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

Afif EL-Khuffash, FRCPI, MD, DCE[1,2], Adam T. James, MB[1], John David Corcoran, MD, FRCPI[1,2], Patrick Dicker, MSc, CStat[3], Orla Franklin, MB, MRCPCH[4], Yasser N. Elsayed, MD[5], Joseph Y. Ting, MD[6], Arvind Sehgal, MD[7,8], Andra Malikiwi, MD[7], Andrei Harabor, MD[9], Amuchou S. Soraisham, MD[9], and Patrick J. McNamara, MD, MRCPCH[10,11]

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

From the [1]Department of Neonatology, The Rotunda Hospital; Departments of [2]Pediatrics and [3]Biostatistics, The Royal College of Surgeons in Ireland; [4]Department of Pediatric Cardiology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland; [5]Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba; [6]Department of Pediatrics, University of British Columbia, Vancouver, British Colombia, Canada; [7]Monash Newborn, Monash Children's Hospital; [8]Department of Pediatrics, Monash University, Melbourne, Australia; [9]Department of Pediatrics, University of Calgary, Calgary, Alberta; [10]Division of Neonatology, The Hospital for Sick Children; and [11]Departments of Physiology and Pediatrics, University of Toronto, Toronto, Ontario, Canada

Funded by the European Union (FP7/2007-2013 under 260777) and Friends of the Rotunda (FoR/EQUIPMENT/101572). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.09.028

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

comparisons with Bonferroni adjustment were conducted if ANOVA was significant. Categorical variables were presented as proportions, and compared using the χ^2 or Fisher exact test as appropriate. We accepted a P value of <.05 as significant. SPSS v 21 (SPSS Inc, Chicago, Illinois) was used to perform the statistical analysis.

Developing the PDAsc

Measurements from the day 2 scan were used to devise the PDAsc. During this timepoint, several echocardiography markers were significantly different between those with and without the primary outcome (a composite of CLD and/or death before discharge). On day 1, the echocardiography markers were more homogenous in the entire cohort with less difference between the 2 groups (**Figure 1**; available at www.jpeds.com). We decided a priori not to interrogate the predictive value of the day 5-7 scan as it would delay the identification of a clinically significant PDA. In addition, clinical signs of a PDA would be more overt by the first week of life.

All echocardiography variables of pulmonary overcirculation and systemic hypoperfusion were considered for inclusion in the multivariate logistic regression model used to devise the PDAsc. In addition, we included functional variables of the left ventricle measured using TDI. Gestation at delivery expressed in whole weeks and days (as 2 decimal points) was included a priori in the model as it is an important determinant of CLD/death evolution in this population. Echocardiography measurements were entered into the model and retained if their association with CLD/death remained significant with gestation. Variables that were highly correlated with others (collinearity) and those with no predictive value (P value > .10) were removed from the final model. Four echocardiography variables were included in the final model: PDA diameter (mm), maximum velocity across the PDA shunt (m/s), LVO (mL/kg/min), and LV diastolic function (LV free wall), measured as an a′ wave using TDI (cm/s). The variables in the final model were tested for collinearity. All the variance inflation factor values were less than 1.5.

We also examined the effect of including cardiorespiratory characteristics measured at the time of the scan in the model (mean airway pressure, inspired oxygen, oxygen saturation, and systolic/diastolic blood pressure) in addition to gestation and the 4 chosen echocardiography markers to assess whether this would improve its predictability. Although there was a statistically significant difference in those measurements between the 2 groups during the day 2 scan, those differences were very small in magnitude and were not clinically relevant (**Table I**). There was a significant positive correlation between gestational age and all of those measurements, and none improved the ability of the model to predict the outcome of interest.

A weighted scoring system based on the beta coefficients of the significant predictors was used to derive the PDAsc.[16] The following equation was used to derive the risk score for each infant: (gestation in weeks × −1.304) + (PDA diameter in mm × 0.781) + (LVO in mL/kg/min × 0.008) + (maximum PDA velocity in m/s × −1.065) + (LV a′ wave in cm/s × −0.470) + 41, where 41 is the constant of the formula. This score ranges between 0 (low risk) and 13 (high risk). The predicted probability for each infant to develop CLD/death was also derived from the model. Infants without a PDA at the time of the scan were assigned a risk of 0 as a severity score cannot be derived from infants without a PDA diameter or maximum PDA velocity measurement.

