Predictors of respiratory instability in neonates undergoing patent ductus arteriosus ligation after the introduction of targeted milrinone treatment

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ABSTRACT

Introduction: The postoperative course of preterm babies undergoing surgical closure of a patent ductus arteriosus (PDA) is often complicated by postligation cardiac syndrome (PLCS). Despite targeted milrinone prophylaxis, some infants continue to experience postoperative respiratory deterioration. Our objective is to describe the immediate postoperative course and identify risk factors for respiratory instability when preterm infants undergoing PDA ligation are managed with targeted milrinone treatment.

Methods: A retrospective review of a cohort of infants undergoing PDA ligation between January, 2010 and August, 2013 was conducted. All infants had a targeted neonatal echocardiogram performed 1 hour after surgery. Infants received prophylactic milrinone treatment if the left ventricular output was <200 mL/kg/min. The primary outcome measure was the development of respiratory instability within 24 hours of surgery. Multivariable logistic regression was performed to identify predictors of respiratory instability.

Results: Eighty-six infants with a median gestational age of 25 weeks (interquartile range [IQR], 24–26) and a birth weight of 740 g (IQR, 640–853) were included in this study. Forty-nine (57.0%) received milrinone prophylaxis. There were 44 (51.2%) infants who developed oxygenation or ventilation failure, and 7 (8.1%) neonates developed PLCS. Infants with longer isovolumic relaxation time (IVRT ≥ 30 milliseconds) were more likely to develop either oxygenation or ventilation failure.

Conclusions: Although the incidence of PLCS has declined after the introduction of targeted milrinone prophylaxis, many preterm infants continue to develop respiratory instability after surgical ligation. In this population, diastolic dysfunction manifested by prolonged IVRT could be associated with an adverse postoperative respiratory course. (J Thorac Cardiovasc Surg 2016;152:498–504)

Isovolumic relaxation time to predict postoperative respiratory instability.

Central Message

Preoperative diastolic dysfunction could be associated with adverse respiratory course in preterm infants undergoing PDA ligation.

Perspective

Although the incidence of postligation cardiac syndrome in preterm babies undergoing surgical closure of patent ductus arteriosus has declined after the introduction of targeted milrinone prophylaxis, many continue to develop respiratory instability postoperatively. Preoperative diastolic dysfunction manifested by prolonged IVRT could be associated with an adverse postoperative respiratory course.

See Editorial Commentary page 505.

Patent ductus arteriosus (PDA) is a common problem in premature infants and optimal treatment remains controversial.^{1,2} Concerns over the increase in pulmonary blood flow

and decrease in systemic perfusion in hemodynamically significant PDA (hsPDA) have directed researchers to study the optimal management of infants with PDA.³ Surgical ligation of an hsPDA is considered when medical intervention either fails or is contraindicated. Data from the Canadian Neonatal Network⁴ reported an incidence of PDA ligation in 10% to 24% of neonates born at less

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Received for publication Oct 8, 2015; revisions received Feb 24, 2016; accepted for publication March 19, 2016; available ahead of print May 10, 2016.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2016.03.085>

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Abbreviations and Acronyms

ACTH	= adrenocorticotrophic hormone
BPD	= bronchopulmonary dysplasia
E/A	= early-to-late-ventricular-filling velocities
F _{IO₂}	= fraction of inspired oxygen
HFOV	= high-frequency oscillatory ventilation
hsPDA	= hemodynamically significant patent ductus arteriosus
IQR	= interquartile range
IV	= intravenous
IVRT	= isovolumic relaxation time
LV	= left ventricle
LVFS	= left ventricular fractional shortening
LVO	= left ventricular output
OF	= oxygenation failure
MAP	= mean airway pressure
PDA	= patent ductus arteriosus
PLCS	= postligation cardiac syndrome
SH	= systemic hypotension
TnECHO	= targeted neonatal echocardiography
VF	= ventilation failure
VTI	= velocity-time integral

than 29 weeks gestation. The postoperative period is complicated by postligation cardiac syndrome (PLCS), characterized by systemic hypotension (SH) and oxygenation failure (OF) in 30% to 50% of these infants.⁵⁻⁸ The reported pathophysiologic contributors include transient left ventricular (LV) dysfunction and increased systemic vascular resistance. Lower gestational age, younger age at surgery, low birth weight, large PDA, and low cortisol levels are associated with increased risk for postoperative cardiorespiratory instability.^{5,9-13}

Previously, our group showed that early postoperative initiation of a prophylactic milrinone infusion to infants with an LV output (LVO) <200 mL/kg/min was associated with a reduction in the incidence of OF or ventilation failure (VF) and the need for inotropes.⁹ Despite this targeted approach, some infants continue to experience postoperative respiratory deterioration. This study describes the impact of targeted milrinone treatment and identifies the risk factors for respiratory instability when preterm infants undergoing PDA ligation are managed with targeted milrinone treatment.

