Hemodynamic, Pulmonary Vascular, and Myocardial Abnormalities Secondary to Pharmacologic Constriction of the Fetal Ductus Arteriosus

A Possible Mechanism for Persistent Pulmonary Hypertension and Transient Tricuspid Insufficiency in the Newborn Infant

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with the technical assistance of Michael Parkey, B.A., and Elizabeth Mayhew, B.S.

SUMMARY The prostaglandin synthetase inhibitor indomethacin was given orally or intravenously to pregnant ewes. This resulted in a significant rise in the fetal pulmonary-to-systemic arterial mean blood pressure difference across the ductus arteriosus, presumably secondary to constriction of the ductus arteriosus. In five experiments the pressure difference could be promptly but temporarily reversed by the administration of prostaglandin E\(_1\) (PGE\(_1\)) into the fetal inferior vena cava. Fetal lungs from study and control animals were fixed by perfusion at measured pulmonary arterial mean blood pressure, and fifth-generation resistance vessels were studied. The medial width/external diameter ratio was significantly increased in the study vs the control lungs due to increased smooth muscle and decreased external diameter. In addition, study fetuses had acute degenerative myocardial changes in the tricuspid valve papillary muscles, the right ventricular free wall and the interventricular septum. Similar changes were not seen in control fetuses. Indomethacin administration during pregnancy causes constriction of the fetal ductus arteriosus, fetal pulmonary arterial hypertension, and right ventricular damage. If severe, this may cause rapid fetal death. If less severe, in the newborn infant, this mechanism may be one cause of persistent pulmonary hypertension due to vasoconstriction and increased pulmonary arterial smooth muscle and/or tricuspid insufficiency due to papillary muscle infarction.

ENDOGENOUSLY PRODUCED prostaglandins actively dilate the fetal ductus arteriosus.\(^1\) Prostaglandin synthetase inhibitors given both directly to the mammalian fetus\(^5,\) \(^6\) and to the pregnant ewe\(^4,\) \(^5\) have been shown to constrict the fetal ductus arteriosus. This results in fetal pulmonary arterial hypertension, which has been shown to cause the development of excessive pulmonary arterial smooth muscle.\(^6\) It has been suggested\(^4,\) \(^6,\) \(^7\) that intrauterine constriction of the ductus arteriosus by either pharmacologic agents\(^5,\) \(^9\) or mechanical means\(^10\) may result in an alteration of the pulmonary vascular bed, and may be one etiologic mechanism of the syndrome of persistent pulmonary hypertension (PPHN) of the newborn infant (or persistent fetal circulation\(^1\)).

It has also been suggested\(^4,\) \(^5,\) \(^7\) that intrauterine constriction of the ductus arteriosus could possibly result in increased right ventricular afterload that would either dilate the right ventricle or damage the tricuspid valve papillary muscles and result in transient or permanent tricuspid insufficiency of the newborn infant. In order to investigate these possibilities, we produced intrauterine constriction of the ductus arteriosus by administration of the prostaglandin synthetase inhibitor, indomethacin, to the pregnant ewe,\(^4\) and studied the fetal pulmonary vasculature and myocardium.

Materials And Methods

Physiologic Preparation

Seven pregnant ewes from 123–139 days gestation (term 145–150 days) were given spinal anesthesia. The uterus was exposed and opened, and polyvinyl chloride catheters were inserted into the fetal inferior or superior vena cava, carotid or femoral arteries, and pulmonary arterial trunk. An intra-amniotic catheter was placed and all the catheters were brought out the left flank of the ewe.

We performed 10 experiments on seven ewes. On the first postoperative day, fetal pulmonary and systemic arterial and vena caval blood pressures and intra-amniotic pressure were measured in each ewe by means of a Beckman Dynograph recorder and Statham P23Db pressure transducers. Intra-amniotic pressure was used as zero reference. In eight of the 10 experiments performed on five ewes, 1 mg/kg maternal body weight of indomethacin (lyophilized powder dissolved in 0.9% sodium chloride solution to a concentration of 4 mg/ml) was given by slow intravenous infusion into the maternal venous catheter. In two ewes, blood pressure values returned to control levels 1–2 days after the original experiment; subsequently, indomethacin was given again and the blood pressure

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measurements were repeated (total of five experiments). One ewe was given indomethacin 0.5 mg/kg maternal body weight intravenously; 75 mg indomethacin was dissolved in water and given orally to another ewe three times daily for 4 days. Fetal pressure recordings were then repeated. Because the fetal ductus arteriosus is actively dilated by prostaglandins (probably PGE₃, PGE₂ or PGI₂) and indomethacin blocks the production of these substances, in five experiments in two ewes, a dose of 5 μg of PGE₂ was given via the fetal inferior vena cava after a pressure difference between pulmonary and systemic arterial blood pressures had been documented to determine if the effects of the indomethacin could be reversed.

