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Pulmonary Vasculature Changes Associated with Idiopathic Closure of the Ductus Arteriosus and Hydrops Fetalis

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SUMMARY. **Antenatal closure of the ductus arteriosus has been considered as a potential risk factor for the development of hydrops fetalis and persistent fetal circulation of the newborn. We present an infant with antenatal ductal closure who had not received prenatal prostaglandin synthetase inhibitors. The pulmonary vascular morphological findings are described and compared to three additional infants in whom the ductus arteriosus was known to be patent; one with neonatal sepsis and two others with hydrops fetalis.**

The infants with fetal hydrops, regardless of etiology, had increased muscularization of the acinar pulmonary arteries. In addition, the infant with antenatal closure of the ductus arteriosus also had both a significant decrease in preacinar arterial external diameter and an increase in medial wall thickness. Antenatal closure of the ductus arteriosus appears to enhance *in utero* pulmonary blood flow and this may be the cause of pulmonary vascular remodeling.

KEY WORDS: **Ductus arteriosus — Hydrops fetalis — Antenatal ductal closure**

Antenatal closure of the ductus arteriosus has usually been associated with heart failure and hydrops fetalis [2, 8]. The heart failure appears to be related to pulmonary hypertension and right ventricular failure [22]. The majority of the reports describing fetuses with antenatal closure of the ductus arteriosus have occurred following the use of prostaglandin synthetase inhibitors, such as salicylates and indomethacin [1, 9, 12, 14]. Antenatal closure of the ductus arteriosus unrelated to either congenital heart defects or prostaglandin inhibitors is thought to be extremely uncommon [8, 10].

Infants with suspected antenatal ductal closure have had evidence of neonatal persistent pulmonary hypertension [1, 12, 14]. A morphometric analysis of the pulmonary vascular bed was performed in two of these infants who died and had received salicylates or indomethacin during pregnancy [12]. Levin et al. showed that these infants had an increased pulmonary arterial medial width to external diameter ratio due to increased smooth muscle in the walls of fifth-generation vessels [12]. They were unable to determine if the vessel changes were secondary to antenatal ductal closure or due to the prostaglandin inhibitor. Becker et al. studied the lungs of two infants who had premature contraction of the ductus arteriosus but found no abnormalities of the pulmonary vessels [2]. It was not noted whether the mother had received prostaglandin synthetase-inhibiting medications.

We present the lung morphometric analysis from an infant with antenatal closure of the ductus arteriosus, who did not receive antenatal prostaglandin inhibitors. To separate the morphometric findings from infants with other causes of fetal hydrops we also analyzed the lungs of two infants with fetal hydrops each with a patent ductus arteriosus. A third lung was analyzed from an infant of similar gestational age who died from neonatal sepsis.

Case Reports

Index Case

A 21-year-old white primigravida woman presented with premature labor at 35 weeks gestation with an otherwise uncomplicated pregnancy. The prenatal history was remarkable for ½ pack per day tobacco use and genital condylomata. There was no history

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of aspirin or nonsteroidal antiinflammatory drug use during the pregnancy.

Upon admission the physical examination revealed the patient to be in stable condition with membranes intact. The vital signs were normal and routine laboratory tests were unremarkable. Fetal ultrasound evaluation revealed polyhydramnios, fetal ascites, bilateral pleural effusions, and a small pericardial effusion. Fetal echocardiography 4 days prior to delivery revealed a structurally normal heart with diminished contractility of both ventricles and mild right ventricular hypertrophy. Doppler ultrasound imaging revealed mild, intermittent tricuspid regurgitation, undetectable flow through the ductus arteriosus and diminished right to left flow through the foramen ovale. An amniocentesis was performed for karyotyping and pulmonary maturity testing. Tocolytic therapy was initiated with terbutaline and subsequently magnesium sulfate, but failed and on day 4 of hospitalization a vaginal delivery followed.

Despite vigorous resuscitative measures, the newborn infant died in the delivery room from respiratory and circulatory failure. The infant was markedly edematous with bilateral pleural effusions and massive ascites. A postmortem hemoglobin was 13.8 g/dl and chromosome analysis revealed a normal male karyotype. Hemoglobin electrophoresis, maternal antibody tests, viral and bacterial cultures, and Kleihauer-Betke assays revealed no etiology for the hydropic condition.

An autopsy revealed evidence of mild right ventricular hypertrophy and the ductus arteriosus was anatomically closed and abnormal-appearing. There was marked wrinkling of the ductal intima indicating antenatal closure. The atrial septum was slightly deviated towards the left atrium and the foramen ovale was noted to be significantly narrowed.

