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ARTICLE

Hemodynamic and clinical consequences of early versus delayed closure of patent ductus arteriosus in extremely low birth weight infants

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Abstract

Objectives To describe changes in hemodynamics, respiratory support, and growth associated with transcatheter PDA closure (TCPC) in ELBW infants, stratified by postnatal age at treatment.

Study design This is an observational study of ELBW infants who underwent TCPC at ≤4 weeks (Group-1; $n = 34$), 4–8 weeks (Group-2; $n = 33$), and >8 weeks of age (Group-3; $n = 33$). Hemodynamic assessment was performed during TCPC. Multivariate Cox-proportionate-hazard modeling was used to identify factors associated with respiratory severity score (RSS) > 2 for >30 days following TCPC.

Results In comparison with Group-1, Group-3 infants had higher pulmonary vascular resistance (PVRi = 3.3 vs. 1.6 WU*m^2; $P = 0.01$), less weight gain between 4 and 8 weeks of age (16 vs. 25 g/day) and took longer to achieve RSS < 2 (median 81 vs. 20 days; $P = 0.001$). RSS > 2 for >30 days was associated with TCPC > 8 weeks (OR = 3.2, 95% CI: 1.75–5.8; $p = 0.03$) and PVRi ≥ 3 (OR = 4.5, 95% CI: 2.7–8.9; $p < 0.01$).

Conclusion ELBW infants may benefit from PDA closure within the first 4 weeks of life in order to prevent early onset pulmonary vascular disease, promote faster growth, and for quicker weaning of ventilator and oxygen support.

Introduction

The presence of a moderate-to-large patent ductus arteriosus (PDA) in extremely low birth weight (ELBW) preterm infants is associated with poor respiratory outcomes and an increased mortality [1]. However, over 40 randomized controlled trials (RCT) using standard management strategies to close these PDAs (medical therapy and surgical ligation) have failed to demonstrate a reduction in neonatal adverse outcomes such as IVH, NEC, BPD, or death [2–4]. When compared to standard medical therapy with fluid restriction, diuretics, and mechanical ventilation, the use of cyclo-oxygenase inhibitors does not appear to have long-term benefits [5]. The effectiveness of drugs (indomethacin, ibuprofen, and paracetamol) used to constrict the PDA in less mature infants (especially ≤26 weeks) is significantly reduced [6, 7]. Surgical ligation provides definitive ductal closure but leads to worse rather than better respiratory outcomes [8, 9]. Neither method provides information on the hemodynamics before or during PDA closure to assess suitability for closure. Transcatheter PDA closure (TCPC) albeit the standard of care in older children, being minimally invasive, is gaining popularity in younger preterm ELBW infants as a management therapy [10–14]. It is the gold standard for diagnostic evaluation of the degree of shunting and the pulmonary vascular resistance. Echocardiograms and clinical assessment can provide some indication of the hemodynamics [15, 16]. However, cardiac catheterization alone can accurately assess the true hemodynamics of the PDA. To date, no previous studies have utilized this gold standard modality to determine the hemodynamic consequence of a PDA in ELBW infants. TCPC offers real-time assessment of the hemodynamics before and after PDA closure. With the advent of performing PDA closure safely [11] using transcatheter device implantations, we deemed it critical to measure the true

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hemodynamic parameters of the PDA that impact outcomes in ELBW infants. The primary objective of this study was to describe changes in hemodynamics, respiratory support, and growth associated with TCPC in ELBW infants, stratified by postnatal age at treatment. Secondary objectives included describing clinical outcomes following early (≤4 weeks of age) vs. delayed (>8 weeks) PDA closure and identify factors associated with worse clinical outcomes.

Infants and methods

Study population

Infants born ≤27 weeks' gestation, weighing ≤1 kg at birth referred for cardiac catheterization and possible TCPC between January 2016 and September 2019 from a single center were included in this study. Approval for the study was obtained from the University of Tennessee institutional review board. All infants were considered to have a hemodynamically significant PDA (hsPDA) when referred for TCPC based on clinical and echo parameters. Hemodynamic significance was determined by PDA size ≥2.5 mm, with diastolic flow reversal in the descending aorta by echocardiogram and the need for mechanical ventilator support. Hemodynamic significance was confirmed by performing a complete hemodynamic evaluation by cardiac catheterization as part of the TCPC. The timing for referral for catheter-based PDA closure was based solely on the discretion of the NICU attending. Infants were retrospectively grouped based on the timing of PDA closure.

Those who had TCPC on or before 4 weeks of age were grouped together (Group-1). Group-3 was categorized as delayed TCPC, after 8 weeks of age. Those infants who had TCPC between 4 and 8 weeks were assigned as Group-2.