Fetal systemic arterial blood gas tensions and pH determinations were performed at the time of the control blood pressure readings and when the blood pressure difference across the ductus arteriosus developed. Standard radiometer electrodes were used.

All comparisons of blood pressure measurements, blood gas tensions and pH were performed using an unpaired t test for similar groups.

### Pulmonary Vessels

After the experiments, the lungs from four study fetuses were fixed by perfusion of the vascular bed at the pulmonary arterial blood pressure measured in vivo by the method previously described. Briefly, a set of 150 7-μ serial sections was prepared from each lobe (the right upper, middle and lower, and the left upper and lower) of each fetus, and fifth-generation resistance vessels were identified, photographed and measured. The mean medial width, external diameter, and medial width/external diameter ratio were determined for each fetus and these values compared with those from six normal fetuses by the t test for independent means. Because in the control fetuses these values were not statistically significantly different throughout the entire period of gestation (85–140 days), the vessels from the study fetuses were compared with the vessels from all six of the control fetuses.

### Myocardium

The hearts from the eight study fetuses (one twin) and three control fetuses (intraoperative deaths from acute hemorrhage) were fixed with 3% glutaraldehyde. There was a delay of 2–6 hours from the time of death to the time of fixation of the hearts in both the study and control fetuses. Tissue blocks were obtained from the anterior and posterior tricuspid and mitral valve papillary muscles, the right and left ventricular free walls, and the interventricular septum. The blocks were embedded in paraffin, and 4-μ sections were stained with hematoxylin and eosin. Each section was coded and studied by one investigator without knowledge of its side or animal of origin. Each section was evaluated for histologic evidence of acute myocardial injury.

### Results

#### Physiologic Studies

In 10 experiments in seven animals, administration of indomethacin to the pregnant ewe resulted in an increase in the fetal pulmonary arterial-to-systemic arterial mean blood pressure difference, from 2.7 ± 2.0 mm Hg (range 0–6 mm Hg) to 14.1 ± 5.9 mm Hg (range 6–22 mm Hg, p < 0.001). This difference was caused by the development of significant pulmonary arterial hypertension (mean blood pressure increase from 46.8 ± 5.9 mm Hg to 55.7 ± 9.3 mm Hg, p < 0.025), not by systemic hypotension. Systemic arterial diastolic blood pressure did not change significantly (35.5 ± 7.4 to 33.9 ± 9.4 mm Hg). In the seven ewes, pulmonary hypertension was known to exist for a minimum of 1 day in two, 2 days in four, and

### Table 1. Fifth-Generation Resistant Vessels in Intrauterine Constriction of the Ductus Arteriosus

<table>
<thead>
<tr>
<th>Normal Gestational age</th>
<th>n</th>
<th>Medial width (μ)</th>
<th>External diameter (μ)</th>
<th>Medial width/external diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>85 days</td>
<td>70</td>
<td>6.09 ± 2.25</td>
<td>40.58 ± 10.97</td>
<td>0.16 ± 0.06</td>
</tr>
<tr>
<td>105 days</td>
<td>100</td>
<td>6.99 ± 4.24</td>
<td>40.80 ± 10.20</td>
<td>0.17 ± 0.04</td>
</tr>
<tr>
<td>120 days</td>
<td>124</td>
<td>5.89 ± 1.07</td>
<td>36.39 ± 7.90</td>
<td>0.16 ± 0.04</td>
</tr>
<tr>
<td>122 days</td>
<td>93</td>
<td>6.42 ± 1.71</td>
<td>44.02 ± 10.45</td>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td>135 days</td>
<td>32</td>
<td>7.12 ± 2.07</td>
<td>42.74 ± 14.37</td>
<td>0.17 ± 0.06</td>
</tr>
<tr>
<td>140 days</td>
<td>101</td>
<td>5.92 ± 1.29</td>
<td>34.19 ± 7.28</td>
<td>0.18 ± 0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experimental Gestational age</th>
<th>n</th>
<th>Medial width (μ)</th>
<th>External diameter (μ)</th>
<th>Medial width/external diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>129 days</td>
<td>25</td>
<td>12.51 ± 3.55</td>
<td>38.19 ± 8.36</td>
<td>0.33 ± 0.11</td>
</tr>
<tr>
<td>135 days</td>
<td>48</td>
<td>7.83 ± 2.22</td>
<td>34.48 ± 5.94</td>
<td>0.23 ± 0.05</td>
</tr>
<tr>
<td>137 days</td>
<td>50</td>
<td>8.65 ± 2.50</td>
<td>29.83 ± 8.22</td>
<td>0.30 ± 0.09</td>
</tr>
<tr>
<td>142 days</td>
<td>50</td>
<td>8.63 ± 2.23</td>
<td>34.71 ± 6.71</td>
<td>0.25 ± 0.05</td>
</tr>
</tbody>
</table>

