ARTICLE

Phenotyping respiratory decompensation following definitive closure of the patent ductus arteriosus in preterm infants

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OBJECTIVE: To identify risk factors associated with high-frequency ventilation (HFV) following definitive closure of the patent ductus arteriosus (PDA).
METHODS: We performed a retrospective study of premature infants (<37 weeks) who were mechanically ventilated before and after surgical or transcatheter PDA closure. Primary outcome was HFV requirement within 24 h of procedure. Logistic regression was used to estimate clinical associations with post procedure HFV requirement.
RESULTS: We identified 110 infants who were mechanically ventilated before PDA closure, of which 48 (44%) escalated to HFV within 24 h after closure. In the multivariable model, surgical ligation (OR 21.5, 95% CI 1.6–284), elevated Respiratory Severity Score (RSS) 1 h post-procedure (OR 1.78, 95% CI 1.07–2.99) and 12 h post-procedure (OR 2.12, 95% CI 1.37–3.26) were independent predictors of HFV.
CONCLUSION: Surgical ligation and elevated RSS values over the first 12 h after PDA closure are risk factors for HFV.

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INTRODUCTION

Preterm infants are often referred for definitive closure of the patent ductus arteriosus (PDA) with failure of, or contraindication to pharmacologic interventions and the inability to wean mechanical ventilation [1]. Following PDA closure many neonates have improved lung compliance, but temporal derangements in cardiopulmonary status with alterations in loading conditions occur in a subset of preterm infants who undergo surgical ligation (SL) or transcatheter closure (TCPC) [2, 3]. Upstream impact on the pulmonary vasculature following definitive closure of the PDA can lead to respiratory decompensation with subsequent escalation to high-frequency ventilation (HFV) in extremely preterm infants [2]. The ability to predict which infants will demonstrate favorable improvement in pulmonary mechanics following definitive closure is hampered by difficulties identifying the proportion of respiratory insufficiency that is related to the hemodynamic significant PDA versus other risk factors associated with prematurity, such as evolving chronic lung disease and prolonged mechanical ventilation.

Echocardiography has been utilized to assess cardiovascular compromise following definitive closure of the PDA [1], but there remains a paucity of non-invasive respiratory markers that are linked to the observed changes in oxygenation and ventilation. Historically, the oxygen index: (OI = mean airway pressure × fraction of inspired oxygen × 100/PaO_2) was utilized to assess the severity of respiratory illness, direct interventions, and evaluate response to therapies such as surfactant, HFV and inhaled nitric oxide [4–6]. In contemporary practice, the routine placement of arterial lines in premature infants is infrequent [7–9], precluding routine calculation of OI and subsequent risk stratification. Respiratory severity score (RSS) is calculated as the product of mean airway pressure ($\bar{P}aw$) and fraction of inspired oxygen (FiO_2), and has been validated as a noninvasive surrogate for OI in newborn infants [10]. Furthermore, RSS has been used to assess the degree of respiratory failure in premature infants [11] as well as categorize the severity of respiratory disease before and after SL [12–15] and transcatheter closure [16–19] of the PDA. While recent studies have separately compared respiratory outcomes with escalation to HFV [2] and changes in RSS [20] between infants who underwent SL or TCPC [20, 21], there is no combined data on RSS to guide escalation of respiratory support with HFV for timely individualization of the mechanical ventilation approaches following definitive closure of the PDA. Accordingly, the objective of this study was to identify risk factors that may be associated with HFV following definitive closure of the PDA in premature infants.

METHODS

Study population

We performed a retrospective analysis of all premature infants born <37 weeks gestational age who received invasive mechanical ventilation before and after definitive closure of the PDA with either SL or TCPC from 2014–2020 at Boston Children's Hospital. Patients were included if they were on invasive mechanical ventilation before and after definitive closure of the PDA. We excluded infants with complex congenital heart disease

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(except insignificant ventricular septal defects or atrial septal defects), known genetic or congenital anomalies, infants on non-invasive mechanical ventilation and those who did not undergo definitive PDA closure. The institutional review board of Boston Children's Hospital approved the study.

Respiratory outcomes

The enrolled subjects were divided into 2 groups according to the presence or absence of HFV in the 24 h following PDA procedure. Our primary outcome of interest was defined as the receipt of HFV within 24 h following ligation or device closure. We chose this time frame because previous reports have observed hemodynamic compromise with deficits in oxygenation and ventilation between 6 and 24 h following the procedure [22–24]. Secondary outcomes included oxygenation failure, defined as an increase in $\bar{P}$aw (cm H_2O) or FiO_2 by 20% of pre-procedure value for ≥1 h; ventilation failure, defined as an escalation to HFV or increase of high-frequency jet ventilation (HFJV) peak inspiratory pressure or high frequency oscillation ventilation (HFOV) ΔP by 20% for ≥1 h; hypotension defined as initiation of a new vasoactive agent or a 20% increase of pre-ligation dose for ≥1 h; and (d) Post Cardiac Ligation Syndrome: defined as a composite outcome including the presence of hypotension, oxygenation failure and ventilation failure [25].

