Natural History of Postnatal Cardiopulmonary Adaptation in Infants Born Extremely Preterm and Risk for Death or Bronchopulmonary Dysplasia

Hussnain Mirza, MD[1], Jorge A. Garcia, MD[2], Elizabeth Crawford, RDCS[3], Julie Pepe, PhD[4], Matthew Zussman, MD[2], Rajan Wadhawan, MD[1], and William Oh, MD[5]

Objective To study the natural history of postnatal cardiopulmonary adaptation in infants born extremely preterm and establish its association with death or bronchopulmonary dysplasia (BPD).

Study design This was a prospective, observational, cohort study of infants born extremely preterm (<29 weeks). Initial echocardiogram was performed at <48 hours of life, followed by serial echocardiograms every 24-48 hours until 14 days of life. Resolution or no resolution of pulmonary hypertension (PH) at 72-96 hours was considered normal or delayed postnatal cardiopulmonary adaptation, respectively. PH between 96 hours and 14 days was defined as subsequent PH. Elevated pulmonary artery pressure throughout the 14 days of life was considered persistent PH. BPD was assessed at 36 weeks of postmenstrual age.

Results Sixty infants were enrolled; 2 died before a sequential echocardiogram could be done at 72-96 hours. Normal and delayed cardiopulmonary adaptation were noted in 26 (45%) and 32 (55%) infants, respectively. Five patterns of postnatal cardiopulmonary adaptation were recognized: normal without subsequent PH (n = 20), normal with subsequent PH (n = 6), delayed adaptation without subsequent PH (n = 6), delayed adaptation with subsequent PH (n = 16), and persistent PH (n = 10). Infants with delayed cardiopulmonary adaptation were of lower gestation and birth weight and required prolonged ventilation and supplemental oxygen ($P < .05$). On multivariate analysis, the incidence of death or BPD was significantly greater among infants with delayed adaptation ($P < .001$).

Conclusion Infants born extremely preterm have normal or delayed postnatal cardiopulmonary adaptation that can be complicated by subsequent or persistent PH. Delayed cardiopulmonary adaptation is associated independently with death or BPD. *(J Pediatr 2018;■■:■■-■■).*

Pulmonary vascular resistance (PVR) is elevated during fetal life.[1] As a result, all infants are born with elevated pulmonary artery pressure (PAP) and go through a process of postnatal cardiopulmonary adaptation. In healthy infants born at term, PVR falls rapidly following the first breath to increase pulmonary blood flow. PAP declines to less than one half of the systemic systolic blood pressure (SBP) within the first 24 hours.[2] The natural history of postnatal cardiopulmonary adaptation in infants born extremely preterm is unknown.

In animal models, even a few minutes of pulmonary hypertension (PH) can induce significant lung injury.[3] Significantly greater risk for bronchopulmonary dysplasia (BPD) recently was reported among infants born extremely preterm with early PH.[4-6] However, the reported incidence of early PH is widely variable, in the range of 9%-42%. This variation is likely due to the difference in the timing of screening for early PH (1-6 weeks of life).[4-6] The optimal time for early PH screening in this high-risk population is unknown.

PH may be a primary or secondary condition. Possible underlying etiologies for neonatal PH include increased PVR due to hypoxia or inflammation, chronic left-to-right shunts, pulmonary hypoplasia, alveolar capillary dysplasia, anatomic obstruction to pulmonary blood flow, and lung atelectasis or hyperinflation.[7-10] In infants born preterm, a number of variables such as severe respiratory distress syndrome,[11,12] impaired myocardial contractility, and poor tolerance to high systemic vascular resistance also may cause elevated PAP.[13] The primary objective of this study was to determine the natural history of postnatal

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
iNO	Inhaled nitric oxide
NICU	Neonatal intensive care unit
PAP	Pulmonary artery pressure
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
SpO_2	Pulse oximetry
RV	Right ventricle/right ventricular
TR_{max}	Peak velocity of tricuspid regurgitation

From the [1]Center for Neonatal Care, Florida Hospital for Children/University of Central Florida College of Medicine; [2]Division of Pediatric Cardiology, Florida Hospital for Children, Orlando, FL; [3]Division of Pediatric Echocardiography, Florida Hospital Cardiovascular Institute, Orlando, FL; [4]Office of Research Advancement and Support, Florida Hospital; and [5]Center for Pediatric Research, Florida Hospital for Children, Orlando, FL

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cardiopulmonary adaptation in infants born extremely preterm. We also hypothesized that infants born extremely preterm with delayed postnatal cardiopulmonary adaptation are at increased risk for death or BPD.

Methods

This was a prospective, observational, cohort study. All infants born extremely preterm before 29 weeks of gestation and admitted to the neonatal intensive care unit (NICU) at Florida Hospital for Children were eligible. We excluded infants with any major congenital anomaly or genetic syndrome.