METHODS**Study Design and Objective**

We conducted a retrospective study of premature infants who underwent PDA ligation at a quaternary neonatal intensive care unit receiving outborn referrals. The primary objective was to describe the frequency of respiratory instability in a cohort of preterm infants who underwent PDA ligation and were managed with a targeted milrinone treatment approach.

The secondary objective was to identify the risk factors for developing oxygenation or VF during this era of targeted milrinone treatment.

Study Population

All premature infants born ≤35 weeks of gestation who underwent a PDA ligation between January, 2010 and August, 2013 at the Hospital for Sick Children (Toronto, Ontario, Canada) were eligible for enrolment. Newborns with congenital heart diseases other than a patent foramen ovale were excluded from this study.

Data Collection

Electronic medical records of all eligible infants were reviewed by 2 physicians independently and the 2 databases were cross-checked. Baseline characteristics, including gestational age, birth weight, gender, age at surgery (days of life), and weight at surgery were collected. The clinical and physiologic indices of cardiorespiratory stability were recorded in our electronic medical records before and 1 hour, 4 hours, 8 hours, 12 hours, and 24 hours after ligation. Data related to the calculation of OF or VF for 1 hour duration were abstracted from the electronic patient health care record. It is the usual practice for health professionals to enter the following cardiorespiratory data (mean airway pressure [MAP], fraction of inspired oxygen [F_{IO₂}] systolic/diastolic/mean arterial pressure, ventilator settings) on an hourly interval. Preductal oxygen saturation levels were maintained at levels between 88% and 92% in the neonatal intensive care unit, with no change in the limits during the perioperative period. Additional indices were recorded when ventilatory parameters were adjusted or there were fluctuations in blood pressure requiring intervention. Infants were usually managed with conventional ventilation as the standard of care. High-frequency oscillatory ventilation (HFOV) was used as a rescue therapy for refractory hypercapnia despite augmentation of delivered inspired pressure on conventional ventilation. Indices of mechanical ventilation, including MAP and F_{IO₂}, were recorded at longitudinal time points. Routine preoperative evaluation of adrenal function with a short adrenocorticotrophic hormone (ACTH) stimulation test is performed before surgery. Baseline serum cortisol was collected as part of the routine preoperative workup. The serum cortisol level was measured again 1 hour later after an intravenous (IV) injection of ACTH to assess the stress response of the adrenal glands.

Echocardiography

A comprehensive echocardiogram was performed before surgical ligation to ensure that other anatomic heart defects were excluded. In addition, a targeted neonatal echocardiogram (TnECHO) was performed to assess the hemodynamic significance of the PDA shunt. Studies were performed using the Vivid 7 or E9 cardiovascular ultrasound system (GE Medical Systems, Milwaukee, Wisconsin, USA) with a 10-MHz high-frequency phased-array transducer probe. Standard two-dimensional, M-mode, color Doppler, pulse-wave Doppler, and continuous-wave Doppler images were obtained for transthoracic echocardiographic analysis. LV fractional shortening (LVFS) and LVO were used as surrogate markers of LV systolic function. The aortic root annulus diameter was obtained from the standard parasternal long-axis view, and the aortic cross-sectional area was calculated as follows: $\pi \times [\text{aortic annulus diameter}]^2/4$. An apical 5-chamber view was used to visualize the LVO outflow tract. By applying a pulse-wave Doppler and positioning the 2-mm sample volume on the LV side of the aortic valve, the velocity curve was obtained, and the velocity-time integral (VTI) was traced. LVO was calculated as follows: $[\text{VTI} \times \text{heart rate} \times \text{aortic cross-sectional area}]$ indexed to body weight. The other measurements were obtained as per our previous studies.¹³ The isovolumic relaxation time (IVRT), the time interval between aortic valve closure and mitral valve opening, and the ratio of early-to-late-ventricular-filling

velocities (E/A) ratio were obtained to assess diastolic dysfunction. The E/A ratio was measured by positioning a pulse-wave Doppler with a 2-mm sample volume across the mitral valve to measure the velocities across the valve in an apical 4-chamber view. The probe was then angulated anteriorly. Again, using pulsed Doppler, a 2-mm sample volume was positioned midway between the aortic and mitral valves to obtain a clear signal showing both the aortic outflow and the mitral inflow to obtain IVRT. All parameters were entered into a database for clinical service and quality assurance.

