Changes in Pericardial Pressure During the Perinatal Period

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Background. To determine how the tissues that surround the heart affect diastolic and systolic function during the perinatal period, we studied the pressure–diameter relation of the left ventricle in partially delivered fetal lambs.

Methods and Results. We anesthetized (1.5–2.0% halothane, balance O2) and ventilated six pregnant ewes (142–144 days of gestation) and then partially delivered each lamb by cesarean section. Each lamb was instrumented to record left ventricular anteroposterior diameters (endocardial ultrasonic transducers), pericardial pressure (liquid-containing balloon), and left ventricular pressure (transducer-tipped catheter). Left ventricular pressure–diameter relations were recorded under three conditions: initially, with a closed chest and closed pericardium (before ventilation); second, after interruption of the umbilical circulation and 1 hour of ventilation; and finally, when the lungs and the pericardium were retracted from the heart. Pericardial pressure (recorded at a common diameter, i.e., the maximal end-diastolic diameter recorded before ventilation) decreased by 48% after 1 hour of ventilation (p<0.05). After ventilation, left ventricular anteroposterior diameters were 4–5% greater (p<0.05) at each end-diastolic pressure compared (12.5, 15.0, 17.5, and 20 mm Hg). Thus, ventilation appeared to increase left ventricular diastolic compliance. Contractility also appeared to increase after ventilation when evaluated using ventricular stroke work as a function of end-diastolic pressure as preload. When we used a more appropriate measure of preload (i.e., transmural end-diastolic pressure), ventilation did not change left ventricular diastolic compliance or contractility. Thus, left ventricular systolic function increased because of an increase in preload.

Conclusions. The tissues surrounding the fetal heart significantly augment pericardial pressure and limit left ventricular preload. The initiation of ventilation reduces pericardial pressure, increases left ventricular preload, and increases left ventricular systolic function. At birth, a decrease in pericardial pressure and the resulting increase in preload may help increase left ventricular output through the Frank-Starling mechanism. (Circulation 1992;86:1615–1621)

KEY WORDS • pericardium • fetal heart • ventricular constraint

Cardiovascular function changes significantly at birth; heart rate, left ventricular stroke volume, left ventricular end-diastolic pressure, and left ventricular dimensions all increase.1–4 It is difficult to explain how left ventricular stroke volume increases at birth. The fetal heart traditionally is thought to have minimal cardiac reserve and to function at its maximum before birth.5–8 Interactions and changes in heart rate, contractility, catecholamine/autonomic stimulation, venous return, and afterload contribute to but do not totally account for the increase in left ventricular stroke volume at birth.1,4,9–13 Little is known about how ventricular preload, a major determinant of ventricular stroke volume, changes at birth.

It is known that the thoracic tissues (pericardium, lungs, and rib cage) constrain the heart by increasing pericardial pressure. Pericardial pressure limits the filling of the left ventricle during diastole and thus limits ventricular preload in the adult dog14–17 and in the young lamb.18 The pericardium also constrains the fetal heart and limits cardiac transmural pressure and thus limits preload.19 However, this limitation was not thought to affect cardiac output (although no concurrent assessment of cardiac output was performed). Recently, we have shown that this limitation of cardiac transmural pressure does, indeed, limit left ventricular stroke volume in exteriorized, anesthetized fetal lambs. In these fetal lambs an apparent lack of cardiac reserve in the control condition was a result of a limitation of ventricular preload.20 To demonstrate the total preload reserve of the heart, we retracted the lungs and pericardium from around the heart to eliminate pericardial pressure. Eliminating pericardial pressure increased cardiac transmural pressure at any end-diastolic pres-
sure and as a result increased left ventricular stroke volume.

It is not known how pericardial pressure influences the filling of the left ventricle of the lamb during the perinatal period. Therefore, we designed a study to assess how the tissues that surround the lamb heart affect pericardial pressure and influence left ventricular diastolic and systolic function in the perinatal period.

