Early Hemodynamic Consequences of Patent Ductus Arteriosus in Preterm Infants with Intrauterine Growth Restriction

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Objective To test the hypothesis that significant patent ductus arteriosus (PDA) may occur very early after birth in preterm infants with intrauterine growth restriction (IUGR), we compared the longitudinal changes in left-to-right shunting through DA between eutrophic and preterm infants with IUGR.

Study design The preterm infants –26 to 32 weeks gestational age (GA), admitted in our neonatal intensive care unit from February to May 2004 were included. They were separated into an "IUGR of placental origin" group and an "eutrophic" group. Significant PDA was assessed by Doppler echocardiography at 6, 24, and 48 hours of age.

Results Thirty-one eutrophic (GA = 29 ± 1.4 weeks; birth weight [BW] = 1300 ± 160 g) and 17 infants with IUGR (GA = 29.3 ± 1.5weeks; BW = 810 ± 140 g) were studied. Six hours after birth, the rate of significant PDA was higher in the IUGR than in the eutrophic group (10/17 [60%] vs 5/31 [15%]; $P < .05$). More DA became significant in infants with IUGR (11/17 [65%]) than in eutrophic infants (12/31 [40%]) ($P < .05$) within the 48 hours after birth.

Conclusion Markers of high pulmonary blood flow and systemic vascular steal occur more frequently and earlier after birth in IUGR of placental origin than in eutrophic preterm infants. The management of preterm infants with severe IUGR of placenta origin should include early echocardiographic monitoring to assess for markers of significant PDA. *(J Pediatr 2007;151:624-8)*

Compared with preterm infants with appropriate weight for gestational age (GA), preterm infants with intrauterine growth restriction (IUGR) of placental origin are at high risk for neonatal death and morbidity.[1] In particular, excess pulmonary hemorrhage and chronic lung disease have been found in preterm infants with IUGR.[2-6] Furthermore, IUGR has been associated with increased severe intraventricular hemorrhage, necrotizing enterocolitis, and renal failure.[1,3-7] These complications are usually considered to be caused by uteroplacental insufficiency, fetal hypoxia, and pronounced redistribution of fetal blood flow leading to multiple organs dysfunction.[8]

However, several lines of evidence suggest that a hemodynamically significant patent ductus arteriosus (PDA) may contribute to an increase of the risk of adverse outcomes in preterm infants with IUGR: (1) a higher incidence of significant PDA was found in small for GA newborn infants[9,10]; (2) PDA is associated with poor outcome in infants with severe IUGR[11]; (3) the characteristic hemodynamic features observed in preterm infants with significant PDA including lower mean arterial blood pressure and blood flow velocity in the superior mesenteric artery, and increased cardiac output and heart rate, have been previously reported in small for GA newborn infants[9,12]; and (4) PDA and IUGR have been associated with similar adverse events such as pulmonary and intraventricular hemorrhage, necrotizing enterocolitis, and renal failure.[1-7,13-16] However, to our knowledge, assessment of PDA has not been investigated in the early postnatal period in preterm infants with IUGR of placental origin.

We hypothesized that significant left-to-right shunting through the ductus arteriosus (DA) may occur very early after birth in preterm infants with IUGR. To test this hypothesis, we compared the longitudinal changes in left-to-right shunting through DA between eutrophic and IUGR preterm newborn infants.

Ao	Aortic root	IUGR	Intrauterine growth restriction
BW	Birth weight	LA	Left atrial
CPAP	Continuous positive airway pressure	LPA	Left pulmonary artery
CRIB	Clinical risk index for babies	NICU	Neonatal intensive care unit
DA	Ductus arteriosus	PDA	Patent ductus arteriosus
GA	Gestational age		

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METHODS

We prospectively included all preterm newborn infants from 26 to 32 weeks GA admitted to our neonatal intensive care unit (NICU) from February and May 2004. Exclusion criteria were: cardiac malformations other than PDA, maternofetal infection, need for vasoactive drugs, IUGR of nonplacental origin, and outborn infants. The infants were separated into two groups: (1) a group of infants with IUGR, defined as a diminished growth velocity in the fetus documented by at least two intrauterine echographic growth assessments and a birth weight (BW) <10th percentile (Lubchenko curves); and (2) a group of eutrophic infants, defined as normal growth velocity in the fetus and a BW >10th percentile. The placental origin of the IUGR had been determined during pregnancy by Doppler evaluation of uterine and umbilical arteries.