Table I. Demographics and antenatal details in the 2 groups

	CLD/death (n = 79)	No CLD/death (n = 62)	*P*
Gestation (wk)	26.1 (1.3)	27.7 (1.1)	<.001
Birth weight (g)	813 (143)	1128 (211)	<.001
Male	52 (66%)	34 (55%)	.2
Cesarean delivery	51 (65)	39 (63)	.9
5-Min Apgar score	8 [6-9]	9 [7-9]	.01
Cord pH	7.30 (0.10)	7.33 (0.06)	.2
Chorioamnionitis	7 (9%)	5 (8%)	1.0
Pre-eclampsia	7 (9%)	0 (0%)	.02
$MgSO_4$	58 (73%)	45 (73%)	1.0
Any surfactant use	75 (95%)	47 (76%)	.001
Antenatal steroids			
None	14 (18%)	6 (10%)	.04
1 Dose	11 (14%)	19 (31%)	
2 Doses	54 (68%)	37 (60%)	
Cardiorespiratory characteristics*			
Mechanical ventilation	51 (65%)	10 (16%)	<.001
Mean airway pressure (mm Hg)	9 (2)	8 (2)	<.001
Inspired oxygen (%)†	21 [21-65]	21 [21-42]	<.001
Oxygen saturations (%)	94 (3)	96 (3)	<.001
pH	7.28 (0.07)	7.32 (0.06)	.003
Total fluid intake (mL/kg/d)	120 [100-140]	120 [100-125]	.24
Systolic blood pressure (mm Hg)	50 [44-54]	52 [47-60]	.03
Diastolic blood pressure (mm Hg)	28 [24-39]	31 [27-36]	.01

$MgSO_4$, magnesium sulphate.
Values are presented as means (SD), median [IQR], and count (%).
*During day 2 echocardiogram.
†Presented as median [range].

We compared the ability of the PDAsc to predict CLD/death against the predictive value of gestational age alone or PDA diameter (measured on day 2) alone. In addition, we compared the PDAsc with another score derived from a combination of 5 clinical characteristics using the same methodology described above: gestation; use of antenatal steroids; days on invasive ventilation; late onset sepsis; and NEC. A receiver operating characteristics curve was constructed to assess the ability of the derived PDAsc to predict CLD/death compared with gestation, PDA diameter, and the clinical variables. In addition, we also assessed the association between the PDAsc and 2 components of the composite outcome separately, in addition to NEC.

Results

One hundred forty-one infants were enrolled in the study. The mean (SD) gestational age and weight at birth of the cohort were 26.8 (1.4) weeks and 952 (235) g, respectively.

Echocardiography scans were available for 134 infants (95%) on day 1, 141 infants (100%) on day 2, and 123 infants (87%) on day 5-7 (the attrition was due to investigator unavailability). A PDA was present in 130 infants (97%) on day 1, 118 (84%) on day 2, and 84 (68%) on day 5-7. Seventy-nine infants (56%) developed the primary outcome of interest (CLD/death), of which 65 developed CLD and 15 died before discharge. The causes of death were as follows: withdrawal of life sustaining treatment for severe IVH (n = 6); gram negative sepsis (n = 2); severe NEC (n = 3); severe respiratory failure (n = 3, one of which also attained the diagnosis of CLD prior to death); and one with a volvulus. Table I illustrates the differences in demographics, antenatal details, and the cardiorespiratory characteristics between the 2 groups. Infants with CLD/death had lower gestational age and weight at birth and a lower 5-minute Apgar score. In addition, there was a higher incidence of pre-eclampsia and a slightly lower use of antenatal steroids in the CLD/death group. Infants with CLD/death also had a marginally lower mean airway pressure, oxygen saturations, pH, and blood pressure. Those differences, however, were not clinically relevant. Table II (available at www.jpeds.com) demonstrates the distribution of other important outcomes between the 2 groups. Infants with CLD/death had a longer duration of mechanical ventilation and a higher incidence of inotrope, furosemide, and postnatal steroid use. PDA treatment beyond the first week of life and culture proven late onset sepsis were also more common in the CLD/death group. There was a high incidence of severe IVH and NEC in the cohort. All cases of NEC occurred beyond the second week of life. None of the infants received PDA treatment over the first week of life.