Hemodynamic assessment

A complete hemodynamic cardiac catheterization was performed as part of the PDA closure procedure. Those who did not have a full hemodynamic assessment were not included in the study. Of note, all procedures were performed via a femoral venous only approach (Fig. 1) due to the risk [17] of arterial spasm and thrombosis with femoral arterial access in low birth weight infants. Hemodynamic assessment included a baseline pulmonary to systemic flow ratio (Qp:Qs) and pulmonary artery systolic pressure (PASP) expressed as a percentage of the systolic blood

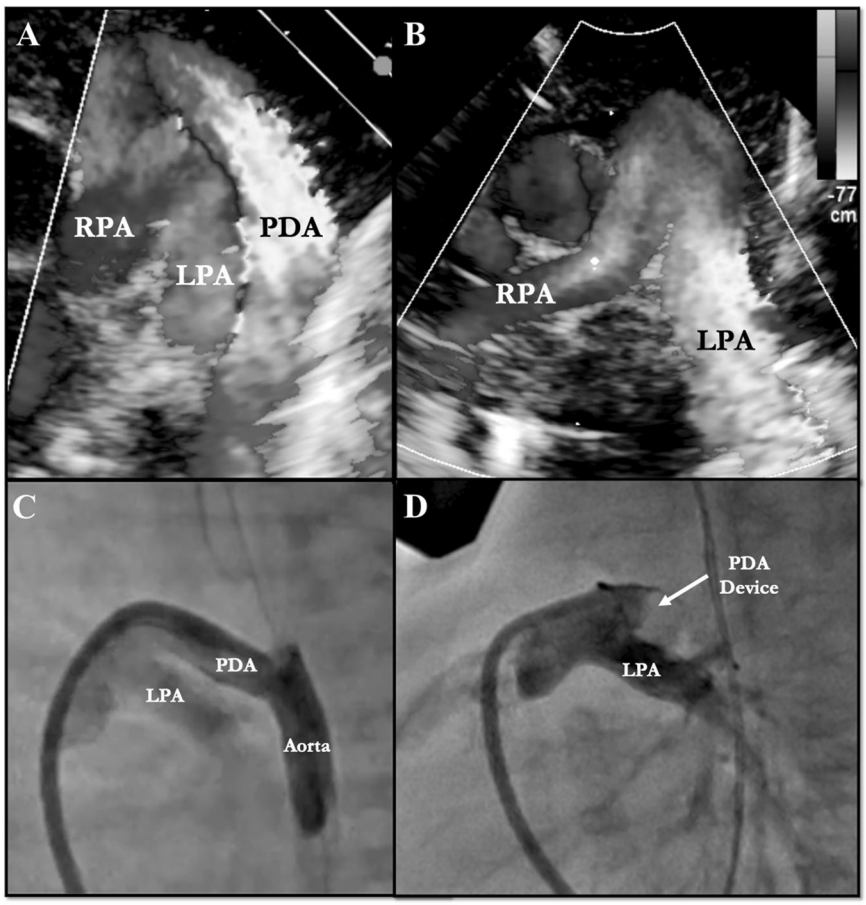

Fig. 1 Echo and angiograms pre- and post-transcatheter PDA closure. a Echo demonstrating a large PDA with left-right shunt (red Doppler signal) into the pulmonary arteries. LPA left pulmonary artery, RPA right pulmonary artery. **b** Echo post-PDA closure. Note the absence of the red Doppler PDA signal. **c** Angiogram pre-transcatheter PDA closure. **d** Angiogram post-transcatheter PDA closure demonstrating device within the PDA.

pressure (SBP). The degree of shunting was calculated by the difference in the actual and effective pulmonary blood flow. Pulmonary vascular resistance (PVRi) in Wood units (WU) indexed for body surface area (m^2) was calculated by the ratio of the transpulmonary pressure gradient and the pulmonary blood flow using the following equation: PVR = (mean PAP − mean LAP)/Qp where mean PAP = mean pulmonary artery pressure, mean LAP = mean left atrial pressure (substituted with Pulmonary Capillary Wedge Pressure), and Qp = pulmonary blood flow. Normal PVRi values range below 3 WU*m^2. In the neonatal period and early infancy, PVRi is higher and decreases with increasing age [18].

If the baseline PVRi was >3 WU*m^2, then pulmonary vasodilator testing using inhaled nitric oxide (iNO) and 100% oxygen was performed. This was followed by remeasurement of all the hemodynamics including Qp:Qs ratio, PASP, and PVRi. Subsequently, the PDA was test occluded with iNO and 100% oxygen and the same hemodynamics were once again recorded. The Qp:Qs, and PVRi were calculated for all three conditions i.e., baseline, vasodilator testing, and with test occlusion of PDA. The PDA was closed only if the PVRi was <5 WU*m^2 with test occlusion of the PDA on oxygen and iNO. Obviously, if the baseline PVRi was normal, the PDA was closed with an occlusion device without pulmonary vasodilator testing.

Assessment of respiratory outcomes

A respiratory severity score (RSS) was calculated and used as the primary outcome variable.

The RSS is a product of the mean airway pressure and the fractional inspired oxygen (FiO_2).

Therefore, a lower score denotes less respiratory support and a value of <2 was considered minimal. The pre-procedure RSS was reported as a mean of all the RSS for 2 days prior to PDA closure. The RSS immediately post-PDA closure (within 2 h) and the time taken for return to pre-procedure RSS were recorded. In addition, the time taken for the RSS to get below a score of 2 was measured. Factors contributing to prolonged (>30 days) elevation of RSS > 2 were identified.

Statistical methods

Categorical data are reported as a count and percentage. Continuous data are reported as median and range to present the minimum and maximum values for demographics and hemodynamic data and as median and interquartile range for respiratory outcome variables. The hemodynamic changes with oxygen and nitric oxide as well as with test occlusion of the PDA, and in growth velocities are expressed as mean ± standard deviation. Chi-square tests were performed for categorical data. The parametric test used to compare numeric data such as growth velocity pre- and post-PDA closure, and Qp:Qs, PVRi, PASP pre- and post-pulmonary vasodilation and test occlusion of the PDA was the Student's *t* test. The Mann–Whitney test was the nonparametric test used for continuous variables.