Values are mean ± sd.
4 days in one. In five experiments, the blood pressure difference across the ductus arteriosus could be reversed transiently with the administration of PGE₁ given directly to the fetus via the inferior vena cava (pulmonary-to-systemic arterial mean blood pressure difference decreased from 18.8 ± 3.9 mm Hg to 6.0 ± 0 mm Hg, p < 0.001). The appearance of the pulmonary-to-systemic arterial blood pressure difference across the ductus arteriosus corresponded to the appearance of indomethacin in the fetal blood and suppression of maternal plasma prostaglandin levels.

Systemic arterial blood oxygen tensions (20.9 ± 4.9 to 18.2 ± 5.9 mm Hg), blood carbon dioxide tensions (36.6 ± 5.5 to 38.8 ± 7.9 mm Hg), and pH (7.38 ± 0.10 to 7.34 ± 0.10) did not change significantly after indomethacin.

**Pulmonary Vessels**

A total of 173 fifth-generation (resistance) pulmonary arteries from four study fetuses was compared with 529 fifth-generation vessels from six control fetuses (table 1). The medial width/external diameter ratio was significantly increased in the vessels from the study fetuses compared with those from the control fetuses. This increase was due to both a significantly increased medial width and a significantly decreased external diameter. The medial width was increased disproporionately to the reduction in vessel external diameter (table 2).

**Myocardium**

Early myocardial degenerative changes were seen in the anterior and posterior tricuspid valve papillary muscles in five of eight specimens, in the right ventricular free wall in three of eight, in the interventricular septum in three of eight, and in the mitral valve anterior and posterior papillary muscles in one of eight. In the affected areas the myocardial fibers showed increased eosinophilia, contraction bands, loss of cross striations, fragmentation of the sarcoplasm, and nuclear pyknosis indicative of acute myocardial injury (fig. 1). No such changes were seen in any sections from the hearts of the three control animals.

**Discussion**

When given to the pregnant ewe, indomethacin crosses the placenta and causes constriction of the ductus arteriosus and fetal pulmonary arterial hypertension. Blocking prostaglandin synthetase probably has a direct effect on pulmonary arterioles as well, because the vasodilators PGE₁ and PGE₂ are ac-

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**Figure 1.** Sections from the tricuspid valve posterior papillary muscle from a control fetus (A) and a fetus with intrauterine constriction of the ductus arteriosus due to the indomethacin (B). Note the loss of cross striations, fragmentation of the sarcoplasm and nuclear pyknosis in the study fetus.
tive in the fetal mammal. However, in the intact fetal circulation, it is unlikely that pulmonary vasoconstriction alone would result in pulmonary arterial hypertension, because the ductus arteriosus should be wide open. Some degree of constriction of the ductus arteriosus must occur for the pulmonary-to-systemic arterial blood pressure difference to be seen.

If severe enough, acute constriction of the fetal ductus arteriosus may possibly interfere with placental blood flow and myocardial performance and prove suddenly fatal to the fetus. If constriction of the ductus arteriosus is less severe or more chronic or both, fetal pulmonary arterial hypertension could result in the development of excessive pulmonary arterial smooth muscle and constriction of pulmonary arterioles. Although some of the increase in the medial width/external diameter ratio in the pulmonary arteries from the study animals could be accounted for by constriction alone, hypertrophy of vascular smooth muscle may begin as rapidly as during the 2-4-day period of these experiments. Hypertrophy of pulmonary vascular smooth muscle stimulated by hypoxia has been shown to occur as early as 2 days in the adult rat, and this process may be even more rapid in the fetus. In the newborn animal, this alteration of the pulmonary vascular bed could possibly result in a syndrome similar to PPHN of the newborn infant.

