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A Patent Ductus Arteriosus Severity Score Predicts Chronic Lung Disease or Death before Discharge

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Objectives To test the hypothesis that a patent ductus arteriosus (PDA) severity score (PDAsc) incorporating markers of pulmonary overcirculation and left ventricular (LV) diastolic function can predict chronic lung disease or death before discharge (CLD/death).

Study design A multicenter prospective observational study was conducted for infants <29 weeks gestation. An echocardiogram was carried out on day 2 to measure PDA diameter and maximum flow velocity, LV output, diastolic flow in the descending aorta and celiac trunk, and variables of LV function using tissue Doppler imaging. Predictors of CLD/death were identified using logistic regression methods. A PDAsc was created and a receiver operating characteristic curve was constructed to assess its ability to predict CLD/death.

Results We studied 141 infants at a mean (SD) gestation and birthweight of 26 (1.4) weeks and 952 (235) g, respectively. Five variables were identified that were independently associated with CLD/death (gestation at birth, PDA diameter, maximum flow velocity, LV output, and LV a′ wave). The PDAsc had a range from 0 (low risk) to 13 (high risk). Infants who developed CLD/death had a higher score than those who did not (7.3 [1.8] vs 3.8 [2.0], $P < .001$). PDAsc had an area under the curve of 0.92 (95% CI 0.86-0.97, $P < .001$) for the ability to predict CLD/death. A PDAsc cut-off of 5 has sensitivity and specificity of 92% and 87%, and positive and negative predictive values of 92% and 82%, respectively.

Conclusions A PDAsc on day 2 can predict the later occurrence of CLD/death further highlighting the association between PDA significance and morbidity. *(J Pediatr 2015;167:1354-61)*.

Treatment of a patent ductus arteriosus (PDA) in extremely low birth weight preterm infants is controversial.[1] Randomized controlled studies of PDA treatment have failed to demonstrate a reduction in PDA-associated morbidities, which include intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), chronic lung disease (CLD), death, and poor neurodevelopmental outcome.[2-8] Those trials demonstrate an overall failure to physiologically categorize PDA severity with methods ranging from using poorly validated clinical signs, treating the PDA as an all or none phenomenon, and those that use a number of echocardiography signs one of which is PDA diameter. Hemodynamic significance relates to the volume of the shunt from the systemic to the pulmonary circulation. The resultant flow across the shunt will lead to increased pulmonary blood flow (pulmonary overcirculation) at the expense of systemic blood flow (systemic hypoperfusion). The magnitude of this shunt (and how the heart handles it) may explain the association between a PDA and the above-mentioned morbidities. Therefore, a more comprehensive appraisal of those physiological features in the presence of a PDA using echocardiography may improve our understanding of hemodynamic significance.

Recently, the relationship between the severity and duration of the ductal shunt and the evolution of CLD in preterm infants has been further highlighted.[9] The presence of significant early shunting leading to increased pulmonary blood flow reduces lung compliance and may expedite the inflammatory process leading to CLD evolution.[10,11] There is further scope to accurately define early hemodynamic significance, determine the optimum time of assessment, and relate these to important outcomes such as CLD. The aim of this study was to identify PDA characteristics associated with CLD or death and devise a PDA severity score (PDAsc) set at an optimal timepoint during the first week of life that can predict CLD or death before discharge (CLD/death).

AUC	Area under the curve	NEC	Necrotizing enterocolitis
CLD	Chronic lung disease	PDA	Patent ductus arteriosus
CLD/death	CLD or death before discharge	PDAsc	PDA severity score
IVH	Intraventricular hemorrhage	TDI	Tissue Doppler imaging
LV	Left ventricular/Left Ventricle	Vmax	Maximum flow velocity
LVO	LV output	VTI	Velocity time index

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Methods

This was a multicenter prospective observational cohort study conducted in tertiary neonatal intensive care units in Ireland, Canada, and Australia. Institutional research ethics board approval was obtained at all participating sites. All preterm neonates admitted to neonatal intensive care units with a gestational age less than 29 weeks were considered eligible for inclusion. Parents of all eligible infants were provided with an information sheet and fully informed with written consent prior to enrollment. Infants with major congenital abnormalities and cardiac lesions other than PDA were excluded from this study. Neither prophylactic indomethacin nor medical treatment of the PDA with nonsteroidal anti-inflammatory drugs was used during the first 7 days of life in enrolled patients. Treatment beyond the first week of life was at the discretion of the attending neonatologist and was primarily driven by dependence on invasive ventilator support. Management of hypotension during the study period was based on local hospital guidelines employing a combination of fluids and inotropes. Echocardiograms performed for the assessment and management of hypotension were not part of this study and no PDA management was instituted to reverse hypotension. The approach to pulmonary hemorrhage management was fluid and red blood cell transfusion and increased mean airway pressure. All cases of pulmonary hemorrhage were relatively mild requiring minimal treatment. Furosemide was not used during the study period (first week of life). All furosemide use occurred beyond the first 2 weeks of age either during blood transfusions or to improve clinical symptoms of evolving CLD. Continuous furosemide infusions were not used in the patient cohort. The results of the echocardiograms were not communicated to the medical team caring for the infants unless they specifically requested a clinically indicated echocardiography assessment or if congenital heart disease was identified.