All data were collected using a structured form and entered into a clinical registry database created in REDCap (Vanderbilt University, Nashville, TN). Demographic data along with perinatal and clinical factors prior to PDA procedure were collected from the medical record of each participant. Ventilator parameters, physiologic variables, and clinical characteristics were extracted from the medical record over five epochs: pre-procedure, post-procedure, and 6, 12, and 24 h post-procedure. RSS was calculated as the product of mean airway pressure and FiO_2 [10]. As a standard of care, infants were managed with conventional mechanical ventilation (CMV) using either pressure-controlled or volume-targeted modes of ventilation. In our institution, HFJV and HFOV are reserved for rescue therapy in the setting of severe respiratory failure (pH < 7.25, PCO_2 > 60 mmHg, or hypoxia, sustained FiO_2 > 60%) refractory to maximal lung protective CMV strategies and have been described in previous publications [26, 27]. The type of HFV and timing of transition was left to the discretion of the medical team.

Definitive closure of the PDA

All PDA ligations were performed in the operating room by a pediatric cardiothoracic surgeon in our hospital. Surgical ligation was accomplished via left thoracotomy and placement of a clip or ligature on the PDA. Prior to May 2019, SL was the primary method of definitive closure in preterm infants; thereafter, but following the 2019 US Food and Drug Administration (FDA) approval of the Amplatzer Piccolo™ Occluder (Abbott Structural Heart, Plymouth, MN, USA) for catheter-based closure for PDA in extremely low birth weight infants, all infants meeting criteria underwent TCPC in the cardiac catheterization laboratory by pediatric interventional cardiologists [28]. When the FDA-approved criteria for TCPC closure were not met, patients underwent a SL Criteria for TCPC eligibility included infants > 3 days of age, >700 grams at time of closure, no evidence of cortication of the aorta or left pulmonary artery stenosis, no active infection, no intracardiac thrombus, or evidence of cardiac output dependence on right to left shunt through the PDA [28]. An appropriately sized transcatheter device to close the PDA was delivered with the use of venous access alone and deployed under transthoracic echocardiogram and fluoroscopic guidance.

Statistical analysis

Descriptive statistics were used to summarize perinatal and postnatal characteristics for infants in the study. Since the data were not normally distributed the Wilcoxon rank sum test was used for comparison of continuous variables. Categorical variables were summarized using frequencies, percent's or proportions and compared using chi-square or Fisher's exact test as appropriate. Our primary goal was to examine the relationship between exposure to definitive PDA closure and subsequent escalation to HFV after closure. Post procedural HFV requirement was defined as a binary variable: received HFV within 24 h of PDA procedure. Univariate analysis was used to estimate the association of RSS and clinical characteristics with post procedure HFV requirement. For the multivariable model, backwards, step-wise logistic regression was performed to adjust for confounders and variables with a P value of >0.10 were removed from the final model [29, 30]. Receiver operating characteristic (ROC) curves were constructed to determine cutoff values at 1 h, 6 h, 12 h post procedure for RSS with the best sensitivity and specificity to predict the need for HFV. Data analysis was performed with SPSS Statistics 24 (IBM, Armonk, NY) and Stata version 16 (StataCorp LLC, College Station, TX). All tests were two-sided and P values < 0.05 were considered significant. Power analysis indicated that the sample sizes of patients requiring and not requiring HFV post procedure ($n = 48$ and $n = 62$) provided 90% power to detect a 30% or larger difference in RSS pre-procedure and 1, 6 and 12 h post using the Wilcoxon rank sum test (G*Power version 3.1, University of Dusseldorf, Germany) [31].

RESULTS

Demographics

From 2014–2020, a total of 168 infants underwent definitive PDA closure at Boston Children's Hospital (Boston, Massachusetts, USA). We identified 110 infants that underwent mechanical ventilation before and after PDA procedure, of which 48 (44%) received HFV and 62 (56%) received CMV post procedure. Of the 110, 88 underwent SL ($n = 44$ received HFV and $n = 44$ received CMV) and 22 underwent TCPC ($n = 4$ received HFV and $n = 18$ received CMV). We were able to perform a 4:1 case-control matched analysis between SL and TCPC (Fig. 1-Supplementary Information). Pre-procedure demographic and clinical characteristics are presented in Table I. Respiratory mechanics and hemodynamics variables are presented in (Tables 1 and 2-Supplementary Information), respectively.

Pre-procedure respiratory variables

Infants transitioned to HFV post procedure had higher median pre-procedure RSS (4 vs. 3.4, $P = 0.027$), FiO_2 (0.37 vs. 0.30, $P = 0.001$) and mandatory frequency (40 vs. 31 breaths/min, $P < 0.001$) compared to those who remained on CMV. In the HFV group there was a smaller median ductal diameter (2.5 mm vs. 3 mm, $P = 0.014$) and younger age at PDA closure (19d vs. 25d, $P = 0.03$) (Table 1).

