before the first breath.

Materials and Methods

Experimental Preparation

Thirteen lambs were delivered by cesarean section of date-bred, Western, mixed-breed ewes at a gestational age of 120–124 days. The ewes were premedicated with intramuscular injection of ketamine (800 mg) and atropine sulfate (3 mg), and surgery was performed under spinal anesthesia. The head and neck of each lamb was delivered and a 4.5 mm endotracheal tube was immediately secured in the trachea by tracheotomy. Each lamb was treated with a 15-ml suspension containing natural sheep surfactant (50 mg lipid/kg) instilled into an endotracheal tube before the first breath. The surfactant was isolated from the lavaged lung fluid of adult ewes and characterized as previously described. The lambs were placed on pressure-limited infant ventilators (Sechrist Industries) at initial settings of 30 breaths/min, a positive end-expiratory pressure of 2 cm H₂O, a peak inspiratory pressure of 28 cm H₂O and an inspiratory time of 1 second. A #5F catheter was placed in the distal aorta through an umbilical artery, and the lambs were paralyzed with pancuronium bromide (0.1 mg/kg). Rectal temperature was maintained at 38–39° with a heating pad and heat lamps. Blood losses were replaced with freshly collected, anticoagulated, filtered, maternal blood. Peak inspiratory pressures, rates and inspired oxygen concentrations were changed only to maintain arterial blood gas tensions (PaO₂, 40–100 mm Hg, PaCO₂, 30–40 mm Hg) and arterial pH (7.30–7.45), as assessed by frequent measurement (BMS-III Blood Micro System). The absence of pneumothorax was confirmed by fluoroscopy of the chest, review of cineangiocardograms, and by postmortem examination of the lungs.
Catheter Placement

The lambs were catheterized under local anesthesia through external cutdowns using fluoroscopy and pressure monitoring (figs. 1 and 2). Fluid-filled polyvinyl catheters were placed into the right jugular vein and advanced to the right atrium and to the main pulmonary artery (#5F flow-directed balloon angiography catheter), the right carotid artery and advanced to the apex of the left ventricle (#3.5F), and the umbilical artery and advanced to the descending thoracic aorta (#5F).

Measurements and Calculations

Pressures were recorded using a multichannel photographic recorder and pressure transducers calibrated with a mercury manometer. The rate-pressure product (peak systolic pressure) was calculated as previously described.12 Left ventricular cardiac output and the distribution of organ blood flows were measured by a 15-second infusion into the left ventricle of 15-μm-diameter, radionuclide-labeled microspheres suspended in 5 ml of maternal blood (57Co, 46Sc, 113Sn, New England Nuclear). Concurrent with each injection of microspheres, a reference sample was withdrawn at a rate of 6 ml/min for 2 minutes from the descending thoracic aorta (confirmed fluoroscopically); the volume withdrawn was simultaneously replaced with maternal blood. The adequacy of the withdrawal of a single reference sample from the descending thoracic aorta of lambs has been well documented.11,13 However, others suggested that incomplete mixing after injection of microspheres into the left ventricle was associated with small discrepancies (mean 11%) of absolute blood flows calculated from simultaneous ascending and descending aortic samples.14 This limitation applies particularly to the calculation of proximal organ flows, such as myocardial blood flow; consequently, this study emphasizes the change of blood flow before and after ductal occlusion.

After the lambs were killed, the organs were removed and weighed, and the amount of each radioisotope was counted in a multichannel gamma spectrometer (CG-30, Inter-technique). Smaller organs were counted directly in counting vials; larger organs were ashed and then counted. All microspheres were assumed to be trapped on the first pass through the capillary beds.13 Enough microspheres were injected to ensure adequate distribution and accurate flow measurements in organs with the lowest blood flow.13

Left ventricular cardiac output (ml/min/kg body weight), its percent distribution, and organ blood flows (ml/min/g) were calculated from the amounts of total microspheres injected, the microspheres in each organ, and the reference sample.13 The magnitude of

Figure 1. Method of ductus arteriosus occlusion. (left) Flow-directed angiographic catheter advanced to pulmonary artery. Aortogram demonstrates opacification of patent ductus arteriosus and pulmonary artery. (middle) The catheter has been advanced to the ductal lumen and the balloon is inflated (with radiopaque contrast). (right) The patent ductus arteriosus (PDA) has been occluded and only the aorta opacifies.