The Kruskal–Wallis H test (one-way ANOVA on ranks) was used to determine statistical differences between two or more groups for independent variables on continuous and/or for ordinal dependent variables. The initial analysis included all three groups together. Individual intergroup comparisons were then completed if an overall intergroup difference was noted in order to illustrate which two groups differed. The data presented in Table 1 are a comparison of all three groups and the overall *P* values. This is because all three groups were either similar or different with regards to each other. For data presented in Tables 2 and 3, the overall *P* value does not indicate which groups differ. Therefore, only the comparison of the groups that differ is presented.

The probability of freedom from events (RSS ≥ 2) was estimated according to the Kaplan–Meier method, and estimates were then compared with the log-rank test. A Cox proportional hazard model was used to identify factors contributing to prolonged (more than 30 days) elevation of RSS > 2.

Indexed growth velocity calculations (g/kg/d) between a certain time interval were calculated by subtracting the weight

Table 1 Demographics.

Variable	Group-1 ($n = 34$)	Group-2 ($n = 33$)	Group-3 ($n = 33$)	*P* value[a]
Gender (% male)	56	52	48	0.826
Gestational age (weeks)	24 (22–27)	24 (22–27)	24 (22–27)	0.244
Birth weight (g)	720 (500–1000)	740 (470–1000)	700 (480–1000)	0.335
Procedure age (days)	21 (9–28)	40 (30–47)	90 (58–177)	<0.001
Procedure weight (g)	860 (640–1200)	1320 (800–2000)	2400 (1350–3600)	<0.001
History of NEC Stage-IIB and -III	4 (12%)	7 (21%)	8 (24%)	0.034
History of IVH Grade-III and -IV	4 (12%)	6 (18%)	6 (18%)	0.441
History of sepsis	8 (23.5%)	11 (33.3%)	15 (45.5%)	0.010

[a]Overall *P* value suggesting whether all three groups were similar or different.

in grams on the first day of the time period from the weight in grams on the last day of the time period, divided by the number of days between the two time points, and then divided by the weight in kilograms on the last day of the time interval.

All statistical analyses were defined by a two-tailed $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics (version 26.0, IBM, Armonk, NY).

Results

A total of 100 infants were included in the study, with an almost equal distribution of the number of infants in each group (34 in Group-1 and 33 each in Groups 2 and 3). All except for two infants had at least one course of medical treatment for PDA closure. These two infants, both belonging to Group-1 had primary TCPC as there were contraindications for medical therapy. Infants in all three groups were similar for gestational age, birth weight, and gender (Table 1). The median age at PDA closure was significantly different based on the selection criteria. Similarly, the median procedure weight at the time of PDA closure for Group-1 infants was significantly lower compared to Group-3 infants (Table 1). Infants in Group-1 had less incidence of sepsis and NEC Stage-IIB and -III prior to TCPC compared to Groups 2 and 3. However, the incidence of IVH Grade-III and -IV prior to TCPC was similar in all three groups. At the time of procedure, 48 infants were ≤1 kg, 32 infants were >1 to ≤2 kg, and 20 infants were >2 kg. The procedure success rate was 100%. There were no procedure-related complications.

Table 2 Baseline hemodynamics.

Variable	Group-1 ($n = 34$)	Group-2 ($n = 33$)	Group-3 ($n = 33$)	P value
Baseline Qp:Qs	2.5 (1.6–4)	2 (1.3–3.1)	1.8 (0.8–4.2)	0.438[a]
PA vs. aorta systolic BP (%)	50 (30–74)	48 (28–86)	76 (46–100)	<0.001[b]
Baseline PVRi (WU*m^2)	1.6 (1–2.3)	2 (1–4.8)	3.3 (2.4–7.6)	<0.001[b]

Qp:Qs pulmonary to systemic flow ratio, *PA* pulmonary artery, *BP* blood pressure, *PVRi* pulmonary vascular resistance indexed.

[a]Overall P value comparing all three groups.

[b]P value represents comparison between Groups 1 and 3. For these variables, Groups 1 and 2 were not significantly different and neither are Groups 2 and 3. However, significant differences are noted between Groups 1 and 3.

Hemodynamic assessment

The median baseline Qp:Qs ratios were not different irrespective of the timing of PDA closure, with all being >1.5:1, suggesting that the majority of PDAs that were referred for transcatheter closure were hemodynamically significant (Table 2). There was a trend for a larger shunt in younger (Group-1; median 2.5:1, range 1.6:1–4:1) infants compared to those infants with delayed PDA closure (Group-3; median 1.8:1, range 0.8:1–4.2:1). Despite the relatively lower baseline shunt volume in older Group-3 infants with delayed PDA closure, the PASPs were higher than infants in Group-1 (median PASP 50% systemic vs. 76% systemic for Group-1 vs. Group-3; $P < 0.001$) secondary to an increased baseline pulmonary vascular resistance (median baseline PVRi = 1.6 vs. 3.3 WU*m^2 for Groups 1 and 3, respectively; $P < 0.001$).

Assessment of respiratory outcomes

All infants were on mechanical ventilator support at the time of TCPC. Though not statistically different, the mean

Table 3 Respiratory severity scores.