Case 2

A 2800-g, 36-week gestation male infant was delivered vaginally after the spontaneous rupture of membranes. Shortly after delivery, the infant developed respiratory distress, poor perfusion, and cyanosis. Laboratory evaluations demonstrated a marked neutropenia, and group B streptococci were isolated from the blood cultures. Subsequently, the infant developed cardiorespiratory failure requiring mechanical ventilation and inotropic support and died at 8 h of age. At autopsy the heart was structurally normal, the ductus arteriosus was patent with an internal diameter of 5 mm, and the lungs were atelectatic.

Case 3

A 33-week gestation neonate was delivered via vaginal delivery to a preeclamptic mother. The biophysical profile and an ultrasound evaluation of fetal well-being indicated that the fetal condition had worsened. At birth, the infant was noted to be edematous and had marked respiratory distress. Further examination revealed bilateral pleural effusions, hepatomegaly, and ascites. The initial hemoglobin was 9.5 g/dl. On day 2 of life the infant died from congestive heart failure and hypotension. A Kleihauer-Betke test revealed 1.6% fetal cells which was equivalent to 56 ml of fetal blood. The clinical diagnosis of fetal hydrops was attributed to a large fetomaternal transfusion. At autopsy, the heart was noted to have mild right ventricular hypertrophy and right atrial enlargement, the ductus arteriosus was patent with an internal diameter of 8 mm, and the foramen ovale was patent and appeared to be of normal caliber.

Case 4

A 30-week gestation pregnancy was known by fetal ultrasonography to be complicated by idiopathic hydrops fetalis and polyhydramnios greater than 11 days duration. A cesarean section was performed following spontaneous rupture of membranes and onset of labor. Marked anasarca, large bilateral pleural effusions, and mild abdominal ascites were noted at birth. The infant was resuscitated and mechanically ventilated but died at 42 h of age from cardiorespiratory failure. Echocardiography during the first day of life revealed a large right-to-left ductus arteriosus shunt. The heart at postmortem examination revealed normal chamber dimensions, the ductus arteriosus was patent with an internal diameter of 5 mm. The lungs were atelectatic and bilateral pleural effusions were noted.

Methods

Lung morphometric analysis was performed on the right lung [6]. The lung was warmed in a water bath to 38°C and the pulmonary artery was then injected under 100 cmH_2O for 4 min with a radiopaque barium–gelatin–latex bead mixture which was heated to 60°C [3, 15]. The lung was then inflated to 24 cmH_2O with 10% buffered formalin and perfused at this pressure for 72 h. After fixation of the lung, its volume was determined by fluid displacement and a lung radiograph was obtained. Sections of the right upper, middle, and lower lobes were processed and embedded in paraffin. The 5-μm thick sections were stained with hematoxylin and eosin and with Miller van Gieson stain.

Volume proportions of the nonparenchymal and parenchymal structures of the lung and linear mean intercept were assessed as previously reported [3, 21]. Arterial wall thickness and extent of muscularization were categorized by the vessel external diameters: 21–49, 50–74, 75–99, 100–199, 200–299, 300–499, 500–699, 700–999, and 1000–1500 μm. Arteries at the terminal bronchiole–respiratory bronchiolar junction and vessels at the level of the second generation of the pulmonary artery (first branch of the right lower lobe) were also separately analyzed.

External diameter (ED) was defined as the distance between the outer edges of the external elastic lamina. Medial thickness (MT) was defined as the distance along the diameter from the luminal surface of the internal elastic lamina to the outer edge of the external lamina. The percent medial thickness was calculated as: $2 \times MT \times 100/ED$.

Radial alveolar counts (mean of 20 radial alveolar counts) were performed according to the method of Emery and Mithal [7]. The weights of the right and left lungs were measured. DNA content was analyzed from the left upper lobe and the total lung DNA was calculated [5]. Based upon ideal body weight, the lung DNA and wet weight to body weight ratios were computed.

Morphologic data were not corrected for tissue shrinkage due to fixation or processing. The data were analyzed by unpaired Student's t test or analysis of variance, and significance of difference between results was determined by Duncan's multiple analysis. Values were considered to be significantly different if $p < 0.05$. Results are expressed as mean values ± SD.