Figure 2. Composite of instantaneous pressure responses before, during and after ductus arteriosus occlusion. (Catheter pressure ports are proximal to balloon.) Full scale is 0–80 mm Hg. (top) Before occlusion, peak aortic (Ao) systolic pressure is slightly greater than peak systolic pulmonary arterial (PA) pressure and pulmonary diastolic and mean pressures are lower than systemic pressure. (bottom) The ductus arteriosus (PDA) is occluded. Systemic pressures rise and pulmonary arterial pressures fall. There is no obstruction or pressure gradient between left ventricle and thoracic aorta.
left-to-right ductal shunt was expressed as the percentage of total left ventricular cardiac output diverted to the lungs. The bronchial blood flow was deducted from the total amount of left ventricular output diverted to the lungs, and the remainder was considered the contribution of left-to-right ductal shunt. The maximum potential bronchial blood flow was assumed to be 10% of the total pulmonary blood flow after ductal occlusion.15 The "effective" systemic blood flow was expressed as left ventricular cardiac output minus the calculated left-to-right ductal shunt.

Appreciable right-to-left atrial shunts were not present in this model.11 Consequently, dye-dilution curves were not obtained. Because labeled microspheres were infused into the left ventricle, the contribution of right-to-left atrial shunt would be included in the calculated left ventricular cardiac outputs and organ blood flows.13 However, actual pulmonary blood flow would be less than the calculated left ventricular output. We considered the ductus arteriosus "restrictive" when peak pulmonary arterial systolic pressure was less than or equal to 90% of peak aortic pressure; under such circumstances large right-to-left ductal shunting is unlikely. However, bidirectional ductal shunting may occur as peak pulmonary arterial pressure approaches systemic levels. A proportionately small, early systolic, right-to-left shunt may be present when the pulmonary arterial pressure rise precedes aortic pressure rise at the site of the ductus arteriosus.7 Such a right-to-left ductal shunt would "dilute" the thoracic reference sample, and the calculated left ventricular output and organ blood flows would be overestimated. We assumed the absence of substantial right left atrial or ductus shunting in this model.11 Thus, pulmonary blood flow was considered equal to left ventricular cardiac output.

Cineangiocardiography

Cine left ventriculograms were obtained without disturbing the lambs immediately after each injection of radionuclide-labeled microspheres. The lambs lay in a left lateral position, which provides a maximum projection of the left ventricular major axis.16 Dilute contrast (Renografin-60, Squibb) was injected through the left ventricular catheter and cineangiocardiograms were recorded on 16-mm film at a rate of 60 frames/sec. Volumes were calculated using the single-plane, area-length method.17 The mean left ventricular end-systolic and end-diastolic volumes and ejection fraction were calculated from two or three nearly consecutive cardiac cycles. The calculated volumes were then corrected using regression equations derived from comparison of volumes calculated from projected 16-mm cine frames of preterm and term lamb left ventricular casts and their displacement volumes.16 Cineangiocardiography provides good estimates of left ventricular volumes and function in small lambs.18 We previously demonstrated a 12% mean difference between such calculated volumes and their water displacement volumes.16 However, the discrepancy between "dilution" (e.g., microsphere) and angiographic methods is well known.19 Furthermore, the angiographic method is limited for the calculation of cardiac output because any error of the estimated stroke volume is multiplied by the cardiac rate. Accordingly, cardiac output in this study was estimated using radionuclide-labeled microspheres.

Experimental Protocol

To evaluate the effect of left-to-right ductal shunting on distribution of left ventricular cardiac output and organ blood flows, we obtained measurements before and after occlusion of the ductus arteriosus. The catheters were placed within 1.5 hours of birth, and the lamb was allowed to stabilize for approximately 20 minutes before measurements were obtained. Baseline blood gases, pH, cardiovascular pressures, left ventricular cardiac output and its distribution were measured and cine left ventriculography was performed. The flow-directed balloon angiographic catheter was then advanced under fluoroscopic guidance into the lumen of the ductus arteriosus and the catheter balloon was inflated to occlude the ductus arteriosus. Occlusion was confirmed by cineangiography and continuous pressure measurements (figs. 1 and 2). A decrease of pulmonary arterial pressure and absence of pressure gradient between the left ventricle and the descending thoracic aorta confirmed optimal ductal occlusion without migration of the catheter balloon and obstruction of the descending thoracic aorta (fig. 2). Soon after ductal closure (mean 11 ± 3 minutes), all measurements were repeated.