Post-procedure respiratory variables

Eight infants were ventilated with HFV (HFJV, $n = 6$, and HFOV, $n = 2$) prior to PDA procedure, of which two were transitioned to CMV following the procedure and returned to HFV within 12 h. Forty subjects (36%) who were initially managed with CMV post-procedure escalated to HFV with 24 h of PDA closure. Following PDA procedure, 48 infants received HFV within 24 h; (HFJV $n = 38$, and HFOV, $n = 10$). These infants were characterized by progressive elevation of median RSS from pre-procedure through 24-hours. In addition, $\bar{P}$aw and FiO_2 at 6, 12, and 24 h post-procedure were higher compared with the CMV cohort ($P < 0.05$ at all time points). Median pH was lower in the HFV group from 6 h through 24 h post-procedure ($P < 0.05$ at all time points) (Table 1-Supplemenary Information).

Primary respiratory outcome

For the univariate analysis, clinical characteristics associated with post procedure HFV included PDA closure technique, gestational age, postnatal age at PDA closure, ductal diameter, male sex, post menstrual age at admission and RSS from admission through 12 h (Table 2). In the multivariable analysis, after adjustment for confounders, older gestational age at birth and later postnatal age at PDA procedure were protective against HFV. In contrast, surgical ligation, elevated RSS at 1 and 12 h post procedure were independent predictors of HFV (Table 3). The ranges of RSS for individual infants were 1.47–18.5 and 1.89–17 for 1 h and 12 h post procedure. Predicted probability of HFV for all subjects according to RSS at 1 and 12 h are presented in (Fig. 1). Receiver Operator Curves analysis was utilized to determine specific cutoff values of Respiratory Severity Score (RSS) in predicting need for post-procedure HFV. An RSS cut-off value > 4 detected HFV

Table 1. Pre-procedure Characteristics.

Variable	HFV ($n = 48$)	CMV ($n = 62$)	*P* value
Neonatal variables			
Gestational age at birth, weeks	25 (24, 26)	26 (24, 27)	0.010
Birthweight, kg	0.72 (0.59, 0.82)	0.77 (0.65, 0.90)	0.073
Age at closure, days	27 (25, 29)	29 (27, 32)	<0.001
Sex (Female)	16 (33)	34 (55)	0.034
Surfactant administration	46 (96)	55 (89)	0.29
Multiple gestation	15 (31)	13 (21)	0.27
Cesarean	32 (67)	46 (74)	0.40
Antenatal Steroids	29 (60)	40 (65)	0.69
Arterial access for procedure	17 (35)	14 (23)	0.38
Maternal complications			
Preeclampsia	4 (8)	12 (19)	0.18
Maternal diabetes	2 (4)	2 (3)	0.99
Chorioamnionitis	6 (13)	9 (15)	0.99
Respiratory variables			
Days of mechanical ventilation	12 (7, 23)	19 (8, 27)	0.075
RSS	4 (3–6)	3.4 (2.7–4.8)	0.027
$\bar{P}aw$, cm H_2O	10 (9–12)	10 (9–12)	0.56
FiO_2	0.37 (0.3–0.5)	0.30 (0.25–0.30)	0.001
PIP, cm H_2O	22 (20–25)	21 (19–23)	0.31
Respiratory rate, breaths/min	40 (31–40)	31 (28–37)	<0.001
PDA characteristics			
Pharmacologic management[a]	45 (94)	47 (76)	0.018
Age at PDA closure, days	19 (14, 26)	25 (18, 41)	0.003
Method of closure[b] TCPC SL	4 (8) 44 (92)	18 (29) 44 (71)	0.008
Dilated LA	32 (67)	45 (73)	0.54
Dilated LV	35 (73)	44 (71)	0.050
Systolic gradient, mm Hg	19.5 (14–25.5)	20 (15–29.5)	0.31
Flow reversal[c]	32 (67)	45 (73)	0.50
Diameter of duct, mm	2.5 (2, 3)	3 (2.5, 3.5)	0.014
Diameter of duct, mm/kg	2.3 (1.8–3.2)	2.1 (1.4–3)	0.19

Data are presented as median (interquartile range) or *n* % for categorical variables.
CMV conventional mechanical ventilation, *HFV* high-frequency ventilation, *TCPC* transcatheter PDA closure, *SL* surgical ligation, *LA* left atrium, *LV* left ventricle, $\bar{P}aw$ mean airway pressure.
P values were calculated using Fisher's exact test or the Mann-Whitney *U* test.
[a]Pharmacologic management was defined as at least one course of Indocin, Ibuprofen, or Tylenol prior to definitive closure.
[b]SL was the primary method of definitive closure in all subjects before 2019; thereafter all infants meeting criteria underwent TCPC in the catheterization laboratory.
[c]Flow reversal is defined as echocardiographic observation of flow reversal during diastole in the descending aorta.

Table 2. Univariate Comparison by mode of ventilation after PDA closure.