Methods

Preparation

Six pregnant ewes (mixed western breeds, 142–144 days of gestation) were anesthetized with sodium thiopental (25 mg/kg) and then ventilated with oxygen and 1.5–2.0% halothane. We performed a cesarean section and delivered the fetal lamb’s head into a saline-filled bag to prevent the fetus from breathing air. Each lamb (weight, 4.7±0.9 kg SD) was tracheotomized, and a closed tracheal tube was inserted. We then delivered the lamb’s upper body and positioned it supine on the ewe’s abdomen, taking care to maintain the umbilical circulation. A heating lamp was directed at the lamb to maintain body core temperature. The sternum of each lamb was split, and the pericardium was incised along the atrioventricular sulcus from the right atrium to the middle of the left atrium. Ultrasonic transducers were positioned on the left ventricular endocardial surface to assess mid left ventricular anteroposterior dimensions (Sonomicrometer 120, Triton Technology Inc, San Diego, Calif.).

We used a small (2×2 cm internal dimensions), flat, liquid-containing, silastic rubber balloon to measure pericardial pressure. The pericardial balloon was connected to a calibrated (0–50 mm Hg) transducer (model P23ID, Gould Inc., Oxnard, Calif.) and amplifier (model 13-4615-50, Gould Inc., Cleveland, Ohio). Each balloon was calibrated before being positioned on the left ventricular free wall. To maintain the original pericardial volume, we loosely approximated the pericardial incision without overlapping the edges. No effort was made to seal the pericardium because the pericardial balloons reflect pericardial pressure (compressive contact stress) accurately under these conditions. Finally, we closed the chest, made it airtight, and evacuated it with constant negative pressure (2–4 cm H₂O).

To measure left ventricular pressure, we inserted a transducer-tipped catheter (SPC-460, Millar Instruments, Houston, Tex.) into the left ventricle through the carotid artery. Left ventricular pressures were set to equal the fluid pressure recorded from the catheter’s central lumen. All pressures were referenced to the midplane of the left ventricle. In addition, we positioned a catheter in the axillary artery to allow sampling for blood gas analysis (IL System 1301, Instrumentation Laboratory Inc., Lexington, Mass.). A catheter was also placed into the left jugular vein to allow access for volume infusions.

Protocol

After a 15–30-minute recovery period, we studied each lamb under three different conditions. In each of the three conditions, left ventricular end-diastolic pressure–diameter relations were recorded over a range of end-diastolic pressures by rapidly removing and subse-

quent ly reinfusing lamb blood. Maternal blood was also infused in volumes sufficient to increase end-diastolic pressure to 20–25 mm Hg. Initially, we generated pressure–diameter relations while the umbilical circulation was intact, the lungs were free of air, and the chest and pericardium were closed. After this initial stage, we reduced the lamb’s blood volume to lower left ventricular end-diastolic pressure to approximately 10 mm Hg and then interrupted the umbilical circulation. At this time, we also began to ventilate the lambs (initially 15 ml/kg, 40 breaths per minute; oxygen and 0.5–1.0% halothane). Ventilatory rate and volume were adjusted to maintain the arterial PaCO₂ between 30 and 40 mm Hg. Throughout the first hour of ventilation, the trachea was momentarily opened to the atmosphere at 5-minute intervals and data were collected without altering blood volume. After 1 hour of ventilation, we again volume-loaded the lamb and recorded the left ventricular end-diastolic pressure–diameter relation. To eliminate any effect of ventilation on pericardial pressure, data were collected only during brief periods (approximately 10 seconds) when the trachea was open to atmospheric pressure. Spontaneous breathing was not observed during the data collection periods. Finally, we recorded the pressure–diameter relation after opening the chest, retracting the lungs, and widely incising the pericardium. At the end of each experiment, the lambs were killed by injection of KCl, and the position of the ultrasonic crystals and the calibration of the pericardial balloon were confirmed.

Assumptions

Assuming that a static equilibrium occurs at end diastole, left ventricular end-diastolic pressure must equal the sum of left ventricular end-diastolic transmural pressure and pericardial pressure. Pericardial pressure results from additional forces (per unit of area) applied to the heart by the surrounding tissues and is recorded by the pericardial balloon. The pressure surrounding the heart (pericardial pressure) becomes atmospheric when the rib cage, lungs, and pericardium are retracted from the heart. Under these conditions, the pressure within the ventricle (left ventricular end-diastolic pressure) equals the difference in pressure across the ventricular wall (i.e., left ventricular end-diastolic transmural pressure). Therefore, when the thoracic tissues have been retracted, a measurement of left ventricular end-diastolic pressure directly measures left ventricular end-diastolic transmural pressure. When the chest is closed, left ventricular end-diastolic transmural pressure can be calculated by subtracting pericardial pressure from left ventricular pressure.