Results

Descriptive characteristics, heart and lung measurements, and histochemical results for each of the

Table 1. Comparative pulmonary measurements in infants with fetal hydrops

	Index case	Case 2	Case 3	Case 4
Gestational age (weeks)	36	36	33	30
Diagnosis	PDA closure	Neonatal sepsis	Fetomaternal transfusion	Idiopathic hydrops
Birthweight (g)	3680	2750	1800	3266
Ideal body weight (IBW) (g)	2600	2600	1800	1300
Heart weight (g)	12	19.9	13.9	9
Lung wet weight (g)	17.5[a]	59.9	24.8[a]	22.7[a]
Displacement lung volume/IBW (ml/g)	0.010[a]	0.044	0.022[a]	0.023[a]
Lung weight/IBW (mg/g)	0.007[a]	0.022	0.014[a]	0.017[a]
Lung DNA/IBW (mg/kg)	26[a]	94	85	43[a]
Ductal diameter (mm)	Closed	5	8	5
Radial alveolar count	4.7 ± 0.4	5.2 ± 0.3	3.3 ± 0.3	2.5 ± 0.5
Terminal bronchiole artery				
External diameter (μm)	39 ± 6[b]	65 ± 16	70 ± 2	39 ± 8[b]
Medial thickness (%)	8.8 ± 2[b]	5.1 ± 1.4	6.6 ± 0.6	13 ± 4[b]
Fraction vessels with muscle[c]	1.0 ± 0[b]	0.4 ± 10	1.0 ± 0[b]	1.0 ± 0[b]
Second-generation pulmonary artery entering right lower lobe				
External diameter (μm)	1467	2607	3099	1769
Medial thickness (%)	11.4	4.3	3.2	3.9
Area of medial muscle (mm^2)	0.326	0.426	0.471	0.187

Values are mean ± SD.
[a] Greater than 2 SD below mean.
[b] $p < 0.001$ compared to infant with neonatal sepsis.
[c] Terminal bronchiolar artery with muscle fully circumscribing vessel.

cases are provided in Table 1. Cardiac weights when expressed per ideal body weight were normal for age in each of the cases. Although the heart weight of the infant with antenatal ductal closure fell within the normal range for its gestational age when expressed per ideal body weight, it was the smallest of the four infants. The ductus arteriosus in this patient was anatomically closed and on section had a marked wrinkling of the intima. The foramen ovale was patent but narrowed. The other three infants had patent ductus arteriosus with normal vessel diameter (Table 1).

The three infants with hydrops fetalis had lung wet weights significantly lighter than normal and the lung volumes were significantly decreased. Lung DNA content was significantly decreased in the infant with antenatal ductal closure, as well as the patient with idiopathic hydrops. The percent of the lung that was parenchyma was normal and similar in the four infants. Radial alveolar counts were within the range of normal for all four infants. The mean linear intercept was significantly increased in the 30-week gestation infant with idiopathic hydrops (case 4), 138 ± 10 μm, in comparison to the other three infants, 88 ± 9 μm.

All the infants with hydrops had increased medial wall thickness of the acinar arteries (Fig. 1). In addition, at the terminal bronchiole–respiratory bronchiolar junction the percent of arteries with medial muscle extending completely around the circumference of the vessel was significantly increased in the infants with hydrops. The two infants known to have chronic hydrops, that is the infant with antenatal ductal closure and idiopathic hydrops, also had smaller terminal bronchiolar EDs compared to the control infant with neonatal sepsis (Table 1). The infant with antenatal ductal closure also had significantly increased medial wall thickness and a smaller external diameter at all levels of the pulmonary arterial tree (Fig. 1). Also, the medial area of the large preacinar arteries was disproportionately greater in comparison to the other infants with larger EDs suggesting that there was an increase in the smooth medial mass.

Discussion

Physiologically, the ductus arteriosus has an important role in maintaining the unique fetal circulation. Approximately 90% of the right ventricular output is shunted across the ductus, while the remainder perfuses the highly resistance pulmonary vascular bed [20]. Acute mechanical closure of the fetal ductus arteriosus causes a rapid onset of tricuspid regurgitation [13, 22]. It also increases pulmonary