Targeted Milrinone Treatment Policy

Since 2010, the standard of practice in our unit has been to obtain a TnECHO 1 hour after surgery. Babies with an LVO <200 mL/kg/min received prophylactic milrinone starting at 0.33 µg/kg/min IV. In addition, a 10-mL/kg normal saline bolus was coadministered during the first hour of IV milrinone infusion. If the infant remained clinically stable, milrinone was discontinued after 24 hours.

Management of Hypotension

An infant was considered to be hypotensive if one of the systolic, diastolic, or mean blood pressure was less than the third percentile for corrected gestational age. The standard practice at our center is to give a fluid bolus for volume replacement and at least 1 inotropic agent (such as dopamine or dobutamine at the discretion of the attending neonatologist) before considering hydrocortisone treatment. Prophylactic hydrocortisone was not recommended.

Outcomes

The primary outcome was the development of respiratory instability (either OF or VF) within 24 hours of surgery in the absence of other major perioperative events, such as pneumothorax or chylothorax. OF was defined as an absolute increase of at least 20% in the MAP or FiO_2 , compared with the preoperative value required for a minimum of 1 hour within the 24-hour postligation period. VF was defined as the need for rescue HFOV because of the inability of conventional settings to maintain adequate ventilation support or a 20% increase in amplitude of the preoperative value as needed for a minimum of 1 hour within the 24-hour postligation period. SH was defined as an arterial blood pressure (systolic, diastolic, or mean values) below the third percentile (as expected for the gestational age) that persisted for at least 1 hour within the 24-hour postligation period or for a shorter period if corrective intervention was provided. PLCS was defined as the development of SH and OF or VF.

Statistics

SPSS 23.0 (IBM Corp., Armonk, New York, USA) was used to perform the statistical analyses. Descriptive statistics were used to characterize patient demographics, echocardiographic parameters, and perioperative outcomes of infants admitted for PDA ligation during the study period. The Kolmogorov-Smirnov test or the Shapiro-Wilk tests were applied to test for normality, as appropriate. The Mann-Whitney *U* test was performed to compare medians if the variables were not following a normal distribution. The χ^2 test or Fisher exact test was performed to compare proportions of categorical variables. Multivariable logistic regression was performed to identify clinical and echocardiographic predictors of respiratory instability (OF or VF). A *P* value <.05 was regarded as significant. A receiver operating characteristic curve was constructed to determine the threshold of preoperative TnECHO markers for predicting the subsequent development of respiratory instability.

Ethics

Approval was obtained from the research ethics board of the Hospital for Sick Children, Toronto, Ontario, Canada.

RESULTS

A total of 86 infants underwent PDA ligation and received pre- and postoperative TnECHO evaluations during the study period (Table 1). The mean gestational age and weight at birth were 25 weeks (interquartile range [IQR], 24-26) and 740 g (IQR, 640-853), respectively. The median age, corrected gestational age, and weight at surgery were 29 days (IQR, 22-40), 30 weeks (IQR, 28-31), and 1010 g (IQR, 896-1300), respectively. In total, 49 (57.0%) infants received milrinone prophylaxis after surgery. Only 1 of these patients developed significant hypotension requiring cessation of milrinone after 19 hours of infusion. Seven (8.1%) infants developed PLCS.

Preoperative Echocardiographic Analysis

In our cohort, OF or VF was observed in 44 (51.2%) infants (Table 1). Infants with and without respiratory instability had similar distributions of gestational age, birth weight, and gender. Those with OF or VF had longer IVRT and lower E/A ratio compared with those without postoperative respiratory instability (Table 2).

Postoperative Respiratory Instability

Among infants who developed OF or VF postoperatively (Table 1), 32 had a $\geq 50\%$ increase in the FiO_2 or MAP compared with their preoperative status. The frequency of VF was 20 (23.3%). The magnitude of change in FiO_2 among infants with OF or VF group ranged from -19 to $+58\%$ (vs -13 to $+9$ in the non-OFF or VF group), whereas the magnitude of change in MAP among infants in the OF or VF group ranged from -4.5 to $+7.0$ cmH₂O (vs -3.2 to $+0.8$ in the non-OFF or VF group). All infants developing VF also had OF. Infants who developed respiratory instability (OF or VF) had median birth weight and gestational age of 745 g (range, 485-1800) and 25 weeks (range, 23-32), respectively. Medians (and ranges) of age, corrected gestational age, and weight at surgery were 33 days (19-62), 30 weeks (27-36), and 1055 g (510-1890), respectively. They tended to have operation at more advanced age compared with those without postoperative respiratory instability, although not reaching statistical significance (median, 33 days vs 26 days; *P* = .072).