Variable	Group-1 ($n = 34$)	Group-2 ($n = 33$)	Group-3 ($n = 33$)	Group-1 vs. -3 P value[a]
Mean baseline RSS	3.1 (2.4–6.3)	4.5 (1.8–9)	4 (1.9–14)	0.389
Immediate post-TCPC RSS	3.4 (2.6–8)	5 (2–10.6)	5.8 (2.5–18)	0.015
Change in RSS pre/post-TCPC (%)	20 (0–47)	13.3 (0–45.3)	29 (7.1–98.7)	0.071
Time taken to return to pre-procedure RSS (h)	6 (0–42)	12 (0–60)	20 (1–170)	0.117
Time to initial extubation (days)	16 (4–44)	12 (2–36)	39 (4–92)	0.001
Time from TCPC to RSS < 2 (days)	20 (1–54)	38 (0–213)	81 (1–646)	0.001

Data expressed as median and interquartile range.

TCPC transcatheter PDA closure, *RSS* respiratory severity score.

[a]Groups 1 and 2 were not significantly different and neither are Groups 2 and 3 for most variables. However, significant differences are noted between Groups 1 and 3 and therefore, only these differences are represented in this table.

baseline RSS was highest for infants in Group-3 (Table 3). However, the RSS immediately post-TCPC was significantly higher for infants in Group-3 compared to Group-1 (median 5.8 vs. 3.4; $P = 0.015$). Though the infants in Group-1 were younger and smaller, they were able to extubate sooner compared to Group-3 (median time to extubate from TCPC was 16 vs. 39 days; $P = 0.001$). Also, infants in Group-3 took a longer time to wean from respiratory support as evidenced by prolonged time taken for RSS to get to a score of <2 from the time of TCPC as compared to infants in Group-1 (median 81 vs. 20 days; $P = 0.001$).

Kaplan–Meier analysis comparing the time taken to achieve an RSS < 2 from PDA closure based on the age at PDA closure (Fig. 2) shows an overall P value of $P = 0.026$ (log-rank test = 7.26) indicating that there are group differences. Specific comparisons reveal that infants with early PDA closure (<4 weeks of age) reach RSS < 2 significantly faster than those with late PDA closure of >8 weeks (log-rank test = 6.43, $P = 0.01$). The predictors of prolonged (>30 days) elevation of RSS ≥ 2 were: TCPC performed at >8 weeks of age and a PVRi ≥ 3 (OR = 3.2, 95% CI: 1.7–5.8, $P = 0.03$ and OR = 4.5, 95% CI: 2.7–8.9, $P < 0.01$, respectively).

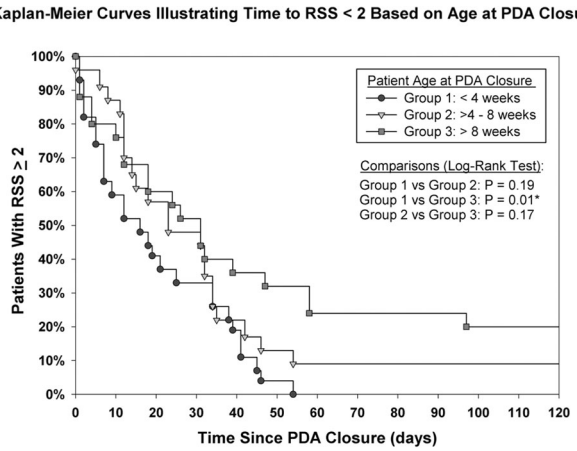

Fig. 2 Kaplan-Meier Curves comparing the time taken to achieve a Respiratory Severity Score < 2 from PDA closure based on the age at PDA closure.

Influence of pulmonary hypertension (PHT)

Sixty-four percent of infants from the entire cohort had an elevated PASP (defined as an PASP > 50% of SBP). However, in 44%, this was secondary to increased pulmonary blood flow from the PDA and not secondary to pulmonary vascular disease. However, 20 infants (17 from Group-3, three from Group-2 and none from Group-1) had true PHT secondary to elevated baseline PVRi ≥ 3 WU*m^2. A comparison of the demographics and outcomes of infants undergoing TCPC with and without PHT is outlined in Table 4. Infants with a baseline elevated PVRi of ≥3 WU*m^2 were further evaluated with vasoreactivity testing and test occlusion of the PDA as shown in Fig. 3 (Graphs A, B, and C). With 100% FiO_2 and 20 ppm iNO, there was an expected increase in Qp:Qs ratio (from 2 ± 0.75 at baseline to 3 ± 1; $P < 0.01$) and a drop in PASP (from 75 ± 9% of SBP at baseline to 58 ± 7% of SBP; $P < 0.01$) due to a decrease in PVRi (4.8 ± 0.9 WU*m^2 at baseline to 3.7 ± 0.5 WU*m^2; $P < 0.001$), suggesting good vasoreactivity of the pulmonary vascular bed. As expected, test occlusion of the PDA decreased the Qp:Qs (to nearly 1:1 in all; $P < 0.001$) with a further, albeit relatively minor decrease in PASP (55 ± 8% of SBP; $P = 0.67$) and almost no change in PVRi (3.7 ± 0.5 WU*m^2; $P = 0.89$). Based on these findings all PDAs were found to be suitable for closure.

Though the gestational age and birth weights were similar, those with PHT were referred for PDA closure later (median procedure age of 84 vs. 32 days; $P < 0.001$) and consequently had a higher pre-procedure RSS (median 5.9 vs. 3.0; $P < 0.001$). This group of infants took a longer time to return to their baseline RSS following TCPC in comparison to infants without PHT (median of 32 vs. 6 h,

Table 4 Demographics and outcomes of patients undergoing TCPC with or without elevated baseline pulmonary vascular resistance.