Data Analysis

All data were recorded on chart paper (ES 1000, Gould Inc., Cleveland, Ohio) and onto FM tape (model 6500, Gould Inc., Cleveland, Ohio). We fitted curves to the means of five consecutive end-diastolic data points collected at each sampling interval using a cubic spline fit (SPSS GRAPHICS Smooth Fit, SPSS Inc., Chicago). Left ventricular end-diastolic diameters were interpolated from these curves over the range of left ventricular end-diastolic pressures common to all animals and all conditions (12.5 mm Hg, 15 mm Hg, 17.5 mm Hg, and 20 mm Hg). A two-way ANOVA for repeated measures
left ventricular end-diastolic diameter increased within 1 hour of the beginning of ventilation (Figure 2B, Table 1). (Note: We excluded one lamb from statistical analysis because of impaired systolic function, although its pressure–diameter relation displayed a similar response to ventilation.) We recorded the largest left ventricular diameters after opening the chest and pericardium (Figure 1 and Figure 2B). In every lamb, the calculated transmural pressure–diameter relation (left ventricular end-diastolic pressure minus pericardial end-diastolic pressure) both before and after ventilation closely approximated the directly measured left ventricular end-diastolic transmural pressure–diameter relation (open-chest and open-pericardial data, see Figures 1, 2B, and 3). This close approximation suggests both that our measurement of pericardial pressure was accurate and that myocardial compliance remained unchanged throughout the study.

At any ventricular diameter, pericardial pressure was greater before ventilation had begun than after 1 hour of ventilation (Figure 1, see vertical arrows). We selected the maximal left ventricular diameter observed before ventilation as a common diameter at which to compare the calculated pericardial pressures. At this diameter, the average calculated pericardial end-diastolic pressure decreased by 48% after ventilation (19±4 mm Hg before ventilation versus 10±2 mm Hg after ventilation, \( p < 0.05 \)).

After 1 hour of ventilation, systolic shortening of the left ventricular anteroposterior diameter increased significantly (Table 1). Left ventricular stroke work also tended to increase for any given left ventricular end-diastolic pressure after 1 hour of ventilation (Figure 2B), although this increase just failed to reach statistical significance (\( p < 0.056 \); see Table 1). The tendency for stroke work to increase after 1 hour of ventilation might suggest that contractility increased. However, when we compared the average pre- and postventilatory left ventricular stroke work data using end-diastolic diameters (Figure 2A) or end-diastolic transmural pressures (Figure 2C, open symbols) as measures of preload, there was no suggestion that contractility had changed. Because all of the data fell along a single curve, an increase in preload completely explained the increase in stroke work. An increase in contractility may, however, explain the increase in systolic shortening in one lamb. In this lamb, the increase in left ventricular shortening after ventilation was independent of changes in end-diastolic diameter.

In each lamb, the left ventricular end-diastolic pressure–diameter relation shifted toward the postventilation values within 10 minutes of beginning ventilation. The time required to approximate the 1-hour–postventilation pressure–dimension relation varied. Two lambs completed the transition within 5 minutes, two lambs required 10–20 minutes, and one lamb required 50 minutes.