Univariate Analysis of the Echocardiography Variables

Echocardiography variables measured across the 3 timepoints were compared between infants with and without CLD/death. Figure 1, A illustrates the change in those measurements between the 2 groups across the 3 timepoints. The 3 PDA-related echocardiography markers used in the regression model are in the first row of Figure 1, A. LVO was higher and PDA Vmax was lower in the CLD/death group across the 3 timepoints. PDA diameter was significantly larger in the CLD/death group on day 2 and day 5-7 ($P < .05$ on ANOVA). The differences in the remainder of the echocardiographic markers across the 2 groups with respect to time were not significant (2-way ANOVA $P > .05$). There was a significant increase in LV a′ over the first week of age in the entire cohort: 4.4 (1.9) vs 5.3 (1.9) vs 5.8 (2.0) m/s (1-way ANOVA $P < .001$). There was no difference in LV a′ between the 2 groups at any timepoint. During the day 2 scan, wave fusion occurred in 31 infants (22%). There was a trend for lower LV a′ on day 2 in infants who developed CLD/death across the 5 gestational age categories (Figure 1, B).

Table III. Results of the regression model used to devise the PDAsc

Predictor variable	Unstandardized β	Standardized β	P
Gestation	−1.304	−0.398	<.01
PDA diameter	0.781	0.079	.07
LVO	0.008	0.272	.03
PDA Vmax	−1.065	−0.163	.02
LV a′	−0.470	−0.236	.01

The unstandardized beta coefficients were used to devise the risk score (see Methods section for details). Negative β coefficients indicate that higher variable values are associated with a decrease in the risk of developing the outcome. Positive β coefficients indicate that higher variable values are associated with an increase in the risk of developing the disease.

PDAsc

Five variables were included in the final logistic regression model devised to predict the primary outcome, CLD/death: gestation (weeks), PDA diameter (mm), Vmax (m/s), LVO (mL/kg/min), and LV a′ (cm/s). The 4 echocardiography variables included in the model were from the day 2 scan, which was performed at a median 43 hours (38-47). Table III illustrates the unstandardized beta coefficients of the variables, which were used to devise the PDAsc, the standardized beta coefficients, which demonstrate the relative importance of each variable in the model, and the significance of each variable. A PDAsc ranging from 0 (low risk) to 13 (high risk) was obtained. The mean (SD) risk score in the population was 6.0 (2.5). Infants with CLD/death had a higher score than those without CLD/death (7.3 [1.8] vs 3.8 [2.0], $P < .001$; Figure 2, A). There was a strong correlation between the predicted probability of developing CLD/death based on the model and the PDAsc (Figure 2, B).

A receiver operating characteristics curve, constructed to assess the ability of the score to predict CLD/death in the population, yielded an area under the curve (AUC) of 0.92 (95% CI 0.86-0.97, $P < .001$). This compared favorably with comparator predictive models based on a combination of clinical characteristics (gestation, antenatal steroids, late onset sepsis, NEC, and ventilation days) (AUC 0.84, $P = .04$), gestation alone (AUC 0.80, $P = .04$), and PDA diameter alone, which had very poor predictability (AUC 0.59, $P = .06$; Figure 3). A cut-off of 5 had a sensitivity of 92%, a specificity of 87%, a positive predictive value of 92%, and a negative predictive value of 82%. In this cohort, 73 infants (52%) had a score of 5 or greater.

The relationship between the PDAsc and CLD/death was further examined by controlling for important outcomes presented in Table II that were associated with CLD/death on univariate analysis. The relationship between the PDAsc and CLD/death remained significant (aOR 2.1 [95% CI 1.5-3.1], $P < .001$) when controlling for other potential predictors of CLD: PDA ligation, late onset sepsis, postnatal steroid use, and furosemide use, none of which remained significantly associated with CLD/death in this model. In addition, we examined the difference in the score between infants with and without CLD alone, death alone,

