Cardiac Morphology and Function in Preterm Growth Restricted Infants: Relevance for Clinical Sequelae

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Objectives To assess cardiac morphology and function in preterm infants with fetal growth restriction (FGR) compared with an appropriate for gestational age cohort, and to ascertain clinical correlation with neonatal sequelae.

Study design With informed consent, 20 infants born between 28 and 32 weeks of gestational age and birthweight (BW) <10th percentile were compared using conventional and tissue Doppler echocardiography with 20 preterm appropriate for gestational age infants. Total duration of respiratory support was recorded.

Results The gestational age and BW of the infants with FGR and appropriate for gestational age infants were 29.8 ± 1.3 weeks vs 30 ± 0.9 weeks ($P = .78$) and 923.4 ± 168 g vs 1403 ± 237 g ($P < .001$), respectively. Preterm infants with FGR had significantly greater interventricular septal hypertrophy, greater free wall thickening, and lower sphericity indices (1.53 ± 0.15 vs 1.88 ± 0.2; $P < .001$), signifying globular and hypertrophied hearts. The transmitral E/A ratio and isovolumic relaxation time, markers of diastolic function, were significantly increased in the FGR cohort (0.84 ± 0.05 vs 0.78 ± 0.03 [$P < .001$] and 61.4 ± 4.1 ms vs 53.2 ± 3.2 ms [$P < .001$], respectively). Ejection fraction, as measured by the rate corrected mean velocity of circumferential fiber shortening was reduced (1.93 ± 0.4 circ/second vs 2.77 ± 0.5 circ/second; $P < .001$) in the FGR cohort. On follow-up, the total duration of respiratory support was significantly longer in the FGR cohort, and correlated with tissue Doppler E/E' ($r = 0.65$; $P = .001$), mean velocity of circumferential fiber shortening ($r = -0.64$; $P = .001$) and mitral annular peak systolic excursion ($r = -0.57$; $P = .008$).

Conclusions Preterm infants with FGR have altered cardiac function evident within days after birth, which is associated with respiratory sequelae. *(J Pediatr 2017;188:128-34).*

Fetal growth restriction (FGR) describes a fetus who does not grow to their expected potential owing to compromise during pregnancy. FGR complicates 5%-10% of human pregnancies, and is associated with increased risks for perinatal morbidity and mortality, commonly exacerbated by preterm birth.[1,2] Low birthweight (BW), whether caused by preterm birth and/or FGR, has profound long-term health consequences for cardiovascular, metabolic, and neurologic dysfunctions.[3-5] The developmental programming concept describes a robust relationship between in utero FGR and cardiovascular or metabolic disorders that may not become evident until adulthood.[6] FGR is caused principally by placental insufficiency, in which the placenta fails to deliver an adequate supply of oxygen and nutrients to the developing fetus. In turn, chronic hypoxia induces circulatory adaptations in the fetus in an effort to maintain brain and heart growth, but these adaptations may also program structural and functional vascular and cardiac changes.[4] During fetal development, cardiac adaptation may be evident on fetal ultrasound imaging as impaired relaxation and increased globularity, and increased myocardial workload, which is accompanied by increased coronary artery flow.[7] At birth, increased atrial natriuretic peptide and cardiac troponin levels in umbilical cord blood have been noted in infants with FGR, indicative of subclinical myocardial involvement.[8,9] Strong echocardiographic (ECHO) evidence exists for the

AGA	Appropriate for gestational age
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BW	Birthweight
ECHO	Echocardiographic
ESWS	End-systolic wall stress
FGR	Fetal growth restriction
GA	Gestational age
IVRT	Isovolumic relaxation time
LV	Left ventricular
MPI	Myocardial performance index
mVCFc	Mean velocity of circumferential fiber shortening
PDA	Patent ductus arteriosus
TDI	Tissue Doppler imaging

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link between FGR and fetal cardiovascular adaptation; however, there remains a knowledge gap in the identification of cardiac impairments in preterm infants with FGR soon after birth.

Conventional ECHO is regarded as the mainstay for analysis of cardiac function and has been used to describe impaired relaxation in term infants with FGR soon after birth.[10,11]

Tissue Doppler imaging (TDI) has increased sensitivity to detect subclinical cardiac dysfunction.[11,12] TDI permits quantitative assessment of the movement and timing of myocardial events, and has provided a quantifiable measure of cardiac function in neonates in other disease states such as severe bronchopulmonary dysplasia (BPD).[13] In fetal assessments of growth restricted infants undertaken at 30 ± 3 weeks' gestational age (GA), Comas et al[12] showed increased left myocardial performance index (MPI) but comparable transmitral E/A velocities, whereas TDI findings suggested altered systolic and diastolic function with lower systolic and diastolic velocities and higher E'/A' ratios. After birth, preterm infants with FGR also showed a hypertrophied interventricular septum and free left ventricular (LV) wall.[14] However, a comprehensive assessment of altered cardiac structure and function soon after birth in preterm infants with FGR has not been undertaken previously. Early identification would allow a mechanistic understanding of the earliest observable cardiac dysfunctions that underlie long-term deficits.