The mean blood gas and pH data were within published ranges except for the initially elevated \( \text{Paco}_2 \) and reduced pH (Table 2). After we began to ventilate the lambs, we optimized ventilatory rate and volume to maintain \( \text{Paco}_2 \) between 30 and 40 mm Hg.
Figure 2. Graphs demonstrate that as predicted earlier, even though contractility does not change (panel A), the fact that ventilation shifts the intracavitary end-diastolic pressure–volume curve to the right (i.e., increases diastolic compliance, panel B) leads to the erroneous conclusion that contractility has increased if contractility is evaluated according to the conventional ventricular function curve analysis (panel C). Squares indicate data recorded before ventilation and triangles indicate data recorded after ventilation. Diamonds indicate data recorded after the chest and pericardium were opened widely. Open squares and triangles indicate transmural pressure data. Stroke work and left ventricular anteroposterior diameter (LVAPD) are expressed as percentages of the values observed when, in the postventilation state, left ventricular end-diastolic transmural pressure was 2.5 mm Hg (n = 5, mean ± SEM). Panel A: Left ventricular function curves using end-diastolic diameter as an indicator of effective preload. Note that pre ventilation and post ventilation data fall along a single curve, indicating no change in contractility. Panel B: Left ventricular end-diastolic pressure–diameter relations. After 1 hour of ventilation, the intracavitary pressure–diameter relation was shifted to the right, suggesting increased ventricular compliance. However, the left ventricular end-diastolic transmural pressure–diameter relation (open symbols) was not shifted, indicating that the passive material properties of the left ventricle did not change significantly. Note also that the open symbols are continuous with the data measured directly after the chest and pericardium were widely opened (diamonds), confirming that our measurement of pericardial pressure was accurate. Panel C: Left ventricular function curves using left ventricular end-diastolic pressure (LVEDP) as a measure of preload. When stroke work is plotted against intracavitary pressures (closed symbols), ventilation shifts the curve upward, suggesting an increase in contractility. However, when transmural end-diastolic pressure is used to represent preload (open symbols), the data form a single curve as was seen in panel A, indicating no significant change in contractility.

Discussion

Our studies have shown that the tissues that surround the heart of the perinatal lamb significantly limit left ventricular diastolic pressure by increasing pericardial pressure. Pericardial pressure decreased when we interrupted the umbilical circulation and ventilated the lambs. At a constant intracavitary pressure, this reduction in pericardial pressure increased left ventricular end-diastolic transmural pressure and left ventricular end-diastolic anteroposterior diameter. These increases constitute an increase in left ventricular preload and should increase stroke volume through the Frank-Starling mechanism.

Although previous investigations have shown that left ventricular diameters increase at birth, the mechanism for this increase was uncertain. Our studies confirm that the anteroposterior diameter of the left ventricle does increase with the initiation of breathing. Our results are also consistent with a previous observation in a single lamb that had suggested that these changes can occur immediately at birth. The increases in ventricular diameter that we observed resulted from a decrease in pericardial pressure. We cannot be certain how pericardial pressure decreased after ventilation was begun. It is unlikely that stretching of the pericardium led to the reduction in pericardial pressure. Unpublished studies from our laboratory show that a single volume challenge to 2-day-old lambs does not change the pressure–diameter relationship of the left ventricle. Furthermore, repeated volume loads to fetal lambs do not shift cardiac function curves.

In our experiments, left ventricular diameters increased by an average of 4–5% after ventilation. This

Table 1. Mean Left Ventricular End-Diastolic Transmural Pressure, Anteroposterior Diameter, Systolic Shortening, and Stroke Work at Four Levels of Left Ventricular End-Diastolic Pressure

<table>
<thead>
<tr>
<th>LVEDP (mm Hg)</th>
<th>Left ventricular end-diastolic transmural pressure (mm Hg)</th>
<th>End-diastolic diameters (mm)</th>
<th>Systolic shortening (mm)</th>
<th>Stroke work (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-ventilation</td>
<td>Post-ventilation</td>
<td>Pre-ventilation</td>
<td>Post-ventilation</td>
</tr>
<tr>
<td>12.5</td>
<td>0.9±1.5</td>
<td>2.8±0.9*</td>
<td>14.51±3.92</td>
<td>15.24±3.69*</td>
</tr>
<tr>
<td>15.0</td>
<td>1.7±1.4</td>
<td>4.0±1.7*</td>
<td>14.81±3.79</td>
<td>15.41±3.72*</td>
</tr>
<tr>
<td>17.5</td>
<td>2.1±1.7</td>
<td>4.8±2.0*</td>
<td>14.94±3.75</td>
<td>15.62±3.72*</td>
</tr>
<tr>
<td>20.0</td>
<td>2.7±1.7</td>
<td>5.6±3.7*</td>
<td>15.17±3.68</td>
<td>15.82±3.70*</td>
</tr>
</tbody>
</table>

Values are mean±SD, n = 5. LVEDP, left ventricular end-diastolic pressure. Stroke work is expressed as percentage of the value observed when, in the postventilation state, left ventricular end-diastolic transmural pressure was 2.5 mm Hg.