Variable	HFV after procedure ($n = 48$)	CMV after procedure ($n = 62$)	*P* value
PDA closure technique			
TCPC	4 (8%)	18 (29%)	0.008
SL	44 (92%)	44 (71%)	
Gestational Age (weeks)	25 (24, 26)	26 (24, 27)	0.010
Weight (kg)	0.72 (0.59, 0.82)	0.77 (0.65, 0.90)	0.073
Day of life at PDA closure	19 (14, 26)	25 (18, 41)	0.003
Age at closure (days)	27 (25, 29)	29 (27, 32)	<0.001
Sex			0.034
Female	16 (33)	34 (55)	
Male	32 (67)	28 (45)	
Diameter of duct (mm)	2.5 (2, 3)	3 (2.5, 3.5)	0.014
RSS pre procedure	4.0 (3.1, 6.0)	3.4 (2.7, 4.8)	0.027
RSS post procedure	4.3 (2.9, 6.5)	3.4 (2.5, 4.5)	0.006
RSS 6 h	5.5 (3.6, 7.6)	3.3 (2.5, 5.2)	<0.001
RSS 12 h	6.3 (4.4, 8.4)	3.3 (2.7, 5.0)	<0.001

Data are presented as median (interquartile range) or number (percentage).
PDA patent ductus arteriosus, *HFV* high frequency ventilation, CMV conventional mechanical ventilation, *SL* surgical ligation, *TCPC* transcatheter PDA closure.
P values were calculated using Fisher's exact test or the Wilcoxon rank sum test, as appropriate.

Table 3. Multivariable analysis by mode of ventilation after PDA closure.

Covariate	Adjusted odds ratio	95% CI	*P* value
PDA Closure Technique			
TCPC	Reference	.	.
SL	21.5	(1.62, 284)	0.018
Gestational Age (weeks)	0.51	(0.30, 0.85)	0.009
Age at closure (days)	0.9	(0.85, 0.97)	0.003
RSS 1 h post procedure	1.78	(1.07, 2.99)	0.027
RSS 12 h post procedure	2.12	(1.37, 3.26)	<0.001

PDA patent ductus arteriosus, *RSS* respiratory severity score, *HFV* high frequency ventilation, *TCPC* transcatheter PDA closure.

requirement at 1 h with a sensitivity of 56% and specificity of 68%, AUC 0.652 (95% CI, 0.55–0.76), and increased by 12 h to 85% and 67%, AUC 0.808 (95% CI, 0.725–0.89).

Secondary cardiopulmonary outcomes

We assessed secondary outcomes including systolic hypotension (defined as initiation of a new vasoactive agent or a 20% increase above pre-ligation dose for ≥1 h), escalation of mechanical

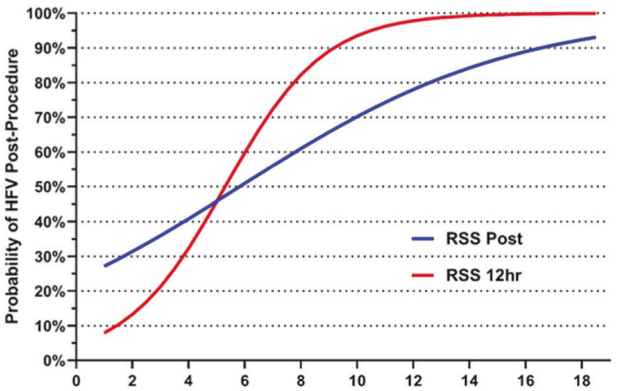

Fig. 1 Predicted probability curves of high-frequency ventilation according to Respiratory Severity Score (RSS) were derived using logistic regression. RSS ranges for individual subjects were 1.47–18.5 and 1.89–17 for 1 h and 12 h post procedure.

ventilation parameters (>20% increase in PIP, $\bar{P}$aw and FiO_2) within 24 h of PDA closure. Escalation of PIP (CMV or HFJV) and HFOV ΔP was similar between the CMV and HFV groups ($P = 0.72$) Table 4. Elevation of $\bar{P}$aw was more commonly observed in the HFV group 46% vs. 18% for CMV ($P = 0.001$). There was no difference between groups with increased FiO_2 ($P = 0.12$) and presence of hypotension ($P = 0.18$). Although PLCS was present in both groups, it occurred more frequently in the HFV group compared with infants who received CMV ($n = 8$, 17% versus $n = 2$, 3%, $P = 0.019$). At 1 h post-closure heart rate and blood pressure were similar between the CMV and HFV groups (Table 2-Supplementary Information).

DISCUSSION

Definitive closure of the PDA can lead to alterations in cardiopulmonary status in some extremely preterm infants with observed escalation of hemodynamic and respiratory support. The main findings of this retrospective case-control study are: (1) a non-invasive measure of pulmonary severity, RSS, at 1 and 12 h were independent predictors of post procedure requirement of HFV; and (2) the odds of receiving HFV following SL were 21-fold higher compared TCPC. The post intervention course can be complicated by oxygenation failure and serial RSS measurements may compliment current clinical and imaging approaches to anticipate and stratify risk for phenotypically respiratory decompensation following procedures to close the PDA.