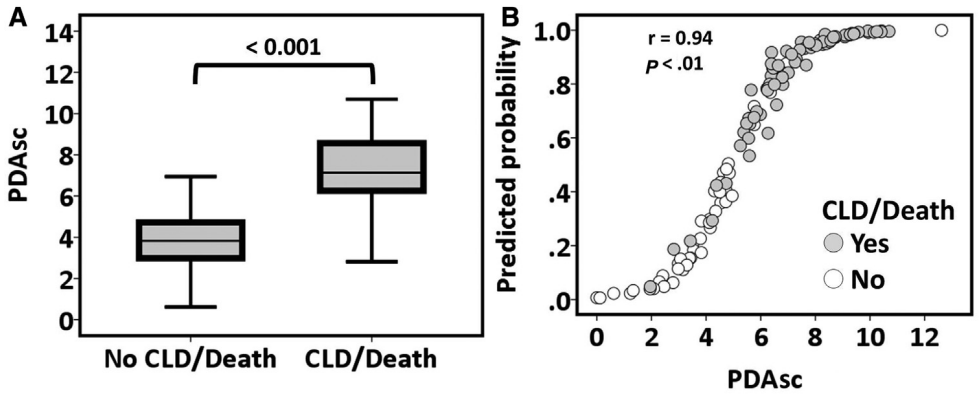

Figure 2. Difference in the **A,** PDAsc between infants with and without CLD/death and the **B,** relationship between the score and the predicted probability of CLD/death in the entire cohort. Infants who developed CLD/death had a higher predicted probability compared with those who did not.

and NEC. Infants with CLD had a significantly higher score (7.2 [1.9] vs 3.8 [2.0], $P < .001$). Similarly, infants that died before discharge has a higher score (7.7 [1.7] vs 5.7 [2.5], $P = .01$). Finally, infants with NEC had a higher PDAsc than those without NEC (7.5 [2.3] vs 5.6 [2.4], $P < .003$). The PDAsc had an AUC of 0.70 (95% 0.57-0.81, $P = .007$) for the ability to predict NEC.

Discussion

We demonstrate that there are early differences in characteristics of the PDA during the first week of life between infants who develop CLD or die before discharge and those who do not develop those outcomes, with increasing divergence of those characteristics over the first week of life. The phenotypic features of these higher risk patients include larger PDA diameter, lower maximum velocity across the PDA (indicating a lack of ductal constriction and an unrestricted flow pattern in the absence of significant pulmonary hypertension), and increased pulmonary blood flow (indicated by a higher LVO). In addition, a PDAsc derived on day 2 of age using gestation along with echocardiography markers of PDA characteristics and LV diastolic function can predict the later occurrence of CLD or death in a group of preterm infants less than 29 weeks gestation.

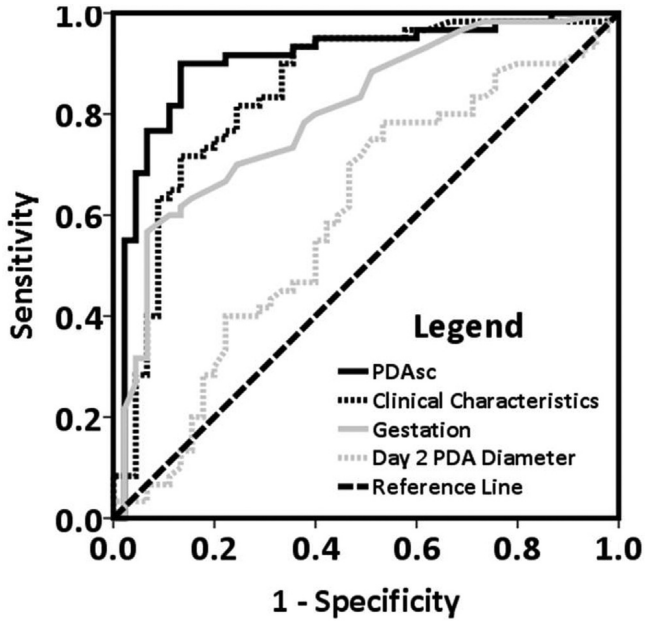

Figure 3. Receiver operating characteristics curve of the ability of PDAsc to predict CLD/death. The PDAsc was compared with a combination of clinical characteristics, gestation, and PDA diameter.