Statistics

Measurements obtained before and after ductal occlusion were analyzed statistically by paired t test. The level of significance was p < 0.05 (two-tailed t test). The data are reported as mean ± SD.

Results

The arterial blood gases and hemodynamic and blood flow data are shown in tables 1 and 2. The baseline measurements were obtained 1.9 ± 0.7 hours after birth, and measurements after ductal occlusion were obtained 2.6 ± 0.7 hours after birth. Although arterial blood gases and pH appear to have changed significantly, they remained normal, indicating normal ventilatory and acid-base balance during the study interval (table 1).

The ductus arteriosus closed spontaneously within the first 2 hours of life in two lambs and they were excluded from the study. The ductus arteriosus was restrictive (pulmonary peak systolic < 0.9 aortic systolic pressure) in nine of the remaining 11 lambs. Nevertheless, in these lambs the left-to-right ductal shunt was 44 ± 4.2% of the left ventricular cardiac output and was negligible after ductal closure (table 1). The calculated mean pulmonary-to-systemic blood flow ratio before ductal occlusion was 1.8:1. Heart rate, left ventricular cardiac output and total pulmonary blood flow did not change significantly after ductal closure. Angiographic left ventricular end-diastolic volume
was slightly increased before occlusion, but ejection fraction was uninfluenced by closure of the ductus arteriosus (table 1). The “effective” systemic blood flow after ductal occlusion increased significantly, from 130 to 228 ml/min/kg (table 1).

The left ventricular end-diastolic pressure, and the peak systolic and mean systemic and pulmonary arterial pressures did not change after ductal occlusion; however, aortic diastolic pressure increased and pulmonary diastolic pressure decreased significantly (table 1). Systemic vascular resistance (0.37 ± 0.26 vs 0.19 ± 0.07 mm Hg/ml-min⁻¹·kg⁻¹) did not change significantly after occlusion; “total” systemic resistance (systemic plus ductal resistance) was obviously less (0.1 ± 0.06 mm Hg/ml-min⁻¹·kg⁻¹) than systemic resistance after ductal occlusion (p < 0.005). Pulmonary vascular resistance (0.13 ± 0.08 mm Hg/ml-min⁻¹·kg⁻¹) did not change significantly (0.09 ± 0.03 mm Hg/ml-min⁻¹·kg⁻¹). However, the pulmonary-to-systemic vascular resistance ratio increased from 0.36 to 0.47 (p < 0.005) after ductal occlusion, primarily due to the general fall of systemic vascular resistance, which in turn was related to the marked increase of “effective” systemic blood flow.

Although left ventricular cardiac output did not change, the percentage of output distributed to most major organs increased after ductal occlusion because blood flow was no longer diverted to the lungs. Furthermore, because the “effective” systemic blood flow increased, the absolute organ blood flows increased significantly (table 2). For example, after ductal occlusion, myocardial blood flow increased approximately 116%, gastrointestinal flow increased 82%, and cerebral flow increased 42%. Although the myocardial blood flow increased significantly, the rate-pressure product did not change (table 1, fig. 3).

**Discussion**

Lambs have been widely used to study cardiovascular and pulmonary function of the premature infant. However, obvious differences in the pathogenesis of respiratory distress are observed in the preterm lamb compared with human premature infants. The more rapid deterioration of pulmonary function and abbreviated survival of premature lambs is primarily explained by pulmonary structural differences and differences of surfactant biosynthesis and release. Whether similar comparative differences of cardiovascular performance exist and whether such differences influence the adaptation of the human preterm infant to extrauterine life are unknown. These potential differences must be considered before extrapolating results from the experimental animal model to the human infant with respiratory distress syndrome.

In prior studies, treatment of premature lambs with natural sheep surfactant during the first hours of life greatly improved pulmonary function and facilitated the study of cardiovascular physiology in very premature lambs. However, marked deterioration of pulmonary function occurred before treatment with surfactant. We have demonstrated that treatment with natural sheep surfactant before the onset of respiration

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Organ Blood Flows Before and After Occlusion of the Patent Ductus Arteriosus</th>
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<tbody>
<tr>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td>Preclosure</td>
<td>2.60 ± 1.8</td>
</tr>
<tr>
<td>Occluded</td>
<td>0.39 ± 0.24†</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± sd (ml·min⁻¹·g⁻¹).