The objective of this study was to assess cardiac morphology and function in preterm infants with FGR compared with an appropriate for gestational age (AGA) cohort using conventional and TDI ECHO. Cardiac function measures in the FGR cohort were correlated with respiratory sequelae.

Methods

The study was approved by the Institutional Research Ethics Board and informed parental consent was obtained. This study was conducted at a quaternary center with facilities to care for preterm infants from 23 weeks GA onward. Twenty infants between 28 and 32 completed weeks of GA with a BW <10th percentile for GA were recruited as FGR cases, and compared with 20 preterm AGA infants of the same GA range. GA was determined by fetal dating ultrasound examination. Infants <28 weeks GA were excluded because they are more likely to have patent ductus arteriosus (PDA), which influences ECHO measurements. All ECHO assessments were performed in the second week of life and infants with a PDA on the initial scan were reassessed at the end of the second week; continued patency of the duct was an a priori exclusion criteria. Infants >32 weeks of age are transferred routinely to stepdown nurseries unless they require continued respiratory support, and thus are less likely to be available for ECHO assessments. Our selected population born between 28 and 32 weeks of gestation also reflects the majority of moderate to severe early-onset FGR cases. Infants with possible asphyxia (5-minute Apgar score <5), congenital malformations/heart disease or chromosomal abnormalities, or born to mothers with diabetes were excluded. Infants were followed prospectively to the time of discharge to ascertain outcomes such as the total duration of respiratory support, the need for home oxygen, and the total duration of hospital stay. Baseline neonatal characteristics were recorded. Body surface area was calculated using DuBois and DuBois formula.[15] Noninvasive blood pressure (BP) measurements were obtained using an appropriate-sized cuff on the right arm with the infant in a quiet state and positioned supine before the ECHO assessment (model Intelli Vue MX 800; Philips, Boeblingen, Germany). The average values of 2 readings were recorded.

ECHO studies were performed by a single operator using the Vivid 7 Advantage Cardiovascular Ultrasound System (GE Medical Systems, Milwaukee, Wisconsin), with the infant in the supine position. Offline analysis was performed using EchoPAC software (GE Healthcare, Horten, Norway) without revealing group identity. No sedation was used, and infants were swaddled by parents or nursing staff. **Table I** (available at www.jpeds.com) depicts the measures studied.[16-26] End-systolic wall stress (ESWS) and isovolumic relaxation time (IVRT) percentage of cardiac cycle were assessed as measures of afterload.[21,27] ESWS was evaluated as described previously.[21] Transmitral A wave velocity time integral/total velocity time integral was assessed as a measure of ventricular compliance.[27] It is a fetal measure and may be affected by breathing and LV filling in the postnatal period. LV wall motion velocities were assessed by pulsed-wave TDI through an apical 4-chamber view as previously described.[19,28] All Doppler measurements were calculated from an average of 3 consecutive cardiac cycles.

For Doppler studies, the angle of insonation was kept to <15° and no angle correction was used. **Figure 1** (available at www.jpeds.com) depicts MPI assessment. The MPI was calculated from Doppler data by the equation (IVCT + IVRT)/LVET, where IVCT is the isovolumic contraction time, IVRT is the isovolumic relaxation time, and LVET is the LV ejection time.

We assessed the effect of FGR vs AGA on cardiac measures via general linear regression models with group as a categorical variable. Data were analyzed using Stata software version 11 (StataCorp, College Station, Texas) and SPSS version 18 (PASW Statistics for Windows; SPSS Inc, Chicago, Illinois). Descriptive statistics were used to summarize baseline clinical and ECHO characteristics. Comparisons between the groups were performed using the Student *t* test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables, and the Fisher exact test for categorical variables. To account for the confounding effects of GA, adjusted analyses were performed by including these variables as covariates in the regression models. Post hoc comparisons were performed using Bonferroni adjustment for multiple comparisons.

Correlations between variables were assessed by Pearson or Spearman rank correlation where appropriate. A 2-sided $P < .05$ indicated statistical significance. Continuous variables were summarized using mean (standard deviation) or median (IQR) where appropriate. Categorical variables were expressed as counts and proportions.