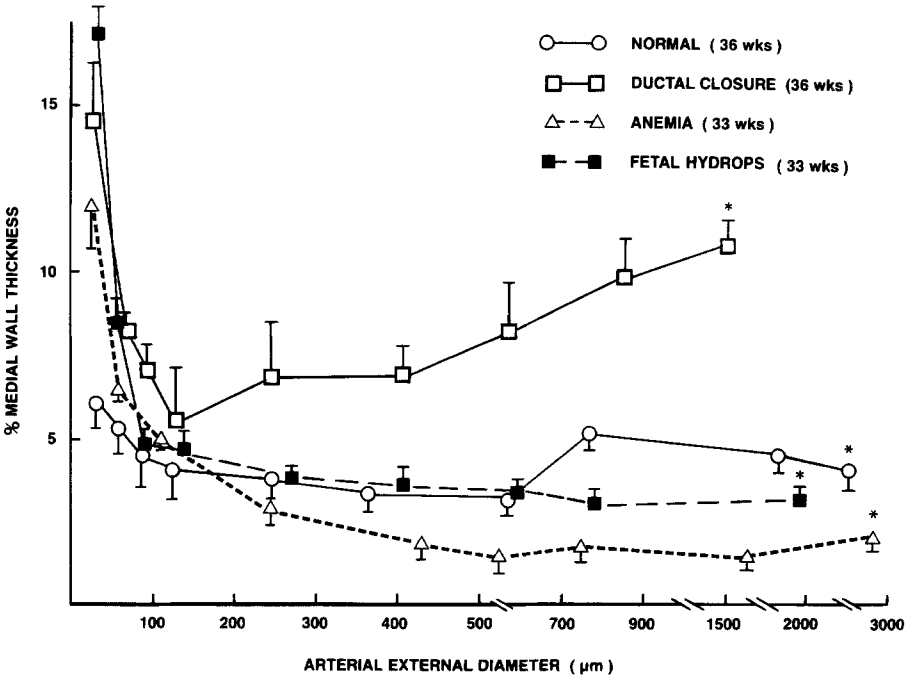

Fig. 1. The relationship between pulmonary artery external vessel wall diameter and percentage of medial wall thickness. The three infants with fetal hydrops had increased percentage medial wall thickness in vessels less than 100-μm external diameter. The infant with antenatal ductal closure had increased percentage medial wall thickness at all levels of the pulmonary vascular bed. The asterisks identify the ED and % medial wall thickness at the level of the second-generation pulmonary artery entering the right lower lobe.

blood flow out of proportion to the increasing pressure indicating a decreased pulmonary vascular resistance [17]. However, it is not known for how long these increases in fetal pressure and flow are maintained.

Morin [16] ligated the ductus arteriosus of fetal lambs 3–17 days before delivery. The lambs at delivery did not have hydrops. These newborn lambs did have a significantly elevated pulmonary arterial pressure and pulmonary resistance. Wild et al. [23] using a similar lamb model showed that the persistent pulmonary hypertension was secondary to increased muscularization of the pulmonary arteries starting at the level of the terminal bronchiole and continuing distally within the acinus. They interpreted their anatomical changes to be similar to the pathologic alterations reported in human neonates dying with idiopathic persistent pulmonary hypertension of the newborn (PPHN) [18]. On the other hand, in a guinea pig model of fetal ductal constriction using indomethacin, DeMello et al. failed to demonstrate evidence of distal extension of muscularization in the acinus [4]. However, they did show increased diameter of the preacinar arteries with an increased medial muscle mass.

Reports of premature closure of the ductus arteriosus in the human fetus have emphasized the complication of heart failure with fetal hydrops, while others have stressed the importance of pulmonary arterial increased muscularization and clinical pulmonary hypertension [2, 8, 12]. However, as shown in Table 1 and Fig. 1, infants born with heart failure and hydrops have increased muscularization of the pulmonary arterioles within the acinus regardless of whether the ductus arteriosus is antenatally patent or closed. In infants with heart failure and hydrops, the pulmonary vascular changes in part may be related to the small lungs and lung hypoplasia, most likely secondary to the large pleural effusions. In infants with congenital diaphragmatic hernia with hypoplastic lungs, neonatal pulmonary hypertension and increased muscularization of the acinar arteries is a common feature [11]. Of interest, the infant with antenatal ductal closure had severe hypoplastic lungs on the basis of small lungs and low DNA. However, the radial alveolar count was normal. This may in part be explained by the study of DeMello et al. [4] who in their model of fetal ductal constriction using indomethacin demonstrated increased radial alveolar counts suggesting accelerated alveolar development.

The infant with antenatal ductal closure had a unique vascular finding. That is, increased percent medial muscle thickness and decreased ED in all pulmonary arteries from the level of the alveolar duct to the large bronchi. This increased percent medial muscle thickness and mass at the bronchial airway level was not seen in the other infants with fetal hydrops (Table 1) and has been rarely reported in infants with PPHN [18, 19]. This difference suggests that the etiology of PPHN and the hypertension associated with antenatal closure of ductus may be different. The enhancement in pulmonary blood flow following closure of the fetal ductus arte-

riosus may play a role in the pulmonary vascular remodeling seen with this condition.

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