Transient tricuspid insufficiency in the newborn infant may be due to cardiac dilatation, but this does not explain cases in which histologic evidence of myocardial ischemia has been found. An increase in right ventricular end-diastolic pressure might produce subendocardial ischemia, particularly in the papillary muscles. The myocardial changes seen in this experimental circumstance are probably not due to a decrease in oxygen supply, since neither the blood oxygen tensions Nor the aortic diastolic blood pressures changed significantly. Prostacyclin (PGI₂) is known to dilate coronary vessels in the adult. It is possible that indomethacin may block PGI₂ in the fetal coronary arteries and interfere with coronary blood flow, thereby causing myocardial damage. Since the myocardial tissues were not rapidly fixed in the fresh state in either the study or control animals, the presence or absence of ischemic lesions is probably not due to a delay in fixation. Furthermore, if the lesions in the study animals were due to delay in fixation they would probably not be found almost exclusively on the right side. Because we found early degenerative myocardial changes, predominantly on the right side and especially of the tricuspid valve papillary muscles, intramural constriction of the ductus arteriosus may be one cause of permanent or transient tricuspid insufficiency and neonatal myocardial ischemia.

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An Evaluation of the Left Atrial/Aortic Root Ratio in Children with Ventricular Septal Defect

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SUMMARY Echocardiograms were performed in 80 infants and children with isolated ventricular septal defect (VSD) who underwent cardiac catheterization. The pulmonary-to-systemic flow ratio (Qp/Qs) was correlated with the echocardiographic left atrial-to-aortic root diameter ratio (LA/Ao), and a relatively poor correlation (r = 0.62) was found.

The end-systolic diameters of the left atrium and aorta at the level of the aortic root, obtained from lateral cineangiograms of 55 of the 80 patients, were compared with the corresponding echocardiographic dimensions. To assess the possible effect of transducer beam angulation upon the echocardiographic determinations, the angiographic measurements were made at 0° position (perpendicular to the frontal plane) and at angles of 5°, 10°, 15°, and 20° from zero, using the aortic root center as the point of intersection. The echocardiographic and angiographic aortic root measurements were comparable (r = 0.95), and the angiographically derived aortic diameter did not vary with different angle projections. However, the left atrial angiographic dimensions were significantly influenced by the angle of projection. We conclude that the echocardiographic LA/Ao ratio cannot reliably estimate the severity of the shunt flow in VSD.

THE INCREASED pulmonary blood flow resulting from ventricular septal defect (VSD) promotes enlargement of the left atrium and the left and right ventricles, but not of the aorta. The size of the left atrium relative to that of the aorta may, therefore, reflect the magnitude of the left-to-right shunt. Assessment of left atrial (LA) size by echocardiography has been carried out by Hirata in adults and, more recently, by Yabek et al. in children in whom the LA echocardiographic dimensions correlated well with the angiographically derived LA volumes. However, Hirata and later Brown et al. reported considerable overlap of the echocardiographic LA dimensions between normal subjects and patients with LA enlargement. They observed a wide range of normal values that improved somewhat after "normalization" of the echocardiographic measurements for body surface area. Brown et al. consequently proposed relating the echocardiographic LA diameter to that of the relatively nondistensible fibrous aortic root (Ao), as a ratio of LA to Ao dimension (LA/Ao ratio). The latter was found to be more sensitive than LA dimension alone for identifying LA enlargement.

The usefulness of "normalized" echocardiographic LA dimensions in the form of LA/Ao ratio or LA dimension/m² for predicting the severity of left-to-right shunting, particularly for serial measurements, has been investigated by a number of workers over the past 5 years, with various results; some have shown good correlation between echocardiographic LA/Ao ratio and Qp/Qs obtained at catheterization. In our experience, however, this correlation has not been consistent; it was excellent in some patients but quite poor in others. This study was carried out to determine the factors responsible for these observations and, in particular, to investigate the effect of LA geometry and transducer beam angulation on the echocardiographic LA and LA/Ao measurements.

Materials and Methods

Echocardiograms were obtained from 80 consecutive patients with isolated VSD, age 0.02–19.5 years (mean 4.8 years) and body surface area 0.18–1.8 m², admitted for hemodynamic evaluation. Six had repeat echocardiographic and catheterization studies 6 months to 2 years later. The echocardiograms were generally taken within 48 hours of catheterization...
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