There has been a recent reemphasis to develop a better definition of PDA "hemodynamic significance," which resulted from the failure of all randomized controlled trials of pre-symptomatic PDA treatment to yield an improvement in short- and long-term PDA associated morbidities.[2,17] All of these studies, however, treated the PDA as an all-or-none phenomenon, with no quantification of the impact the PDA has on pulmonary or systemic blood flow. Those trials relied almost solely on PDA diameter to determine significance. This over-simplification ignores the effect of shunt volume in determining PDA significance. The PDA in the premature infant's early life should be regarded as a continuum from being physiologic, and potentially beneficial to being pathologic (when pulmonary vascular resistance drops) leading to systemic hypoperfusion and pulmonary congestion. There are several challenges with defining hemodynamic significance associated with a PDA. A variety of definitions for hemodynamic significance have been employed which incorporate clinical and echocardiography variables without clear validation and justification.[11] In addition, the cut-offs at which echocardiography PDA characteristics are assigned significance are often allocated based on whether infants received treatment or not rather than associating them with morbidity,[18,19] or are based on the short-term occurrence of clinical features of a PDA such as bounding pulses, a murmur, and an active precordium.[20]

There have been recent attempts to relate early PDA features to the later evolution of PDA-associated morbidities, particularly respiratory morbidities such as CLD. In the premature newborn baboon model, exposure to a PDA with an increased pulmonary blood flow leads to impaired pulmonary function and arrested alveolar development and surface area. Pharmacologic closure of the PDA in this animal model reduces the detrimental effects of preterm delivery on pulmonary function and surface area.[10] In preterm infants, Sehgal and McNamara[21] demonstrated that a composite score of PDA significance based on echocardiography criteria measured at the time of PDA treatment (at a median of 7 days) is associated with CLD. Although this study strengthens the evidence of the association between a PDA and CLD, applying a staging system for ductal diseases severity at an earlier timepoint may facilitate better targeted treatment. Sellmer et al[22] demonstrated that large PDAs assessed on day 3 of age are associated with IVH, CLD, and mortality, although causality may not be directly extrapolated. More recently, Schena et al[9] demonstrated that infants exposed to a more severe PDA (based on a scoring system proposed by McNamara and Sehgal[18]) for a longer period during their hospital stay are more likely to develop CLD. Interestingly, after adjusting for PDA severity, PDA ligation was no longer associated with CLD in their cohort.[9] The lack of association between PDA ligation and CLD when PDA severity is accounted for is gaining an increased recognition.[23,24] Although none of these temporal studies prove a cause and effect relationship between a PDA and CLD, the evidence is strengthening for a select population with increased shunt volume.

There exists a need for a discriminative and predictive score to measure the degree of hemodynamic significance of a PDA in the first 48 hours of life[25] and associate this score with the development of morbidities associated with a PDA. As gestational age has an independent role in the evolution of important morbidities, it should be included in devising the score. This score should also include markers of shunt size (PDA diameter and Vmax) and shunt volume (LVO). A larger PDA diameter with unrestrictive low velocity flow will lead to increased pulmonary blood flow identified by an increased LVO. The effect of increased pulmonary blood flow on the preterm neonatal lung may be similar to that of the baboon model described above.

In addition, consideration should be given to left heart diastolic function as this plays a key role in handling the increased blood volume returning to the heart. LV diastolic function may be an important determinant of how the heart can accommodate the increased preload resultant from the shunt. Compromised diastolic function may contribute to increased pulmonary venous pressure, thereby worsening the effect of increased pulmonary blood flow. Preterm infants have impaired diastolic function because of their stiffer myocardium and are, therefore, heavily reliant on the late diastolic phase of atrial contraction for ventricular filling. Impaired diastolic function in the setting of increased pulmonary venous return will lead to increased left atrial pressure and eventual pulmonary venous congestion.[26] Therefore, devising a score of hemodynamic significance applied during the early neonatal period using echocardiography markers that incorporate diastolic function of the LV may lead to a better characterization of the pathologic nature of the PDA. The PDAsc derived in this study encompasses all the components mentioned above. This score was highly predictive of the composite outcome (CLD/death). As CLD and death were predominantly mutually exclusive outcomes, the score was also significantly higher in infants with the individual components of the outcome. In addition, a higher score was observed in infants with PDA-associated morbidities such as NEC and also was predictive of NEC with an AUC of 0.70. Interestingly, PDA ligation was no longer associated with CLD when the score was taken into account. These data further emphasize the increasing realization that PDA severity and hemodynamic impact rather than the ligation per se, is likely to have a causal effect. The cut-off of 5 yielded the best sensitivity and specificity. More importantly, it yielded the best positive and negative predictive value, which is more generalizable to other populations. This cut-off could, therefore, be used to further validate the predictability of this score in a different population or to determine selection for treatment in a randomized controlled setting.