Variable	PVRi < 3 WU*m^2 ($N = 80$)	PVRi ≥ 3 WU*m^2 ($N = 20$)	P value
Gestational age (weeks)	24 (22–27)	24 (22–27)	0.5
Procedure age (days)	32 (9–69)	84 (44–177)	<0.001
Birth weight (g)	650 (480–1000)	670 (470–1000)	0.74
Procedure weight (g)	1180 (640–2160)	2240 (1720–3600)	<0.001
Mean baseline RSS	3.0 (1.8–6.3)	5.9 (4.0–14)	<0.001
Immediate post-TCPC RSS	3.5 (2–8)	6.7 (5.3–18)	<0.001
Time taken to return to pre-procedure RSS (h)	6 (0–42)	32 (11–170)	<0.001
Time to initial extubation (days)	18 (2–44)	30 (10–92)	<0.001
Time to RSS < 2 (days)	23 (0–64)	61 (24–646)	<0.001

TCPC transcatheter PDA closure, *PVRi* pulmonary vascular resistance, *RSS* respiratory severity score.

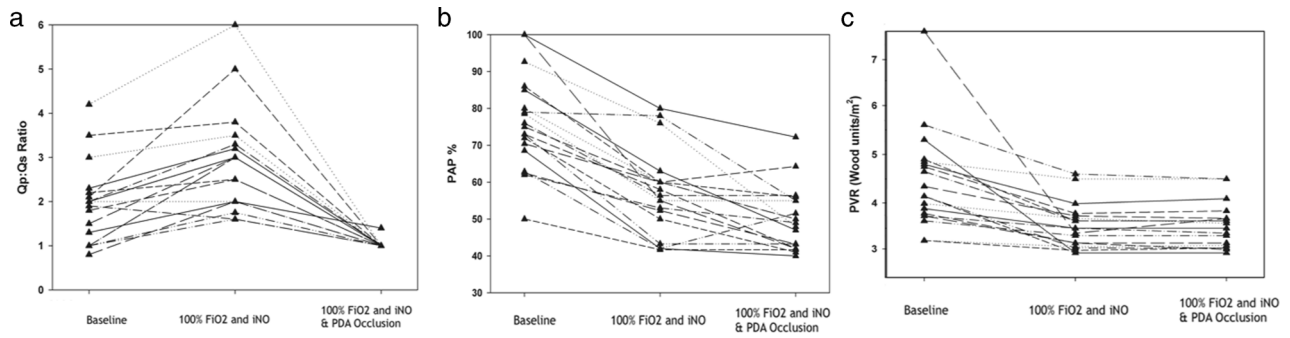

Fig. 3 Hemodynamic assessment of 40 infants with pulmonary hypertension (PHT), which is defined as pulmonary vascular resistance >3 WU*m^2 under three differing conditions—at baseline, with 100% oxygen (FiO_2) and 20 ppm iNO and with test occlusion of the PDA. a Change in pulmonary to systemic blood flow ratio (Qp:Qs) under the three hemodynamic conditions. Note that the use of pulmonary vasodilator therapy using 100% FiO_2 and 20 ppm iNO is associated with increased shunting across the PDA and increase in pulmonary blood flow and decrease in systemic blood flow as evidenced by an increase in Qp:Qs ratio. With test occlusion of the PDA, the Qp:Qs is 1:1 suggestive of no residual shunting across the PDA. **b** Change in pulmonary artery systolic pressure expressed as a percentage of the systolic blood pressure (PAP%). At baseline, all infants with PHT have >50% systemic pulmonary artery systolic pressure and as high as 100%. With pulmonary vasodilator therapy using 100% FiO_2 and 20 ppm iNO, there is decrease in PAP% suggestive of reactive pulmonary capillary bed. With PDA occlusion, there is further decrease in PAP% as the pulmonary blood flow is decreased. **c** Change in pulmonary vascular resistance (PVR) with change in loading conditions. At baseline, all infants have PVR > 3WU*m^2. With pulmonary vasodilator therapy using 100% FiO_2 and 20 ppm iNO, there is decrease in PVR suggestive of reactive pulmonary capillary bed. With PDA occlusion, there is no further decrease in PVR as decrease in pulmonary blood flow only affects the PAP% and not the PVR (pressure = flow × resistance).

$P < 0.001$, OR = 3.9), making them higher risk infants to undergo the procedure. Infants with PHT, though older than those without PHT, took longer to extubate from the time of PDA closure (median time to extubate—30 vs. 18 days; $P < 0.001$) and, it took them longer to achieve an RSS of <2 after PDA closure compared to those without PHT (median time to RSS < 2 from TCPC 61 vs. 23 days; $P < 0.001$) indicating the need for prolonged respiratory support.

Assessment of growth velocity

The mean weight gain for infants in Group-1 in 4 weeks immediately following PDA closure was 24.7 ± 7.9 g/day (which was faster than the 14.3 ± 9.2 g/day in 2 weeks prior to PDA closure ($P = 0.032$)). The mean indexed weight gain for Group-1 pre-and post-PDA closure was 15.7 ± 8.6 g/kg/day and 19.9 ± 7.8 g/kg/day ($P = 0.036$). The mean weight gain for infants in Group-3 in the 2 weeks prior to (18.8 ± 8.8 g/day; 10.4 ± 6.3 g/kg/day) and the 4 weeks post-PDA closure (20.4 ± 10.3 g/day; 9.9 ± 6.1 g/kg/day) was not significantly different ($P = 0.358$).