Changes in respiratory mechanics has necessitated use of HFV following definitive closure of the PDA, with a reported prevalence ranging from 37 to 67% [12, 14], and consistent with our own findings of 44% of infants needing HFV following closure. Serrano et al. described post-procedural HFV requirement between SL and TCPC, and found that 20% of infants who underwent SL received HFV as opposed to none in the TCPC group, with the SL group demonstrating a higher post-procedural FiO_2 (0.64 vs. 0.43, $P = .004$) and a larger total change in peak FiO_2 (0.23–0.9, $P = .008$) [2]. These results underscore our findings that infants who had SL represented 92% of those who subsequently escalated to HFV within 12 h of surgery: SL 50% ($n = 44/88$) compared with 18% ($n = 4/22$), as the odds of receiving HFV following SL were 21-fold higher compared to TCPC. Similarly, other investigators have not only described a lower need for hemodynamic support [2], but also favorable improvements in cardiopulmonary outcomes with more rapid respiratory recovery [17, 21] and shorter duration of mechanical ventilation in infants who underwent TCPC. While some speculate that the more favorable cardiopulmonary outcomes observed following TCPC may be directly related to the absence of thoracotomy rather than

Table 4. Components of post ligation cardiac syndrome.

Variable	CMV ($n = 62$)	HFV ($n = 48$)	*P*
PIP > 20%	6 (9%)	3 (6%)	0.72
$\bar{P}$aw >20%	11 (18%)	22 (46%)	0.001
FiO_2 > 20%	43 (69%)	40 (83%)	0.12
Hypotension	12 (19%)	15 (31%)	0.18
PLCS	2 (3%)	8 (17%)	0.019

Data are presented as *n* (%).
CMV conventional mechanical ventilation, *HFV* high-frequency ventilation, *PIP* peak inspiratory pressure, $\bar{P}aw$ mean airway pressure, FiO_2 fraction of inspired oxygen, PLCS post cardiac ligation syndrome.

PDA closure itself, there remains evidence of PLCS following TCPC [2, 3]. The changes in the heart following SL are likely different than following TCPC and compounded by the disruption of respiratory mechanics following thoracotomy and the need for manual retraction of the left lung to access the PDA, a process that may induce further trauma to the fragile surfactant deficient lung tissue. Moreover, compression of the left lung may result in cytokine cascades, activation of inflammatory pathways, coupled with additional alveolar stretch and barotrauma of the right lung in an attempt to maintain adequate oxygenation and ventilation. Escalation of mechanical ventilation settings and FiO_2 increases the risk of hyperoxia mediated lung damage, can exacerbate underlying lung disease, and contributes to ventilator induced lung injury [32]. Collectively, these observations add to the burgeoning body of literature that is suggesting TCPC may afford appreciable benefits in post procedural respiratory mechanics over SL.

The ability to predict escalation of respiratory support following definitive closure is critical and may allow for timely individualization of the ventilation strategy in this high risk population. To our knowledge, this study is the first to utilize serial RSS measurements before and after definitive PDA closure to assess respiratory severity and subsequent escalation to HFV. RSS has been shown to have a strong linear correlation to OI [10], and is a validated non-invasive metric to assess the severity of respiratory failure in premature infants undergoing mechanical ventilation [11]. Multiple studies have utilized RSS to characterize derangements in oxygenation and ventilation status following PDA ligation [12–15, 20, 21] or transcatheter closure [16–21], but none have focused only on determining the need for HFV after definitive closure with comparisons between both interventions. Francis and colleagues evaluated temporal trends in respiratory and cardiovascular morbidity within 48 h of SL and reported significant escalation of RSS from pre-operative value of 4.6 (3–6.1) to 6 (3.5–8); a finding that persisted until 12 h, before returning to baseline [15]. Sathanandam et al. conducted a propensity score analysis that compared respiratory outcomes between infants who underwent SL or TCPC, and demonstrated that infants who underwent TCPC were characterized by lower delta change between pre and post procedure RSS (18% vs. 76%, $P < 0.01$), a more rapid return to baseline RSS (8 vs. 28 h, $P < 0.01$) and extubated earlier (14 vs. 26 days, $P < 0.01$) than their surgical counterparts [20].

The identification of a cut-off value of RSS is critical to detect respiratory compromise in preterm infants and several recent studies have explored cut-off values during over the first month of age [33–36] that were associated with morbidity and mortality in extremely preterm infants. Shah et al. divided RSS into 3 risk strata: <2 (low), 2-5 (moderate) and >5 (high), and demonstrated an increased odds of severe morbidity and mortality for infants in both the moderate *OR* 3.1 (1.7–5.4) and high-risk strata *OR* 4.5 (2.5–8.2). Interestingly, infants who ultimately required medical or

surgical treatment for PDA comprised around 50% of both moderate and high risk strata [33]. Bhattacharjee and colleagues showed that a cut-off > 4 was associated with death prior to 36 weeks PMA [34]. Similarly, Jung et al. found that cut-off values between 3 and 4 over the first month of age was associated with severe BPD or death during the neonatal period [35]. Malkar et al. found that cut-off value > 6 at 30 days of age was associated with increased mortality [36]. Lagatta et al. showed that among infants with severe BPD requiring mechanical ventilation at 36 weeks' postmenstrual age, PH was associated with a more than four-fold increase in RSS. These contemporary findings compliment the observation in our study that a RSS > 4 was independently associated with post procedure HFV.