It is worth noting that markers for systemic hypoperfusion (such as descending aortic end diastolic flow) were not included as a component of the score because of collinearity with the markers for pulmonary overcirculation. The relative influence of each variable in the score was illustrated by the standardized beta coefficient in **Table III**. Although gestation had the biggest influence (with the largest standardized beta value), LVO and LV a′ had values of almost similar magnitude emphasizing their importance in predicting the outcome of interest. The relatively lower standardized beta coefficient value for PDA diameter illustrate that PDA size in isolation is a poor surrogate for hemodynamic significance as the pressure gradient across the PDA, rather than the size, is the major determinant of shunt volume during the early transitional period.

The PDAsc compared favorably with a score based on a combination of important clinical characteristics to predict CLD/death. These clinical characteristics were chosen for comparison as they are all strongly associated with CLD and/or death: gestational age, use of antenatal steroids, sepsis, NEC; and duration of invasive ventilation. Although a clinical score based on a combination of clinical characteristics had a relatively good predictive ability with an AUC of 0.85, their utility for early targeted PDA treatment is questionable as the majority of thresholds in this risk score are only attained beyond the first 2 weeks of life. Similarly, the PDAsc performed better than gestation alone, or PDA diameter alone highlighting the benefit of a more comprehensive appraisal of PDA significance during the early neonatal period. The addition of cardiorespiratory variables to the regression model, particularly mean airway pressure, did not improve the predictability of the PDAsc. We found that gestational age had a large influence on these clinical

characteristics; therefore, as such, including gestational age in the model was likely to account for the impact of these characteristics. In addition, using mean airway pressure may be problematic as variation in clinical practice across centers (rather than the clinical status of the infant) is a major determinant of the level of respiratory support those infants receive.

There was a relatively high incidence of IVH and NEC in the study cohort. This may be a result of the selective nature of the population (less than 29 weeks) and may relate to the nontreatment of the PDA. One center (The Rotunda Hospital, Dublin, Ireland) used paracetamol for late medical closure of the PDA in infants with contraindications to the use of nonsteroidal anti-inflammatory drugs in order to avoid PDA ligation. We would like to stress that lack of robust data supporting this practice.[24] Although a relatively large number of infants were included in this study, the observational nature of this study may have introduced selection bias to the patient cohort. In addition, although a standardized protocol for PDA assessments was used in all participating centers, interobserver variability during image acquisition and/or off-line measurement analysis could have influenced the results. In particular, TDI measurements require equipment and expertise that may not be present in all units. We used a simple definition of CLD (need for oxygen at 36 weeks corrected) without taking into account the severity of the condition. This was performed to have a dichotomous outcome for the purposes of the regression model and to facilitate generalizability of the score. Our sample size did not support further outcome stratification into a more complex endpoint. This approach may have missed milder forms of the disease. We did not test the utility of the score in another cohort, and, therefore, the generalizability of this score is unproven.

The ability to accurately predict PDA associated morbidities such as CLD/death using a PDAsc can pave the way for a more targeted treatment. The cut-off used in this cohort places about 50% of infants under 29 weeks gestation in the high-risk category thereby limiting the number of infants exposed to PDA treatment. This PDAsc should be validated in a similar cohort of preterm infants in a prospective manner and may be used to devise a randomized controlled trial of targeted PDA treatment. ■

Submitted for publication Jun 8, 2015; last revision received Aug 20, 2015; accepted Sep 8, 2015.

Reprint requests: Afif EL-Khuffash, FRCPI, MD, DCE, Department of Neonatology, The Rotunda Hospital, Parnell St, Dublin, Ireland. E-mail: afifelkhuffash@rcsi.ie

