Evolution of Left Ventricular Function in the Preterm Infant

Akiko Hirose, MD, Nee S. Khoo, MBChB, Khalid Aziz, MBBS, FRCPC, Najlaa Al-Rajaa, MD, Jutta van den Boom, MBChB, Winnie Savard, BScN, MN, Paul Brooks, MBBS, and Lisa K. Hornberger, MD, *Edmonton, Alberta, Canada*

Background: The aim of this study was to evaluate left ventricular function in preterm infants from 28 days to near term using echocardiography.

Methods: Thirty clinically stable preterm infants delivered at <30 weeks' gestational age were prospectively enrolled. At 28 days, conventional, tissue Doppler, and speckle-tracking echocardiography evaluations of left ventricular function were performed, with comparison made to findings in 30 healthy term infants of similar postnatal age. Sixteen preterm infants underwent repeat examinations near term.

Results: Compared with controls, preterm infants at 28 days had decreased peak mitral valve (MV) E-wave velocities ($P < .01$), E/A ratios ($P < .0001$), annular e′ velocities ($P < .0001$), and e′/a′ ratios ($P < .0001$); increased MV E/e′ ratios ($P < .01$); and lower basal circumferential early diastolic and higher late diastolic strain rates. No significant differences were found in fractional shortening, ejection fraction, and longitudinal or circumferential strain and strain rate between preterm infants and controls. Although preterm infants at 28 days had higher heart rates compared with controls (161 ± 15 vs 142 ± 16 beats/min), no significant correlations existed between heart rate and MV E, E/A ratio, e′, e′/a′ ratio, and E/e′ ratio. Near term, the differences in diastolic function persisted, including decreased MV e′/a′ ratio ($P < .05$), increased E/e′ ratio ($P < .01$), and increased late diastolic strain rate.

Conclusions: Clinically stable preterm infants have normal left ventricular systolic function but altered diastolic function, with greater dependence on atrial contraction, the latter of which persists despite nearing term. These findings may be relevant to the management of preterm infants and may relate to the longer term myocardial dysfunction observed in affected adults. (J Am Soc Echocardiogr 2014;■:■-■.)

Keywords: Premature infant, Myocardial function, Echocardiography

Both clinical and translational investigations have suggested that the fetal myocardium changes its systolic and diastolic functional performance throughout gestation, with increasing ability to contract and relax and increasing compliance.[1–9] At birth, dramatic changes occur as a consequence of the transition from fetal to neonatal circulation. These include increases in combined cardiac output with the transition from a parallel to an in-series circulation and acute changes in the preload and afterload of both ventricles.[10,11] Premature birth results in an earlier transition to the postnatal circulation during a period in which the myocardium may be less mature. The functional maturation of the myocardium of preterm infants remains incompletely understood.

The aim of our prospective study was to investigate left ventricular (LV) systolic and diastolic functional characteristics of preterm infants delivered before 30 weeks of gestation, with comparison with healthy term neonates of comparable postnatal age using state-of-the-art echocardiographic investigations. We hypothesized that the myocardium of the preterm heart would exhibit differences in both systolic and diastolic function from that of the term heart more akin to the function of the fetal heart, but that these differences would resolve near term.

METHODS

Study Population

We prospectively enrolled clinically stable, appropriate for gestational age preterm infants delivered at <30 weeks' gestational age and admitted to the neonatal intensive care unit at Royal Alexandra Hospital, University of Alberta, from January 2010 to December 2012. We excluded any neonate with a congenital

From the Fetal & Neonatal Cardiology Program, Department of Pediatrics, Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada (A.H., N.S.K., N.A.-R., J.v.d.B., W.S., P.B., L.K.H.); Department of Pediatrics, Division of Neonatology, University of Alberta, Edmonton, Alberta, Canada (K.A.); and the Department of Obstetrics and Gynecology, Women's & Children's Health Research Institute, Mazankowski Alberta Heart Institute, Cardiovascular Research Centre, University of Alberta, Edmonton, Alberta, Canada (L.K.H.).

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Reprint requests: Lisa K. Hornberger, MD, Fetal & Neonatal Cardiology Program, Pediatric Cardiology, Stollery Children's Hospital, WMC 4C1.19 8440-112 Street, Edmonton, AB T6G 2B7, Canada (E-mail: *lisa.hornberger@albertahealthservices.ca*).

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Abbreviations

CPAP = Continuous positive airway pressure

LV = Left ventricular

PDA = Patent ductus arteriosus

SR = Strain rate

anomaly or syndrome and those with important complications of prematurity potentially affecting cardiorespiratory function, including respiratory distress syndrome requiring ventilation at the time of the investigation, sepsis, moderate or large patent ductus arteriosus (PDA) or necrotizing enterocolitis. We also excluded those with maternal disease such as diabetes, all monochorionic twins, and any babies who were small for gestational age given the potential impact of such conditions on myocardial function. This investigation was approved by the human ethics board of the University of Alberta, and written informed consent was obtained from each participating patient's parents.