* p < 0.05.
† p < 0.01.
provided a premature lamb with relatively physiologic metabolic and respiratory status during the first hours of life. Yet, even after this earlier therapy, characteristic deterioration of blood gas values occurred. Nevertheless, study of the potential hemodynamic manifestations of patent ductus arteriosus in premature animals was possible under nearly optimal physiologic conditions.

In other studies, the treatment of the lambs by endotracheal instillation of surfactant within the first hours of life was associated with increasing left-to-right ductal shunting. Similarly, pathologic left-to-right ductal shunting occurred after endotracheal administration of surfactant to preterm infants with respiratory distress syndrome. Thus, the potential benefits of giving pulmonary surfactant to preterm infants with respiratory distress syndrome could well be nullified by the complicating features of the left-to-right ductal shunt.

In this study, the ductus arteriosus closed spontaneously in two of 13 lambs and was partially constricted in nine others. Consequently, substantial right-to-left ductal shunting was unlikely in the majority of lambs. Nevertheless, there was generally a large left-to-right ductal shunt into the lower resistance pulmonary vascular bed and a proportionately reduced “effective” systemic blood flow. After acute ductal occlusion, the cardiac rate, left ventricular end-diastolic pressure, ejection fraction and cardiac output remained unchanged (table 1). However, the “effective” systemic blood flow increased significantly and by an amount approximately equivalent to the flow previously diverted through the ductus arteriosus to the lungs. In addition, the total pulmonary blood flow before and after ductal occlusion was unchanged, for the systemic venous return increased after occlusion by an amount approximately equal to that previously diverted through the ductus arteriosus. Thus, although the left ventricle pumped a relatively greater proportion of the combined ventricular output than did the right ventricle, there was no apparent appreciable influence of the left-to-right ductal shunt on the total left ventricular cardiac output. In contrast, other investigators induced a marked increase of pulmonary blood flow and left ventricular cardiac output in adult dogs in which prosthetic aortopulmonary communications were inserted. However, marked increases of the cardiac rate and decreases of the systemic systolic and diastolic pressures were observed upon opening the shunt in their acute model. Furthermore, it was suggested that the responses of the adult dog may be different from those in the newborn with a natural left-to-right ductal shunt.

The left ventricular ejection fraction is a widely ac-

cepted index of left ventricular systolic performance. Factors potentially increasing the left ventricular ejection fraction in the intact heart include increased preload and “contractile state” or reduced afterload. A relatively reduced left ventricular Starling performance curve has been demonstrated in the term newborn lamb when compared with sheep. Conversely, in the term newborn lamb, cardiac output is relatively high and the contractile state is maintained at a relatively increased level. In this study, the left ventricular ejection fraction was relatively high when compared with term newborn lambs and uninfluenced by the presence of a left-to-right ductal shunt (table 1). Left ventricular preload (end-diastolic volume) was slightly increased and afterload (systemic plus ductal resistance) was decreased before ductal occlusion. Consequently, a relatively greater ejection fraction would be expected before ductal occlusion.

In addition, the left ventricular output was comparable to cardiac output measured in similar preterm lambs and most studies of term lambs, but was somewhat less than that measured in one study of newborn term lambs. Thus, although left ventricular ejection performance was apparently normal, the inability to compensatorily increase cardiac rate, left ventricular ejection fraction and, ultimately, cardiac output in face of the left-to-right ductal shunt might represent the limited Frank-Starling performance of the preterm left ventricle, or a “relative” deterioration of cardiac performance may have occurred soon after birth. Alternatively, the left ventricle may operate at its “maximum” contractile state and pump performance shortly after birth, and therefore may be incapable of further improvement.