References

1. Evans N. Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? Semin Fetal Neonatal Med 2015;20:272-7.
2. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003;(2):CD003745.
3. El-Khuffash AF, Slevin M, McNamara PJ, Molloy EJ. Troponin T, N-terminal pro natriuretic peptide and a patent ductus arteriosus scoring system predict death before discharge or neurodevelopmental outcome at 2 years in preterm infants. Arch Dis Child Fetal Neonatal Ed 2011;96:133-7.
4. Cunha GS, Mezzacappa-Filho F, Ribeiro JD. Risk factors for bronchopulmonary dysplasia in very low birth weight newborns treated with mechanical ventilation in the first week of life. J Trop Pediatr 2005;51:334-40.
5. Shortland DB, Gibson NA, Levene MI, Archer LN, Evans DH, Shaw DE. Patent ductus arteriosus and cerebral circulation in preterm infants. Dev Med Child Neurol 1990;32:386-93.
6. Van Overmeier B. Patent ductus arteriosus: how aggressive should we be? Neonatology 2007;91:318.
7. Brooks JM, Travadi JN, Patole SK, Doherty DA, Simmer K. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. Arch Dis Child Fetal Neonatal Ed 2005;90:235-9.
8. El-Khuffash A, Barry D, Walsh K, Davis PG, Molloy EJ. Biochemical markers may identify preterm infants with a patent ductus arteriosus at high risk of death or severe intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed 2008;93:F407-12.
9. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr 2015;166:1488-92.
10. Chang LY, McCurnin D, Yoder B, Shaul PW, Clyman RI. Ductus arteriosus ligation and alveolar growth in preterm baboons with a patent ductus arteriosus. Pediatr Res 2008;63:299-302.
11. Zonnenberg I, de Waal K. The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review. Acta Paediatr 2012;101:247-51.
12. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr 1978;92:529-34.
13. Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P, et al. Targeted Neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training writing group of the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). J Am Soc Echocardiogr 2011;24:1057-78.
14. El-Khuffash AF, McNamara PJ. Neonatologist-performed functional echocardiography in the neonatal intensive care unit. Semin Fetal Neonatal Med 2011;16:50-60.
15. James AT, Corcoran JD, Jain A, McNamara PJ, Mertens L, Franklin O, et al. Assessment of myocardial performance in preterm infants less than 29 weeks gestation during the transitional period. Early Hum Dev 2014;90:829-35.
16. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
17. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM, Nwaesei C, et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). J Pediatr 2006;148:730-4.
18. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal Ed 2007;92:424-7.
19. Youn Y, Lee JY, Lee JH, Kim SY, Sung IK, Lee JY. Impact of patient selection on outcomes of PDA in very low birth weight infants. Early Hum Dev 2013;89:175-9.
20. Alagarsamy S, Chhabra M, Gudavalli M, Nadroo AM, Sutija VG, Yugrakh D. Comparison of clinical criteria with echocardiographic findings in diagnosing PDA in preterm infants. J Perinat Med 2005;33:161-4.

21. Sehgal A, Paul E, Menahem S. Functional echocardiography in staging for ductal disease severity: role in predicting outcomes. Eur J Pediatr 2013;172:179-84.
22. Sellmer A, Bjerre JV, Schmidt MR, McNamara PJ, Hjortdal VE, Host B, et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. Arch Dis Child Fetal Neonatal Ed 2013;98: 505-10.
23. Weisz DE, More K, McNamara PJ, Shah PS. PDA ligation and health outcomes: a meta-analysis. Pediatrics 2014;133:1024-46.
24. El-Khuffash A, James AT, Cleary A, Semberova J, Franklin O, Miletin J. Late medical therapy of patent ductus arteriosus using intravenous paracetamol. Arch Dis Child Fetal Neonatal Ed 2015; 100:253-6.
25. Guyatt GH, Kirshner B, Jaeschke R. Measuring health status: what are the necessary measurement properties? J Clin Epidemiol 1992;45: 1341-5.
26. Dokainish H. Left ventricular diastolic function and dysfunction: central role of echocardiography. Glob Cardiol Sci Pract 2015;2015:3.