Severe cardiopulmonary instability with respiratory insufficiency and systemic hypotension can often be seen in the period following definitive closure of the PDA, described as a form of low cardiac output syndrome or post ligation cardiac syndrome (PLCS) [13, 23, 37–41]. PLCS is associated with increased mortality [23] and morbidity [22] with risk factors including earlier age at ligation [37], lower birth weight [42], younger gestational age [42–44], large PDA [39], and level of preoperative cardiorespiratory support [25, 44, 45]. In this study we observed that each additional week of gestational age and day of postnatal age at definitive PDA closure by SL or TCPC conferred protection from HFV, further supporting these previous risk factors. In addition, male sex was also associated with use of HFV; consistent with evidence showing female infants have lower respiratory morbidity and mortality compared to their male counterparts [46].

These findings may have important clinical implications for extremely preterm infants following definitive closure of their PDA. The management strategy of PCLS strives for prevention with identification of the baseline preoperative risk factors in conjunction with early modulation of the postoperative physiology of elevated afterload, reduced preload, systolic and diastolic dysfunction and the upstream impact on the pulmonary vasculature [3, 47]. The major emphasis to prevent instability has focused on modulating echocardiographic evidence of low cardiac output with initiation of targeted prophylaxis of milrinone within 1 h following closure [25]. While this approach has been shown to decrease the incidence of PLCS, many centers do not utilize targeted afterload reducing medications or obtain echocardiograms within 1 h following definitive closure. Reliance on traditional markers of cardiac output (e.g., heart rate and blood pressure) also has limitations; in this study there were no differences at 1 h following closure of the PDA. Furthermore, the hemodynamics approach neglects the respiratory phenotype following definitive closure. As such, the clinical impact of this study lies in the identification of a non-invasive respiratory severity cut-off that may be more adaptable across patients and centers, and serve as another identifiable risk factor for cardiopulmonary instability following definitive closure.

The strengths of this study need to be interpreted within the framework of its limitations. Causality cannot be proven from the retrospective, nonrandomized design and the association between RSS value and post-procedural HFV may be related to practice variation, chance, random error, bias or other confounding factors. Moreover, we included 8 infants who were managed on HFV before PDA closure, which likely influenced then need for HFV post procedure. However, we thought it was clinically relevant to describe the risk factors and range of RSS values for all HFV managed infants (pre and post procedure). Future studies with well-defined populations are needed to understand if it's the common preterm related co-morbidities or their associations reflecting the clinical effects of related risk factors on this high-risk population of preterm infants. Despite the small sample size, we verified that the effect on the primary outcome persisted despite adjustment for known confounders such as sex, gestational age, birthweight and PDA characteristics. Although prospective randomized controlled studies would be ideal to identity respiratory or cardiac risk factors that impact escalation of support following definitive closure, randomizing between SL or TCPC lacks equipoise in several centers where TCPC has become standard of care. Future work is needed to explore other study designs (e.g., propensity score matching or prospective case control) to minimize potential for bias related to account for known confounders or temporal changes in baseline management [48]. We evaluated short-term outcomes, but were not able to evaluate important long-term outcomes including BPD [49, 50], associations with pulmonary hypertension [16], survival without severe morbidity, and neurodevelopment as most infants (75%) were transferred back to referring institutions before these outcomes could be quantified. To capture these important long-term outcomes in future projects, we are in the process of completing data use agreements with referral hospitals.

CONCLUSION

The respiratory phenotype associated with definitive closure of the PDA is clinically characterized by changes in both oxygenation and ventilation, and may prompt escalation to HFV in extremely preterm infants. We found that a RSS cut-of greater than 4 at 1 and 12 h following closure was associated with the need for HFV, with additional risk factors including SL and male sex. Each additional week of gestational age and day of postnatal age at definitive PDA closure by SL or TCPC conferred protection from HFV, supporting previously identified risk factors of post cardiopulmonary instability. While future prospective studies are needed to confirm these results, an elevated RSS at one hour following closure may compliment current clinical and imaging modalities to promote early identification of the respiratory phenotype of PLCS with the overall goal of optimizing respiratory support following definitive PDA closure.