The study was approved by our institutional review board. Infants were enrolled after we obtained a parental informed consent. Initial echocardiogram was obtained within the first 48 hours of life and serial echocardiograms were performed every 24-48 hours until 14 days of life. Study echocardiograms were performed via a predefined imaging protocol to assess tricuspid regurgitation (peak velocity of tricuspid regurgitation [TR_{max}]), patent ductus arteriosus (PDA) gradient, end-systolic interventricular septal position (in multiple acoustic planes), gradient across ventricular septal defect, patent foramen ovale/atrial septal defect flow, and screening for pulmonary vein stenosis, mitral valve stenosis, cor triatriatum, or left ventricular outflow track obstruction. If an echocardiogram was requested by the neonatology team, study data were retrieved from the clinically indicated imaging. Echocardiograms were interpreted by 1 of the 2 pediatric cardiologists.

All infants were monitored for changes in fraction of inspired oxygen (FiO_2) and pulse oximetry (SpO_2) during the echocardiography. The FiO_2 was adjusted to keep the SpO_2 in a clinically acceptable range as defined in our NICU clinical guidelines (alarm limits at 85%-95%). Mode of respiratory support and systemic SBP were noted at the time of echocardiography. Systemic SBP was determined via a transducer connected to the umbilical arterial catheter. In the absence of an umbilical arterial catheter, an appropriate-size limb cuff was used to measure the systemic SBP via oscillometer.

In reading the echocardiograms, our primary focus was to identify and measure TR_{max}. We calculated right ventricular (RV) pressure gradient using the modified Bernoulli equation (RV pressure = $4 \times [TR_{max}^2]$). PAP was estimated by adding 5 to the RV gradient (to adjust for right atrial pressure). In the absence of measurable TR_{max}, PAP was estimated by calculating the PDA gradient, if available. We applied standard methodology to calculate the PDA gradient, ie, systemic SBP – $(4 \times PDA_{max}^2)$ for left to right shunting or systemic SBP + $(4 \times PDA_{max}^2)$ for right-to-left or bidirectional shunting. PH was defined as mild or none if estimated PAP was less than one half of systemic systolic blood pressure, moderate if PAP is more than one half, but less than systemic systolic blood pressure, and severe if PAP is equal or greater than systemic systolic blood pressure.

In the absence of TR_{max} or PDA, PAP was estimated by the end-systolic interventricular septal configuration at the papillary muscle level in short-axis view from multiple acoustic windows, ie, left parasternal, right high parasternal, and subcostal. Abnormal septal position was reported only if it was evident in ≥2 acoustic views. Mild or no PH was represented by the normal end-systolic septal configuration, a flat septal position was taken as evidence for moderate PH, and reverse bowing of septum was considered severe PH.[6,14] Clinically significant findings on the study echocardiograms, ie, severe PH, large PDA, severe ventricular dysfunction, etc, were conveyed to the attending neonatologist responsible for the clinical care of the infant. Management of the infants was at the discretion of the attending physicians.

If the estimated PAP at 72-96 hours of life was <50% of the systemic systolic blood pressure, the infant was considered to have normal postnatal cardiopulmonary adaptation. Echocardiographic evidence of PH at 72-96 hours of life was categorized as delayed postnatal cardiopulmonary adaptation. Subsequent PH was defined as echocardiographic evidence of PH during days 5-14 of life. Continuously elevated PAP up to the age of 14 days was termed persistent PH. BPD was diagnosed if there was a need for positive pressure ventilation or supplemental oxygen to maintain normal oxygen saturation at 36 weeks of postmenstrual age. We did not perform an oxygen reduction challenge for infants on supplemental oxygen at 36 weeks of postmenstrual age. Maternal and neonatal demographic and clinical data were collected from electronic medical charts.

Statistical Analyses

Two-tailed proportions test was used for power analysis. For a power of 80% and alpha of 0.05, assuming a ratio of 1:1 for normal and delayed postnatal cardiopulmonary adaptation and estimated incidence of death or BPD up to 80% for delayed postnatal cardiopulmonary adaptation and 40% for the normal postnatal cardiopulmonary adaptation, the calculated sample size was 56 infants. Assuming 6%-8% mortality in infants born extremely preterm after the enrollment and before successful implementation of serial echocardiographic measurements, we planned to enroll a total of 60 infants in the study.

Descriptive statistics for continuous variables are reported as median and IQR. For categorical variables, frequencies and percentages are reported. Infants with and without delayed postnatal cardiopulmonary adaptation were compared via the χ^2 test of independence or Mann–Whitney *U* comparison. Bivariate analysis and logistic regression were performed to determine the risk for death or BPD among infants with delayed vs normal postnatal cardiopulmonary adaptation. Logistic regression tests included Box–Tidwell, Hosmer–Lemeshow, and residual analysis. All tests were 2-tailed, and a value of 0.05 was selected for statistical significance.

Results

From March 2015 through April 2016, 77 infants of <29 weeks of gestation were admitted or transferred to the NICU of Florida Hospital for Children. Three infants died before the initial echocardiogram, 5 mothers were not available for acquisition of informed consent within 48 hours of delivery, 8 mothers declined consent, and 1 infant was excluded due to the complex congenital cardiac defect.

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