Antenatal, birth, and clinical characteristics were collected including gestational age and birthweight at delivery, sex, mode of delivery, 5-minute Apgar score, cord pH, the use of antenatal steroids, magnesium sulphate administration, the presence of pre-eclampsia, and chorioamnionitis. The following clinical outcomes were also recorded: culture proven sepsis; inotrope and furosemide use; postnatal steroids administration; PDA treatment beyond day 7 of age (including PDA ligation); NEC with radiologic evidence of pneumatosis intestinalis; IVH assessed on day 7 of age and classified according to Papile classification[12]; CLD defined as the need for oxygen at 36 weeks postmenstrual age; treated retinopathy of prematurity; length of hospital stay; and death before discharge.

Echocardiography Assessment

Echocardiography scans were performed at 3 time periods: a median (IQR) of 10 hours (7-12) (day 1), 43 hours (38-47) (day 2), and 144 hours (125-164) (day 5-7). Evaluations were performed using the Vivid (GE Medical, Milwaukee, Wisconsin) or Phillips (Andover, Massachusetts) echocardiography systems in accordance with recent published guidelines.[13] A comprehensive anatomic assessment was conducted for the first echocardiogram of each infant to rule out congenital heart disease other than a PDA or a patent foramen ovale. All scans were stored in an offline archiving system for later measurements.

A comprehensive echocardiography assessment of PDA characteristics, markers of pulmonary overcirculation and systemic hypoperfusion, and left ventricular (LV) function was performed. The following echocardiography measurements were obtained during each assessment (description of the methodology used to obtain those measurements are detailed elsewhere)[13-15]: narrowest PDA diameter (mm) measured using 2-dimensional methods at the pulmonary end (color Doppler was not used to assess PDA diameter); maximum shunt velocity across the PDA (maximum flow velocity [Vmax] in m/s); LV output (LVO in mL/kg/min); mitral valve inflow E wave, A wave, and E:A; pulmonary vein diastolic velocity (m/s); left atrial to aortic root ratio; and descending aortic, celiac artery, and middle cerebral artery end diastolic flow (in m/s). Tissue Doppler imaging (TDI) of the apical 4-chamber view was used for LV systolic (s′), early diastolic (e′), and late diastolic (a′) velocities using a pulsed wave Doppler sample gate of 2 mm at the level of the lateral mitral valve annulus. If the e′ and a′ waves were fused, we measured the single wave as an a′ wave.

Measurement technique was standardized across all hospitals. Specifically, LVO was measured as follows: the aortic root diameter was measured at the hinges of the aortic valve leaflets from the long axis parasternal view used to calculate the aortic cross-sectional area. The velocity time index (VTI) of the ascending aorta was measured from the pulsed wave Doppler from the apical 5-chamber view. The cursor was aligned to become parallel to the direction of flow. No angle correction was used, and an average of 3 consecutive Doppler wave forms was used to estimate the VTI. LVO (mL/kg/min) was determined using this formula: (aortic cross-sectional area × VTI × heart rate) ÷ weight.

Statistical Analyses

The cohort was divided into 2 groups based on the presence of the primary outcome defined as a composite of CLD/death. We investigated longitudinal trends in echocardiography variables, measured across the 3 timepoints, between infants with and without CLD/death. This analysis was performed to identify the ideal timepoint for creating the PDAsc to predict CLD/death. Univariate analysis was conducted on all the measured echocardiography variables comparing infants with and without CLD/death. Continuous variables were tested for normality using the Shapiro-Wilk test and presented as means (SD) or median (IQR) as appropriate. Two group analyses were conducted using a Student t test or a Mann-Whitney U test as appropriate. A 2-way repeated measures ANOVA was used to assess the difference in the echocardiography measurements between infants with and without CLD/death across the 3 timepoints. Pair wise