It has been suggested that a reduction of systemic blood flow associated with left-to-right ductal shunting in the premature infant might cause ischemia and dysfunction of vital organs. After birth, oxygen consumption increases markedly. These increased metabolic demands of the newborn are met primarily by increasing the cardiac output. The oxygen requirements of many neonatal organ systems are provided by maintaining a relatively higher blood flow per gram of tissue and a relatively lower oxygen extraction compared with adult animals. Moreover, the need for greater organ blood flow may be further dictated by high levels of fetal hemoglobin. In view of these considerations, the newborn infant may be particularly susceptible to the potential reduction of systemic perfusion associated with patent ductus arteriosus. The significant reductions of organ blood flows associated with left-to-right ductal shunting we observed within the first hours of life might lead to organ

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**Table 1.** (Continued)

<table>
<thead>
<tr>
<th>LVEDV (ml)</th>
<th>EF (%)</th>
<th>Ao pressure (mm Hg)</th>
<th>PA pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Rate-pressure product (beats-mm Hg-min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sys/dias Mean</td>
<td>Sys/dias Mean</td>
<td></td>
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<tr>
<td>2.4 ± 0.6</td>
<td>74 ± 8</td>
<td>51 ± 7/35 ± 4</td>
<td>38 ± 6/25 ± 5</td>
<td>5.0 ± 3.1</td>
<td>8474 ± 1083</td>
</tr>
<tr>
<td>2.0 ± 0.4†</td>
<td>72 ± 4</td>
<td>56 ± 11/40 ± 8†</td>
<td>35 ± 8/18 ± 4†</td>
<td>5.2 ± 3.2</td>
<td>8739 ± 1739</td>
</tr>
</tbody>
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ischemia (table 2). For example, the neonatal gastrointestinal tract might be particularly susceptible to ischemia in the presence of such marked reductions of gastrointestinal flow (approximately 49%). Such a relationship between the association of necrotizing enterocolitis and patent ductus arteriosus of prematurity has been suggested. Other investigators using Doppler methods have suggested reduced diastolic cerebral blood flow velocity in premature infants with patent ductus arteriosus. These observations are consistent with our finding of significantly decreased cerebral blood flow in the lambs before occlusion of the ductus arteriosus. The association of cerebral ischemia and cerebral hemorrhage has been well documented in the premature infant. The contribution of cerebral hypoperfusion or ischemia secondary to left-to-right ductal shunting in the pathogenesis of cerebral hemorrhage remains to be evaluated.

The mechanical and autoregulatory factors that influence the quantity and distribution of coronary blood flow are complex. The increased myocardial blood flow after occlusion of the ductus arteriosus was most likely associated with a diminished coronary vascular “resistance,” for transcoronary perfusion pressure changed minimally. Furthermore, the rate-pressure product, which correlates well with instantaneous myocardial oxygen consumption (MVO₂) in sheep and newborn lambs, did not change after occlusion (table 1, fig. 3). This is not surprising since the principal determinants of MVO₂ were similarly unchanged (i.e., ventricular pressures, volume, cardiac rate, and presumably contractile state). Thus, the increased myocardial blood flow coincident with unchanged MVO₂ after occlusion was apparently associated with “non-demand-related” coronary vasodilation, which may have been related to the falling PO₂ and rising PCO₂ after occlusion. Increased aortic diastolic pressure or transcoronary perfusion pressure may have further contributed to the increased myocardial flow. Despite the apparent relative reduction of myocardial flow in proportion to MVO₂ (fig. 3), it is unlikely that myocardial ischemia occurred, for the initial coronary flow and ventricular performance were acceptable in lambs with ductus arteriosus. In view of the relatively high myocardial blood flow required immediately after birth, a sustained imbalance of myocardial oxygen supply and demand might ultimately lead to myocardial ischemia and dysfunction.

In conclusion, clinical attention in the preterm infant with patent ductus arteriosus syndrome has been primarily directed at the adverse consequences of “volume overload” upon the immature left ventricle and associated pulmonary complications. In premature lambs during the hours immediately after birth, the patent ductus arteriosus is associated with left-to-right shunt, reduced “effective” systemic blood flow, and organ hypoperfusion. The latter may occur even in the absence of overt left ventricular dysfunction. However, the inability to increase left ventricular output and “effective” systemic blood flow enough to compensate for the left-to-right shunt may represent ventricular dysfunction or the limited capacity of the preterm left ventricle. The ventricular performance may be further limited by reduction of coronary blood flow. The improvement of cardiopulmonary status associated with ductal closure in preterm infants has been well described. Our observations in preterm lambs further suggest the potential benefits of early ductal closure to maintain or reestablish effective systemic perfusion in the preterm infant with a left-to-right ductal shunt.

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