It is also worth noting that specifically between 4 and 8 weeks of life, the weight gain for infants in Group-1 (who had PDAs closed before this time) was 25.0 ± 8.2 g/day (20.8 ± 6.9 g/kg/day), which was much more rapid than those in Group-3 (who still had the PDA during this time), whose weight gain was 16.2 ± 6.4 (13.5 ± 5.3) during the 4–8 weeks of life ($P = 0.002$). The growth during the 4–8 weeks period is important for the overall outcome of these ELBW infants. This further supports the notion that earlier PDA closure would be beneficial for ELBW infants.

Discussion

This study is distinctive in evaluating real-time hemodynamics of PDA closure in ELBW infants. There have been previous case series [19–21] evaluating hemodynamics with test occlusion of the PDA in older children and adults but none have identified the difference in hemodynamics based on timing of closure in ELBW infants. Though this study has multiple limitations, it clearly describes the hemodynamic significance of PDA in ELBW infants at various time points. In infants born ≤27 weeks' gestation, weighing ≤1 kg, closing a hsPDA may carry certain advantages including, faster weaning off mechanical ventilator and oxygen supplementation and improved weight gain.

PHT is a delayed sequela of a persistent, large left-to-right shunt in term infants. Although this study does not look into the late development of PHT in infants undergoing early PDA closure, persistent ductal patency seems to lead to accelerated pulmonary vascular disease in ELBW infants. With the primary clinical focus on the systemic steal of a large PDA, the risk of developing PHT is often overlooked during decision-making for PDA closure.

The overall mortality of BPD and PHT in preterm children is as high as 18–30% at 2 years of age [22]. 64% of infants in this study had an elevated PASP. In the presence of a large PDA, there can be equalization of pressures between the aorta and the pulmonary artery. Elevated PASP per se is not analogous with PHT. The diagnosis of PHT is truly based on elevated pulmonary vascular resistance (PVRi), which unfortunately cannot be calculated using clinical criteria or noninvasive testing. PHT is the product

of both pulmonary blood flow (Qp) and PVRi (pressure = flow × resistance). Therefore, in order to efficiently treat PHT, the Qp has to be controlled by closing the PDA for pulmonary vasodilators to be adroitly functional, which could hypothetically reduce the previously stated 2-year mortality. The use of pulmonary vasodilator therapy in ELBW infants with a hsPDA can worsen the hemodynamic load on the pulmonary vasculature. As was demonstrated by vasoreactivity testing, even for infants in Group-3, there was a fall in the PASP suggestive of reversible PHT in the majority. As illustrated in the hemodynamic graphs (Fig. 3) test occlusion of the PDA, helped to decipher the contribution of left-to-right shunt and PVRi to PHT and helped assess if it was safe to close these PDAs. On the contrary, PDAs with right-to-left shunting providing a "pop off" for systemic perfusion should not be closed. In these infants, vasodilator therapy can be initiated with plans for re-evaluation of hemodynamics after providing time for vascular remodeling.

The debate of, "if", "when", and "how" to close a hsPDA in ELBW infants rages on [23–25]. Let's first tackle the question of "when" the optimal timing of PDA closure is. Based on this study, the benefits of early closure include rapid improvement in the respiratory status of ELBW infants and normal growth velocity. Though the groups are not comparable, early PDA closure was associated with short periods of intubation, mechanical ventilation, and oxygen supplementation as shown by a fast decrease in RSS to <2. This study also identifies PHT and delayed PDA closure as risk factors for worse respiratory outcomes and hence attempts to answer the relevant question as to when a PDA should be closed. This study also endeavors to answer the question of "how" the PDA should be closed. Medical therapy does not ensure 100% closure of the PDA with a variable success rate and side effect profile [26, 27]. Surgical ligation is too invasive and is associated with multiple adverse effects [28, 29]. TCPC does have an initial learning curve. However, once the operator experience improves, such as at our center, it can be performed with good success with no significant adverse events [11]. Transcatheter closure also has the advantage of obtaining invaluable information on hemodynamic significance (Qp:Qs ratio) and pulmonary vascular resistance, which is not possible with either surgical ligation or medical therapy.

The only question that now remains is whether the PDA should be closed in ELBW infants. What can be agreed upon from previous studies is that the increased risk of neonatal morbidities is only associated with moderate-to-large PDAs and not with small shunts and that moderate-to-large PDAs lower systemic blood pressure and alter pulmonary compliance [30]. The benefit of any therapy should be to improve outcomes. In the past, a multitude of RCTs failed to demonstrate any benefit to PDA closure. The effectiveness of drugs used to constrict the PDA (indomethacin, ibuprofen, and paracetamol) in less mature infants (especially ≤26 weeks) is significantly reduced [6]. One could argue that these RCTs included an imperfect therapy, therefore leading to the wrong conclusions. Many of these RCTs did not have a good definition for a hsPDA, thereby lumping all comers. The therapy that was chosen were either the use of COX inhibitors, which are not 100% effective, and take too long to show effect, or surgical ligation that was too invasive. In this study, hemodynamic significance was definitely assured by performing a diagnostic catheterization prior to PDA closure and measuring the pulmonary blood flow (Qp) and its ratio to systemic cardiac output (Qs). This is the first-time definitive closure of PDAs whose hemodynamics were measured prior to closure was shown to have benefit in outcomes. The benefits being, early extubation, faster decline in RSS, improved growth velocity and perhaps avoidance of development of PHT. The converse was also measured. Persistent patency of a hsPDA in ELBW infants was shown to be associated with early onset PHT, prolonged elevation of RSS and poor growth rate prior to PDA closure. Since our experience with TCPC has grown and procedural complications are minimal [12], our center has a lower threshold to intervene. Since January 2016, the age at which TCPC was performed at our center has steadily declined. We started out with older children with BPD and PHT. Almost all these patients belonged to Group-3. More recently, the age at which ELBW infants are referred for TCPC has been between the second and third week of life, principally all belonging to Group-1. This change in clinical practice secondary to the entire team getting comfortable with the procedure and post-procedure care has led to improved outcomes [31]. In fact, we do not encounter infants with severe PHT being referred for cardiac catheterization anymore.