REFERENCES

1. Rios DR, Bhattacharya S, Levy PT, McNamara PJ. Circulatory insufficiency and hypotension related to the ductus arteriosus in neonates. Front Pediatr. 2018;6:62.
2. Serrano RM, Madison M, Lorant D, Hoyer M, Alexy R. Comparison of 'post-patent ductus arteriosus ligation syndrome' in premature infants after surgical ligation vs. percutaneous closure. J Perinatol. 2020;40:324–9.
3. Nealon E, Rivera BK, Cua CL, Ball MK, Stiver C, Boe BA, et al. Follow-up after Percutaneous Patent Ductus Arteriosus Occlusion in Lower Weight Infants. *J Pediatr*: Elsevier Inc; 2019. pp. 144–50.e143.
4. Willson DF, Thomas NJ, Markovitz BP, Bauman LA, DiCarlo JV, Pon S, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. JAMA. 2005;293:470–6.
5. Stewart DL, Dela Cruz TV, Duncan SD, Cook LN. Response to high frequency jet ventilation may predict the need for extracorporeal membrane oxygenation. Eur Respir J. 1996;9:1257–60.
6. Golombek SG, Young JN. Efficacy of inhaled nitric oxide for hypoxic respiratory failure in term and late preterm infants by baseline severity of illness: a pooled analysis of three clinical trials. Clin Ther. 2010;32:939–48.
7. Shahid S, Dutta S, Symington A, Shivananda S, McMaster University N. Standardizing umbilical catheter usage in preterm infants. Pediatrics. 2014;133:e1742–1752.
8. de Brito CS, de Brito DV, Abdallah VO, Gontijo, Filho PP. Occurrence of blood-stream infection with different types of central vascular catheter in critically neonates. J Infect. 2010;60:128–32.
9. Deindl P, Waldhor T, Unterasinger L, Berger A, Keck M. Arterial catheterisation in neonates can result in severe ischaemic complications but does not impair long-term extremity function. Acta Paediatr. 2018;107:240–8.
10. Iyer NP, Mhanna MJ. Non-invasively derived respiratory severity score and oxygenation index in ventilated newborn infants. Pediatric Pulmonol. 2013;48:364–9.
11. Malkar MB, Gardner WP, Mandy GT, Stenger MR, Nelin LD, Shepherd EG, et al. Respiratory severity score on day of life 30 is predictive of mortality and the length of mechanical ventilation in premature infants with protracted ventilation. Pediatric Pulmonol. 2015;50:363–9.
12. Seo YM, Sung IK, Yum SK. Risk factors associated with prolonged mechanical ventilation after surgical patent ductus arteriosus ligation in preterm infants. J Matern Fetal Neonatal Med. 2020;8:1–8.