*Significantly different from pre-ventilation values, p < 0.05.
change was less than the 9% increase reported for human infants at birth.2 However, we may have already significantly reduced pericardial pressure by delivering the lamb's chest from the uterus. In utero, the forces applied to the fetus by the amniotic fluid and the maternal tissues should also augment pericardial pressure. This concept is supported by observations that left ventricular diameters change in response to changes in intrauterine pressure.1 Furthermore, in one lamb,1 left ventricular diameter increased immediately after vaginal delivery of the chest and increased further with the onset of ventilation. It is likely that the liquid-filled lungs and the positive pleural pressure (relative to atmospheric pressure2-7) of the fetus may apply more force to the heart than the air-filled lungs of the neonate. The time required to clear liquid from the lungs remains uncertain28-30 and can be up to 24 hours. Pericardial pressure may continue to decrease during the prolonged transition from liquid-filled lungs to air-filled lungs. Thus, our results most likely underestimate the total change in pericardial pressure that occurs with a vaginal delivery and the onset of breathing.

It is conceivable that our experimental manipulations may have artificially increased pericardial pressure. We used small, transverse incisions in the pericardium to avoid altering the characteristics of the pericardial sac overlying the ventricle. To avoid exaggerating pericardial pressure, we minimized the amount of instrumentation within the pericardial space and did not seal the pericardial incisions. Because each lamb acted as its own control, even the possibility of some unrecognized pericardial alteration does not, in any way, alter our most important finding—that the initiation of ventilation decreased pericardial pressure.

It has been suggested that fetal ventricular function is limited because of a less compliant myocardium.26 Our results indicate that reduced myocardial compliance is not responsible for the limitations in fetal cardiac function because the transmural pressure–diameter relation remains unchanged in the prevention, postventilation, and open-chest states. In another sense, a change in apparent ventricular compliance is the essence of our explanation for shifts in the pressure–diameter relation. Although the compliance of the myocardium remains constant, changes in pericardial pressure shift the end-diastolic pressure–diameter relation and therefore change the apparent ventricular compliance. The thoracic tissues determine the magnitude of pericardial pressure and the effective compliance of the left ventricle before and after birth.

Based on our current and previous results,20 we believe that the pericardial pressure significantly limits left ventricular diastolic filling and stroke volume. These results conflict with other studies that did not detect any effect of the pericardium on fetal cardiac function.7,8,19,27 These studies did, however, report that the pericardium influences the pressure–volume relations of the left and right ventricles in isolated fetal lamb hearts.27 Furthermore, pericardial pressure also limits the transmural filling pressure of the right atrium.28 The failure to record any effect of pericardial pressure on cardiac output in the past studies of chronically instrumented fetal lambs may arise from methodological problems. Reliance on fluid-filled catheters to record pericardial pressure in an unscaled pericardium may have underestimated pericardial pressure14 and consequently underestimated the magnitude of the pericardial effect. We have avoided this problem by using the liquid-containing balloon to record pericardial pressure. The excellent correspondence between our calculated left ventricular end-diastolic transmural pressure–diameter relations and the directly measured transmural pressure–diameter relations (Figure 1, Figure 2B) confirms that our pericardial balloons accurately recorded pericardial pressure (also see Figure 3).

Our results support the contention that elevations in end-diastolic pressure do not accurately reflect increases in left ventricular volume if pericardial pressure increases concomitantly.28 The apparent increase in stroke work observed at equal end-diastolic pressures (Figure 2C) could suggest that contractility increased after ventilation.29 However, analysis of the cardiac function curves in which more reliable measures of preload (left ventricular end-diastolic diameter [Figure 2A] or left ventricular end-diastolic transmural pressure [Figure 2C]) are used strongly suggests that the increase in cardiac function results solely from an increase in preload. Because end-diastolic pressure does not accurately reflect left ventricular preload, end-diastolic pres-

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**Table 2. Mean Blood Gas Data Recorded Under Each Condition of Study**