Obviously, this is only anecdotal. However, we believe that we are on to something propitious as an increasing number of centers have recently started transferring patients in for this procedure. If the results were not encouraging, referring institutes would not take the risk of transferring fragile ELBW infants over long distances. Therefore, the debate of whether the hsPDA needs to be closed in the early neonatal period in ELBW infants can only be addressed by a properly designed RCT comparing this therapy with no intervention on the PDA. In the meantime, TCPC does offer an alternative for an age-old problem.

Our recommendation is a stepwise approach including initial medical therapy. At 2–3 weeks of age, if the moderate-to-large PDA persists with increased ventilatory or supplemental oxygen requirements and feeding issues, it should be considered for closure. We would recommend TCPC as the best method to close it after failed medical

therapy as it is associated with the least adverse events, at least in an experienced center.

This study is limited by being retrospective and not randomized. There is also a selection bias in that possibly the infants in Group-3 were not stable at an earlier age and hence were referred late and had worse respiratory outcomes. Though the groups are similar, multiple other comorbidities and confounding factors usually associated with ELBW infants were not factored while interpreting the results. However, the point of this study was only to address the hemodynamics of a persistent hsPDA and its significance and not on all co-morbidities.

Enrollees in this study did not have any worsening of pre-existing co-morbidities after TCPC. Infants in Group-1 had less incidence of sepsis and NEC Stage-IIB and -III prior to TCPC compared to Groups 2 and 3. There was no recurrence of NEC post TCPC, and no infant that did not have NEC prior to TCPC developed NEC post procedure. Selection bias also exists in the pattern of referrals. As TCPC proved to be feasible and associated with negligible adverse events, the age at which ELBW infants were referred for TCPC declined overtime. The subset of infants that had an elevated PVRi needing hemodynamic assessment gradually decreased overtime as the number of early referrals for TCPC increased. We are in the process of prospectively following these infants that underwent early versus delayed closure of hsPDA for longer term neurodevelopmental outcomes.

Other recent studies inspecting medical [32] and surgical [33] therapies have evaluated early versus late closure of the PDA and have demonstrated lesser incidence of BPD, ventilator dependence, and feeding intolerance, respectively, but have needed further evaluation of long-term outcomes. In the last 30–40 years the pendulum on whether to close or not to close has changed and hence the medical community remains divided on this issue. However, most of these questions have been based on medical and surgical ligations. With advancing technology and growing experience in ELBW infants [11, 13], TCPC offers a safer [11], more advanced diagnostic and clinically informative therapeutic option to answer all of these questions. With the recent FDA approval of a device for TCPC because it was found to be safe and effective [34], the natural next step will be to demonstrate benefits, identify who benefits the most and at what age will these benefits be most significantly appreciated.

Conclusions

It may be beneficial to close hsPDA in the first 4 weeks of life and before the onset of elevated PVRi in ELBW infants. Early PDA closure may also afford faster weaning off ventilator and oxygen support and allows for better weight gain. In addition to providing immediate closure of the PDA, TCPC also provides useful hemodynamics to ascertain safe closure and appropriate infant selection.

Future directions

Before adopting early, indiscriminate use of TCPC, it is essential that we design RCTs that examine both the short-term and long-term benefits for the infant [30]. To evaluate long-term benefits of PDA closure it is essential to identify the population that will be of most benefit, the appropriate timing of the intervention to achieve that benefit and the fitting method of intervention. A well-designed RCT in preterm infants ≤27 weeks of gestation with hsPDA in the neonatal period is needed. The ideal study would be to evaluate no intervention versus TCPC as early as 7–10 days of life. Evaluation of long-term neurodevelopmental outcomes in this cohort is most vital.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. Pediatrics. 2009;123:e138–44.
2. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010;30:241–52.
3. Clyman RI, Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson S, et al. An exploratory randomized controlled trial of treatment of moderate-to-large patent ductus arteriosus at 1 week of age. J Pediatr. 2019;205:41–8.
4. Benitz WE. Committee on fetus and newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016;137:e20153730.
5. Benitz WE, Bhombal S. The use of non-steroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants. Semin Fetal Neonatal Med. 2017;22:302–7.
6. Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson S, Lindqvist J, et al. Comparative effectiveness of drugs used to constrict the patent ductus arteriosus: a secondary analysis of the PDA-TOLERATE trial (NCT01958320). J Perinatol. 2019;39:599–607.
7. Shelton EL, Waleh N, Plosa EJ, Benjamin JT, Milne GL, Hooper CW, et al. Effects of antenatal betamethasone on preterm human and mouse ductus arteriosus: comparison with baboon data. Pediatr Res. 2018;84:458–65.
8. Clyman R, Cassady G, Kirklin JK, Collins M, Philips JB III. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. J Pediatr. 2009;154:873–6.