Heart rate, arterial blood pressure (noninvasive measurement), blood gases, and serum lactate concentrations were recorded at 6 hours of age. A clinical risk index for babies (CRIB) score was calculated. Echocardiography was carried out 6 hours after birth using a General Electric® VIVID echocardiographic system (GE Vingmed Ultrasound AS N-3190, Hosten, Norway) with a high-frequency 7.5 MHz transducer. An average of three to five consecutive readings for the vessel diameter and flow velocity integrals was used. The angle of insonation was <20 degrees. The following Doppler echocardiographic variables were measured:

- LA:Ao ratio: M mode pictures of LA (left atrial) and the Ao (aortic root) were obtained from a parasternal long axis view;
- Internal diameter of the DA by both B mode and color Doppler from the high-left parasternal view;
- End-diastolic flow velocity of the LPA was measured with pulsed Doppler using a high-left parasternal view;
- Left ventricle shortening fraction from a parasternal long axis view;
- Superior mesenteric resistance index was also recorded as an estimate of the diastolic steal.

Significant left-to-right shunting through the DA was defined by the detection of the following concomitant four echocardiographic criteria[12]: ductal diameter (B mode and color Doppler) ≥1.5 mm, left atrial/aortic root ratio (LA:Ao) ≥1.4, pulsatile low blood flow velocity in the DA, and an end-diastolic flow velocity of the LPA ≥0.20 m/s. Significant PDA was treated with intervenous ibuprofen (Pedea®, Orphan Europe, loading dose of 10 mg/kg then two maintenance doses of 5 mg/kg at 24-hour intervals). DA was reevaluated by an echocardiogram with color-Doppler-flow at 24 and 48 hours after birth in infants who did not receive ibuprofen, that is, in infants whose DA was considered as nonsignificant at 6 hours of age. An ibuprofen course was then started if substantial PDA was detected. An additional echocardiogram was performed on day 7 after birth in each of the included infants.

Mortality, respiratory (duration of mechanical ventilation, duration of nasal continuous positive airway pressure [CPAP], chronic lung disease defined as oxygen dependency at 36 postconceptional weeks), and digestive (necrotizing enterocolitis, date at full-feeding) outcomes were compared between both groups.

Table I. General characteristics of the studied population

	Eutrophic (n = 31)	IUGR (n = 17)	*P*
Gestational age (weeks)	29 ± 1.4	29.3 ± 1.5	NS
BW (g)	1300 ± 160	810 ± 140	<.01
Birth height (cm)	39 ± 1	33 ± 1	<.01
Head circumference (cm)	27.2 ± 0.5	24.4 ± 0.5	<.01
Antenatal corticosteroids	27 (87%)	16 (94%)	NS
RDS	20 (64%)	9 (52%)	NS
CRIB score	2.5 ± 0.6	4.5 ± 0.7	<.05

Data are expressed as mean ± SD.
BW, birth weight; *CRIB,* clinical risk index for babies; *IUGR,* intrauterine growth restriction; *NS,* nonsignificant; *RDS,* respiratory distress syndrome.

The parents were informed of the management protocol. As the present protocol was part of the usual management of premature newborn infants in our NICU, no consent from the parents was requested.

Statistical analysis: Tests were performed using StatView® for PC (Abacus Concepts; Statview, Cary, NC). Quantitative variables were compared using Student's nonpaired *t* test, qualitative variables were compared using χ^2 tests. Log-rank test was performed to compare the cumulative rate of significant DA between groups. A $P < .05$ was considered as statistically significant.

RESULTS

Within the study period, 55 preterm infants from 26 to 32 weeks GA were admitted in our NICU. Four were outborn and three required vasoactive drugs for severe sepsis (two eutrophic, one IUGR): they were excluded from the study. Forty-eight infants were eligible for inclusion. There were 31 eutrophic (GA = 29 ± 1.4 weeks; BW = 1300 ± 160 g) and 17 growth-restricted newborn infants (GA = 29.3 ± 1.5 weeks; BW = 810 ± 140 g). The GA did not differ significantly between groups, but BW, birth height, and head circumference were significantly lower in the IUGR group, as expected (Table I). Exogenous surfactant (Curosurf® 200mg/kg, SERONO, France) was given to each infant within the first 30 minutes of life, except in two infants with IUGR and three eutrophic infants without respiratory failure.

The groups were not statistically different for antenatal corticosteroids and the occurrence of respiratory distress syndrome (Table I). The CRIB score was higher in the IUGR group (Table I). At birth, blood lactate concentration was higher in the IUGR than in the eutrophic group (eutrophic vs IUGR: 4.5 ± 1.9 vs 6.2 ± 2.4 mmol/L, $P < .05$).

At 6 hours of age, both groups were similar regarding heart rate (eutrophic vs IUGR: 125 ± 13 vs 140 ± 12 beats/min), and systolic (57 ± 9 vs 56 ± 7 mmHg) and mean