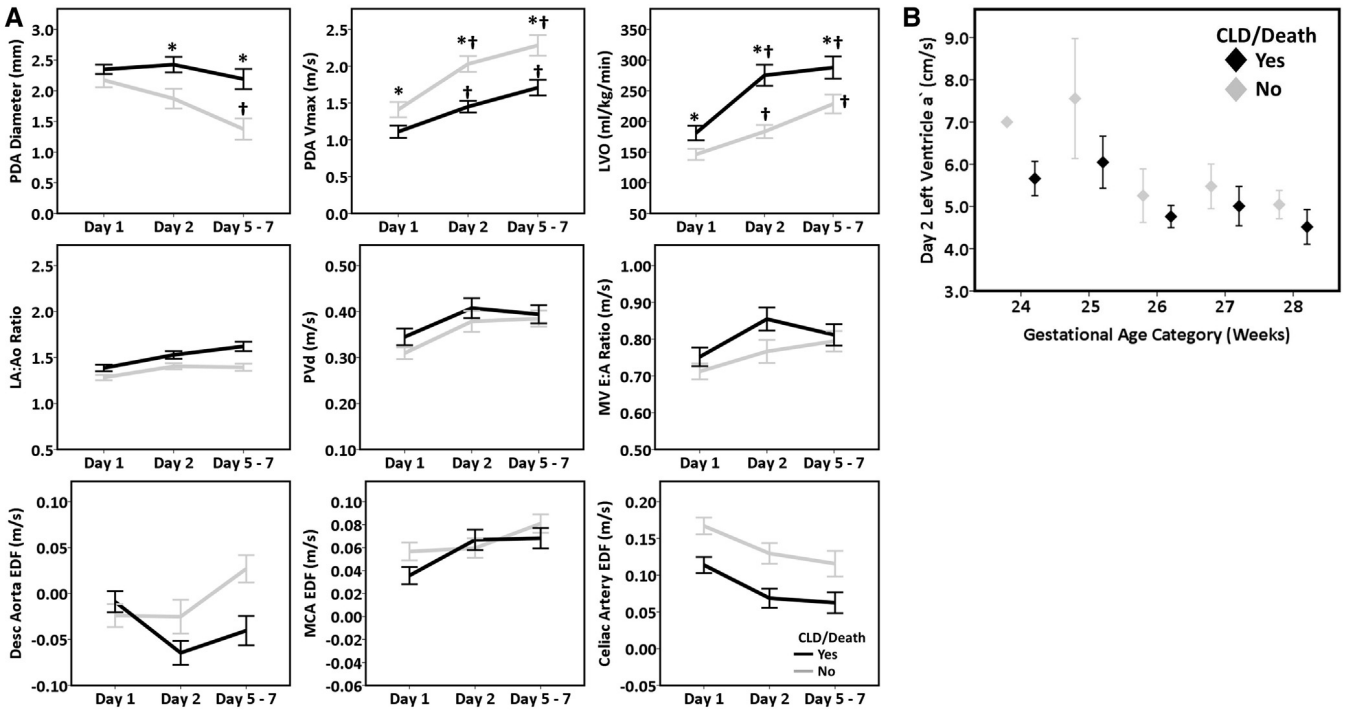

Figure 1. **A,** Echocardiography measurements across the 3 timepoints. Values are presented as means. The error bars represent the SEM. Two-way repeated measures ANOVA was used to compare the 2 groups across the 3 timepoints. *Indicates a *P* value of <.05 for between group pair wise comparison (CLD/death vs no CLD/death). †Indicates a *P* value of <.05 for within group comparison with respect to time. **B,** LV a′ values on day 2 in infants with and without CLD/death stratified by gestational age. The error bars represent the SE of the mean. *EDF*, end diastolic flow; *LA:Ao*, left atrial to aortic root ratio; *MCA*, Middle cerebral artery; *MV*, mitral valve; *PVd*, pulmonary vein diastolic flow velocity.

Table II. Distribution of other outcomes and interventions between the 2 groups

	CLD/death (n = 79)	No CLD/death (n = 62)	*P*
Grade 3 or 4 IVH by Day 7	11 (14%)	4 (7%)	.2
Pulmonary hemorrhage	8 (10%)	2 (3%)	.2
NEC	16 (20%)	7 (11.3%)	.2
Clinical suspicion	3	2	.6
Medical treatment	5	3	
Surgical treatment	8	2	
Invasive ventilation d (survivors)	18 [7-36]	1 [0-4]	<.001
Inotrope use (any)	26 (33%)	5 (8%)	<.001
Use of furosemide	53 (72%)	13 (22%)	<.001
Postnatal steroids	23 (29%)	1 (2%)	<.001
PDA treatment (beyond d 7)	49 (62%)	8 (13%)	<.001
Ibuprofen	38 (48%)	8 (13%)	<.001
Paracetamol	19 (24%)	1 (2%)	<.001
Surgical ligation	9 (11%)	1 (2%)	.04
Culture-proven sepsis	35 (44%)	5 (8%)	<.001
PVL (in survivors)	10 (15%)	3 (5)	.07

PVL, periventricular leukomalacia.
Values are presented as count (%). All the culture proven sepsis cases were late onset (beyond day 5).