9. Sung SI, Chang YS, Chun JY, Yoon SA, Yoo HS, Ahn SY, et al. Mandatory closure versus nonintervention for patent ductus arteriosus in very preterm infants. J Pediatr. 2016;177:66–71.
10. Philip R, Waller BR 3rd, Agrawal V, Wright D, Arevalo A, Zurakowski D, et al. Morphologic characterization of the patent ductus arteriosus in the premature infant and the choice of transcatheter occlusion device. Catheter Cardiovasc Inter. 2016;87:310–7.
11. Sathanandam S, Balduf K, Chilakala S, Washington K, Allen K, Knott-Craig C, et al. Role of transcatheter patent ductus arteriosus closure in extremely low birth weight infants. Catheter Cardiovasc Inter. 2019;93:89–96.
12. Sathanandam S, Agrawal H, Chilakala S, Johnson J, Allen K, Knott-Craig C, et al. Can Transcatheter PDA closure be performed in neonates ≤1000 grams? The Memphis experience. Congenit Heart Dis. 2019;14:79–84.
13. Agrawal H, Waller BR 3rd, Surendan S, Sathanandam S. New patent ductus arteriosus closure devices and techniques. Inter Cardiol Clin. 2019;8:23–32.
14. Sathanandam S, Justino H, Waller BR 3rd, Radtke W, Qureshi AM. Initial clinical experience with the Medtronic Micro Vascular Plug™ in transcatheter occlusion of PDAs in extremely premature infants. Catheter Cardiovasc Inter. 2017;89:1051–8.
15. Johnson JN, Sathanandam S, Naik R, Philip R. Echocardiographic guidance for transcatheter patent ductus arteriosus closure in extremely low birth weight infants. Congenit Heart Dis. 2019;14:74–8.
16. 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:F424–7.
17. Alexander J, Yohannan T, Abutineh I, Agrawal V, Lloyd H, Zurakowski D, et al. Ultrasound guided femoral arterial access in pediatric cardiac catheterizations: a prospective evaluation of the prevalence, risk factors, and mechanism for acute loss of arterial pulse. Catheter Cardiovasc Inter. 2016;88:1098–107.
18. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015;132:2037–99.
19. Niu MC, Mallory GB, Justino H, Ruiz FE, Petit CJ. Treatment of severe pulmonary hypertension in the setting of the large patent ductus arteriosus. Pediatrics. 2013;131:e1643–9.
20. Yan C, Zhao S, Jiang S, Xu Z, Huang L, Zheng H, et al. Transcatheter closure of patent ductus arteriosus with severe pulmonary arterial hypertension in adults. Heart. 2007;93:514–8.
21. Feng J, Kong X, Sheng Y, Yang R. Patent ductus arteriosus with persistent pulmonary artery hypertension after transcatheter closure. Ther Clin Risk Manag. 2016;12:1609–13.
22. Slaughter JL, Pakrashi T, Jones DE, South AP, Shah TA. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol. 2011;31:635–40.
23. Sathanandam S, Whiting S, Cunningham J, Zurakowski D, Apalodimas L, Waller BR, et al. Practice variation in the management of patent ductus arteriosus in extremely low birth weight infants in the United States: survey results among cardiologists and neonatologists. Congenit Heart Dis. 2019;14:6–14.
24. Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN. Changes in the diagnosis and management of patent ductus arteriosus from 2006 to 2015 in United States Neonatal Intensive Care Units. J Pediatr. 2017;189:105–12.
25. Benitz WE. Hey, doctor, leave the PDA alone. Pediatrics. 2017;140:e20170566.
26. Oncel MY, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Pediatr. 2014;164:510–4.
27. Zecca E, Romagnoli C, De Carolis MP, Costa S, Marra R, De Luca D. Does Ibuprofen increase neonatal hyperbilirubinemia? Pediatrics. 2009;124:480–4.
28. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics. 2007;119:1165–74. 28
29. Mirea L, Sankaran K, Seshia M, Ohlsson A, Allen AC, Aziz K, et al. Treatment of patent ductus arteriosus and neonatal mortality/morbidities: adjustment for treatment selection bias. J Pediatr. 2012;161:689–94.
30. Clyman RI, Benitz WE. Transcatheter patent ductus arteriosus closure-will history repeat itself? J Perinatol. 2019;39:1435–6.
31. Apalodimas L, Waller IIIBR, Philip R, Crawford J, Cunningham J, Sathanandam S. A comprehensive program for preterm infants with patent ductus arteriosus. Congenit Heart Dis. 2019;14:90–4.
32. Liebowitz M, Clyman RI. Prophylactic indomethacin compared with delayed conservative management of the patent ductus arteriousus in extremely preterm infants: effects on neonatal outcomes. J Pediatr. 2017;187:119–26.
33. Liebowitz M, Fonseca E, Georgiev SG, Gorenflo M, Loukanov TS. Patent ductus arteriosus in preterm infants: benefits of early surgical closure. Asian Cardiovasc Thorac Ann. 2014;22:391–6.
34. Sathanandam SK, Gutfinger D, O'Brien L, Forbes TJ, Gillespie MJ, Berman DP, et al. Amplatzer Piccolo Occluder clinical trial for percutaneous closure of the patent ductus arteriosus in patients ≥700 grams. Catheter Cardiovasc Interv. 2020. https://doi.org/10.1002/ccd.28973. [Epub ahead of print].