<table>
<thead>
<tr>
<th>Condition of Study</th>
<th>P\textsubscript{a}CO\textsubscript{2} (mm Hg)</th>
<th>P\textsubscript{a}O\textsubscript{2} (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventilation values</td>
<td>57±12</td>
<td>18±4</td>
<td>7.20±0.09</td>
</tr>
<tr>
<td>Postventilation values</td>
<td>31±5</td>
<td>96±23</td>
<td>7.38±0.08</td>
</tr>
<tr>
<td>Open-chest values</td>
<td>32±7</td>
<td>162±67</td>
<td>7.35±0.09</td>
</tr>
</tbody>
</table>

Values are mean±SD.
sure should not be used uncritically to assess cardiac function.\textsuperscript{29} A shift in the diastolic pressure–volume relation (Figure 2B) can produce a shift in the conventional ventricular function curve (i.e., stroke work versus left ventricular end-diastolic pressure, Figure 2A) even when contractility remains constant (Figure 2C; see also Figure 6 of Reference 2B).

How the slightly increased \( \text{PacO}_2 \) and decreased pH affected our results is uncertain. Acute respiratory acidosis (without ischemia) does not alter left ventricular diastolic compliance in adult dogs.\textsuperscript{30} Changes in pericardial pressure, not changes in myocardial compliance, completely account for the shift in the left ventricular end-diastolic pressure–diameter relation that we saw after ventilation (Figure 1, Figure 2B). Systolic function may, however, have been limited before ventilation by the hypercarbia and acidosis. Severe acidosis (pH 7.0) in the presence of hypoxemia does increase left ventricular end-diastolic pressure and decrease left ventricular \( \frac{dP}{dt} \) in young lambs\textsuperscript{31}; however, it is unlikely that the correction of this acidosis and the changes in blood gas status are the main contributors to the increase in systolic shortening that we observed after ventilation, as contractility did not change (Figure 2). Furthermore, we have recently studied the effect that pericardial pressure has on left ventricular stroke volume in partially exteriorized, anesthetized fetal lambs that were not ventilated. Throughout the study, these lambs had a similar blood gas and acid–base status as observed in the prevention portion of our current study. Even in the presence of slight acidosis (pH 7.22), left ventricular stroke volume increased significantly (65%) when we simply reduced pericardial pressure to zero.\textsuperscript{20}

It is also possible that the decrease in halothane concentration at the onset of ventilation may have contributed to the increase in systolic shortening. Similarly, this does not appear to be a major factor, because contractility did not change. Furthermore, the above-mentioned increase in left ventricular stroke volume\textsuperscript{20} occurred at a constant anesthetic level (1.5–2.0% maternal halothane). Parenthetically, anesthesia and acidosis are common complications of many deliveries; the conditions of our study may also be pertinent to these cases.

We also must consider the influence that right ventricular filling has on the left ventricle. Ventricular interaction may significantly influence left ventricular function in the perinatal period.\textsuperscript{11,32} We believe that changes in ventricular interaction are important in determining perinatal left ventricular output. Ventricular interaction and pericardial pressure are interdependent\textsuperscript{33}: An increase in right ventricular volume can decrease left ventricle volume both by displacing the ventricular septum to the left and simultaneously increasing pericardial pressure over the left ventricular free wall. The expanding right ventricle appears to compress the left ventricle between an encroaching septum and a constraining pericardium. Conversely, a decrease in right ventricular volume (for example, in response to a decrease in pulmonary vascular resistance) can increase left ventricular volume by allowing the ventricular septum to move to the right and by reducing pericardial pressure over the left ventricular free wall. This mechanism could explain in part our observations.

**Summary**

The present studies have shown that the tissues that surround the fetal heart significantly augment pericardial pressure and limit left ventricular preload (transmural end-diastolic pressure) by restricting diastolic filling. The initiation of ventilation reduces pericardial pressure, increases left ventricular end-diastolic transmural pressure, left ventricular anteroposterior diameter, and left ventricular systolic shortening. These studies suggest that, at birth, a decrease in pericardial pressure and the resulting increase in left ventricular end-diastolic volume may increase left ventricular output through the Frank-Starling mechanism independent of changes in contractility or afterload.

**References**

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