Echocardiography was performed in 30 preterm infants at 28 days of age to avoid the period of acute hemodynamic changes related to the presence of a large PDA, acute respiratory pathology, and changing pulmonary vascular resistance. In 16 infants, echocardiographic examinations were repeated near term (corrected gestational age, 38.5 ± 2.4 weeks). Echocardiography was performed in 30 prospectively recruited healthy term newborns at a similar postnatal age for comparison.

Echocardiographic Examinations

All echocardiographic examinations included two-dimensional imaging, M-mode imaging, and pulsed-wave and tissue Doppler interrogation for the detailed evaluation of cardiac anatomy and myocardial function, with a specific focus on LV function. These examinations were performed using a Vivid 7 or Vivid q (GE Healthcare, Milwaukee, WI) with a 10-MHz phased-array transducer, optimizing two-dimensional images for a higher frame rate for speckle-tracking echocardiography. The study was carried out in the neonatal intensive care unit or in a quiet examination room, with the infant lying quietly awake or asleep in a supine position. Heart rates and blood pressure were documented at the time of acquisition of functional data. All imaging was recorded for further offline measurement and analysis.

LV shortening was measured from M-mode tracings acquired with interrogation of the left ventricle in a standard parasternal long-axis view. LV ejection fraction was calculated using the Teichholz method from M-mode images.[12]

Blood flow through the mitral valve was interrogated using pulsed Doppler from the apical four-chamber view, with placement of a 2- to 3-mm sample volume immediately distal to the tips of the valve leaflets. Peak E wave (early diastolic phase), A wave (atrial systolic phase), and their ratio (E/A) were obtained from three cardiac cycles and averaged (Figure 1). Annular myocardial velocities were acquired using Doppler tissue imaging from an apical four-chamber view by placing a 2- to 3-mm sample volume along the LV free wall just below the mitral valve annulus. Myocardial velocities of s′ (ventricular systole), e′ (early diastole), and a′ (atrial systole); isovolumic contraction time; isovolumic relaxation time; and ejection time were measured on three cardiac cycles and averaged (Figure 1). E/e′ ratio, e′/a′ ratio, and myocardial performance index ([isovolumic relaxation time + isovolumic contraction time]/ejection time) were calculated. Two-dimensional grayscale images were analyzed by speckle-tracking echocardiography using commercially available software (EchoPAC version 7.1, GE Medical Systems, Waukesha, WI) for strain and strain rate (SR) estimation. For longitudinal analysis, grayscale images were recorded from the apical four-chamber view. For circumferential analysis, images were recorded from the parasternal short-axis view at the LV base and apex. Global peak strain, SR, early diastolic SR, and late diastolic SR were measured in each imaging plane.

Statistical Analysis

All measures are expressed as mean ± SD. Differences in measures between groups were compared using Student *t* tests for normally distributed data and Mann-Whitney *U* tests for data not normally distributed. Normality of the distribution of the data was determined by the Kolmogorov-Smirnov normality test. P values $< .05$ were considered significant. All data analysis was performed with commercially available statistical software (Prism for Windows version 5.04; GraphPad Software, La Jolla, CA).

RESULTS

General Clinical Characteristics

Thirty infants were enrolled for the preterm and 30 for the control term group. Reasons for preterm delivery included preterm labor ($n = 13$), preterm premature rupture of membranes ($n = 11$), abruption ($n = 4$) and hemolysis, elevated liver enzymes, and low platelet count syndrome ($n = 2$). Table 1 summarizes the general clinical data of the groups. No significant difference was observed in postnatal age between preterm and term infants at the time of the echocardiographic evaluation (28.2 ± 0.5 and 27.9 ± 6.8 days, respectively). Small, restrictive PDAs were observed in five preterm infants, all of whom had no clinical symptoms or signs related to the PDAs, and the following were seen on echocardiography: normal left atrial and LV size, no mitral insufficiency, and no holodiastolic flow reversal in the abdominal aorta. Sixteen of the 30 preterm infants underwent repeat assessment at or near term (corrected gestational age, 38.5 ± 2.4 weeks; range, 36–42 weeks). None of the 16 were on supplemental oxygen at the time of the repeat study. Of the remaining 14 preterm infants, 12 were not reevaluated, because they had been discharged from the neonatal intensive care unit to an outlying local nursery ($n = 1$) or home and were unable (because of distance) or not willing to return for follow-up ($n = 11$). Two others could not have their repeated studies assessed, because of technical issues with data storage. No infants needed rehospitalization during the follow-up period.

LV Function in Preterm Infants

Table 2 summarizes the systolic and Doppler-based diastolic LV functional data for the preterm infant cohort obtained at 28 days' postnatal age, with comparison with data from the term controls. No differences in LV shortening or ejection fraction were observed between preterm infants and controls. MV peak E ($P < .01$), E/A ratios ($P < .001$), peak e′ ($P < .001$), and e′/a′ ratios ($P < .001$) were significantly lower in preterm than in control infants. E/e′ ratios were higher in preterm infants ($P < .01$). Heart rates in preterm infants were higher than in controls ($P < .001$); however, there were no significant correlations between heart rate and peak E, E/A ratio, e′, and e′/a′ ratio. No significant difference for any functional parameter was found between preterm infants on continuous positive airway pressure (CPAP) and those not on CPAP. No significant difference in LV longitudinal and apical circumferential strain and SR were observed