13. Ting JY, Resende M, More K, Nicholls D, Weisz DE, El-Khuffash A, et al. Predictors of respiratory instability in neonates undergoing patient ductus arteriosus ligation after the introduction of targeted milrinone treatment. J Thoracic Cardiovasc Surg. 2016;152:498–504.
14. Hsu KH, Wong P, Ram Kumar S, Evans J, Noori S. Predictors of respiratory improvement 1 week after ligation of patent ductus arteriosus in preterm infants. J Pediatr. 2019;205:49–54 e42.
15. Francis JV, Padmanabhan S, Jaques L, Courtot J, Sehgal A. Respiratory and cardiovascular morbidity in the first 48 h post surgical ligation of the patent ductus arteriosus. J Neonatal-Perinatal Med. 2011;4:21–6.
16. Philip R, Waller BR, Chilakala S, Graham B, Stecchi N, Apalodimas L, et al. Hemodynamic and clinical consequences of early versus delayed closure of patent ductus arteriosus in extremely low birth weight infants. J Perinatol. 2021;41:100–8.
17. Rodriguez Ogando A, Planelles Asensio I, de la Blanca ARS, Ballesteros Tejerizo F, Sanchez Luna M, Gil Jaurena JM, et al. Surgical ligation versus percutaneous closure of patent ductus arteriosus in very low-weight preterm infants: which are the real benefits of the percutaneous approach? Pediatric Cardiol. 2018;39:398–410.
18. Regan W, Benbrik N, Sharma SR, Auriau J, Bouvaist H, Bautista-Rodriguez C, et al. Improved ventilation in premature babies after transcatheter versus surgical closure of patent ductus arteriosus. Int J Cardiol. 2020;311:22–7.
19. Schwartz MC, Nykanen D, Winner LH, Perez J, McMahan M, Munro HM, et al. Transcatheter patent ductus arteriosus occlusion in small infants. Congenit Heart Dis. 2016;11:647–55.
20. 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 Interv. 2019;93:89–96.
21. Abu Hazeem AA, Gillespie MJ, Thun H, Munson D, Schwartz MC, Dori Y, et al. Percutaneous closure of patent ductus arteriosus in small infants with significant lung disease may offer faster recovery of respiratory function when compared to surgical ligation. Catheter Cardiovasc Interv. 2013;82:526–33.
22. Ulrich TJB, Hansen TP, Reid KJ, Bingler MA, Olsen SL. Post-ligation cardiac syndrome is associated with increased morbidity in preterm infants. J Perinatol. 2018;38:537–42.
23. Harting MT, Blakely ML, Cox CS Jr., Lantin-Hermoso R, Andrassy RJ, Lally KP. Acute hemodynamic decompensation following patent ductus arteriosus ligation in premature infants. J Invest Surg. 2008;21:133–8.
24. Clyman RI, Wickremasinghe A, Merritt TA, Solomon T, McNamara P, Jain A, et al. Hypotension following patent ductus arteriosus ligation: the role of adrenal hormones. J Pediatr. 2014;164:1449–55 e1441.
25. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr. 2012;160:584–9 e581.
26. Wheeler CR, Stephens H, O'Donnell I, Zurakowski D, Smallwood CD. Mortality risk factors in preterm infants treated with high-frequency jet ventilation. Respiratory Care. 2020;65:1631–40.
27. Wheeler CR, Smallwood CD, O'Donnell I, Gagner D, Sola-Visner MC. Assessing initial response to high-frequency jet ventilation in premature infants with hypercapnic respiratory failure. Respiratory Care. 2017;62:867–72.
28. 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;96:1–11.
29. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*, Third edition/ edn. Wiley: Hoboken, New Jersey, 2013.
30. Zhou X-h, McClish DK, Obuchowski NA. *Statistical methods in diagnostic medicine*, 2nd edn. Wiley: Hoboken, N.J., 2011.
31. Staffa SJ, Zurakowski D. Statistical power and sample size calculations: A primer for pediatric surgeons. *J Pediatr Surg*: Elsevier Inc.; 2020. pp. 1173–9.
32. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, reese J, et al. Patent Ductus Arteriosus of the Preterm Infant. *Pediatrics*; 2020. pp. 1–17.
33. Shah SI, Aboudi D, La Gamma EF, Brumberg HL. Respiratory Severity Score greater than or equal to 2 at birth is associated with an increased risk of mortality in infants with birth weights less than or equal to 1250 g. Pediatric Pulmonol. 2020;55:3304–11.
34. Indrani B, Anirudha D, Marc C, Hany A. Predicting outcomes of mechanically ventilated premature infants using respiratory severity score. Taylor & Francis; 2020. pp. 1–9.
35. Jung YH, Jang J, Kim H-S, Shin SH, Choi CW, Kim E-K, et al. Respiratory severity score as a predictive factor for severe bronchopulmonary dysplasia or death in extremely preterm infants. BMC Pediatrics; 2019;28:1–8.
36. Malkar MB, Gardner WP, Mandy GT, Stenger MR, Nelin LD, Shepherd EG, et al. Respiratory Severity Score on Day of Life 30 is Predictive of Mortality and the Length of Mechanical Ventilation in Premature Infants With Protracted Ventilation. Pediatric Pulmonol; 2015;140:363–9.
37. Teixeira LS, Shivananda SP, Stephens D, Van Arsdell G, McNamara PJ. Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to early need for intervention. J Perinatol. 2008;28:803–10.
38. McNamara PJ, Stewart L, Shivananda SP, Stephens D, Sehgal A. Patent ductus arteriosus ligation is associated with impaired left ventricular systolic performance in premature infants weighing less than 1000 g. J Thorac Cardiovasc Surg. 2010;140:150–7.
39. Noori S, Friedlich P, Seri I, Wong P. Changes in myocardial function and hemodynamics after ligation of the ductus arteriosus in preterm infants. J Pediatr. 2007;150:597–602.
40. Giesinger RE. Impaired right ventricular function is associated with adverse outcome following hypoxic ischemic encephalopathy. Am J Respir Crit Care Med. 2019. pp. 1–48.
41. Halliday M, Kavarana M, Ebeling M, Kiger J. Milrinone use for hemodynamic instability in patent ductus arteriosus ligation. J Matern Fetal Neonatal Med. 2017;30:529–33.
42. Moin F, Kennedy KA, Moya FR. Risk factors predicting vasopressor use after patent ductus arteriosus ligation. Amer J Perinatol. 2003;43:313–20.
43. Natarajan G, Chawla S, Aggarwal S. Short-term outcomes of patent ductus arteriosus ligation in preterm neonates: reason for concern? Amer J Perinatol. 2010;150:431–7.
44. Naik-Mathuria B, Chang S, Fitch ME, Westhoff J, Brandt ML, Ayres NA, et al. Patent ductus arteriosus ligation in neonates: preoperative predictors of poor postoperative outcomes. J Pediatr Surg. 2008;140:1100–5.
45. McNamara PJ, Stewart L, Shivananda SP, Stephens D, Sehgal A. Patent ductus arteriosus ligation is associated with impaired left ventricular systolic performance in premature infants weighing less than 1000 g. J Thorac Cardiovasc Surg. 2010;162:150–7.
46. Townsel CD, Emmer SF, Campbell WA, Hussain N. Gender differences in respiratory morbidity and mortality of preterm neonates. Front Pediatr. 2017;5:6.
47. EL-Khuffash AF, Jain A, McNamara PJ. Ligation of the patent ductus arteriosus in preterm infants: understanding the physiology. J Pediatr. 2013;40:1100–6.
48. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46:348–55.
49. Clyman RI, Hills NK. The effect of prolonged tracheal intubation on the association between patent ductus arteriosus and bronchopulmonary dysplasia (grades 2 and 3). J Perinatol. 2020;40:1358–65.
50. Clyman RI, Hills NK, Liebowitz M, Johng S. Relationship between duration of infant exposure to a moderate-to-large patent ductus arteriosus shunt and the risk of developing bronchopulmonary dysplasia or death before 36 weeks. Am J Perinatol. 2020;37:216–23.

AUTHOR CONTRIBUTIONS

CRW and PTL devised the study protocol and analysis plan which was approved by all authors. DG, HS, and AK collected data. DZ provided expert assistance with statistical analysis and interpretation. JCI, KGF, RC and DP provided anesthesia, cardiology and procedural expertise. All of the listed authors made substantial contributions either to the conception of the study, data acquisition, analysis and interpretation of data. CRW and PTL wrote the first draft, but all listed authors critically revised it for intellectual content and approved the final version of the manuscript and have agreed to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

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