Postoperative 1-Hour Echocardiographic Analysis

All 86 babies had LVO measured on the 1-hour postoperative TnECHO (Table 2). Infants who developed respiratory instability had median LVO at 1 hour after operation of 188 mL/kg/min (range, 86-344). There were no differences in postoperative LVFS, IVRT, or E/A ratios among babies with and without respiratory instability, although infants with OF or VF tended to have lower LVO and were more likely to receive milrinone prophylaxis (Tables 1 and 2).

TABLE 1. Demographic and clinical characteristics of infants with postoperative respiratory instability

	No OF or VF	OF or VF	P value
Number of patients	42	44	
Gestational age (w)*	25 (25-27)	25 (24-26)	N/A
Birth weight (g)*	725 (639-915)	745 (640-809)	N/A
Gender (male), n (%)	19/42 (45.2)	20/44 (45.5)	N/A
Apgar score at 5 min	7 (5-8)	6 (5-8)	N/A
Antenatal steroids, n (%)†	16/38 (42.1)	20/33 (39.4)	N/A
Intraventricular hemorrhage grades 3 or 4, n (%)	6/42 (14.3)	4/44 (9.1)	.453
Necrotizing enterocolitis, n (%)‡	11/42 (26.2)	13/43 (30.2)	.679
Age at surgery (days of life)*	26 (20-38)	33 (25-40)	.057
Corrected gestational age at surgery (w)*	30 (28-31)	30 (29-31)	.740
Weight at surgery (g)*	960 (892-1230)	1055 (896-1366)	.238
Preoperative mean airway pressure (mm Hg)*	9.0 (8.1-10.0)	9.0 (8.0-11.0)	.809
Preoperative FiO_2 (%)*	29 (24-40)	31 (27-40)	.101
Post-ACTH stimulation test cortisol <500 nmol/L, n (%)§	6/30 (20.0)	6/35 (17.1)	.767
Post-ACTH stimulation test cortisol <750 nmol/L, n (%)§	15/30 (50.0)	18/35 (51.4)	.909
Preoperative inotropic use, n (%)	5/42 (11.9)	2/44 (4.5)	.260
Milrinone treatment, n (%)	20/42 (47.6)	29/44 (69.5)	.087

OF, Oxygenation failure; VF, ventilation failure; N/A, not applicable (baseline demographic characteristics); FiO_2 , fraction of inspired oxygen; ACTH, adrenocorticotropic hormone. *Median (25th centiles, 75th centiles). †Defined as 2 or more doses; only 71 infants with complete information. ‡One missing value. §65 infants had ACTH stimulation test performed.

The medians of differences between pre- and postoperative IVRT in infants with and without OF or VF were 14 milliseconds (IQR, 7-24) and 27 milliseconds (IQR, 8-41), respectively, and the difference between the 2 groups was not statistically significant ($P = .107$).

Predictors of Respiratory Instability

Logistic regression modeling was performed to identify clinical and echocardiographic predictors of respiratory instability (OF or VF) (Table 3), which explained 30.9% of variance (Nagelkerke $R^2 = 0.309$) and correctly classified 72.6% of all cases. The following predictors were entered into this model: gestational age, preoperative IVRT, size of PDA, MAP before surgery, age of surgery, and LVO at 1 hour postoperatively. Prolonged IVRT was predictive of respiratory instability ($P = .002$) (Figure 1) and lower LVO showed a trend towards increased likelihood of developing it ($P = .073$).

IVRT yielded an area under the curve of 0.753 (95% confidence interval, 0.635-0.871; $P < .001$) for predicting development of OF or VF, with a cutoff value of 30 milliseconds, providing a sensitivity of 82.9% and specificity of 60.6% (Figure 2). The positive predictive value of an IVRT more than 30 milliseconds to predict development of OF or VF was 69.0%.

PLCS

In our cohort, only 7 (8.1%) infants developed PLCS. Their median birth weight and gestational age were 760 g (range, 600-940) and 25 weeks (range, 24-26), respectively. Medians (and ranges) of age, corrected gestational age, and weight at surgery were 30 (22-62) days, 29 (28-34) weeks, and 1030 (780-1792) g, respectively. Their median LVO at 1 hour after operation was 155 mL/kg/min (range, 86-270). All except 1 received milrinone prophylaxis, who had a LVO of 270 mL/kg/min at 1 hour after operation. Fluid

TABLE 2. Echocardiographic characteristics of infants with postoperative respiratory instability

	No OF or VF	OF or VF	P value
Total number of patients	42	44	
Preoperative LVO (mL/kg/min)	442 (354-548) (32 infants)	444 (342-557) (37 infants)	.889
Preoperative IVRT (milliseconds)	30 (26-39) (33 infants)	44 (30-50) (35 infants)	<.001
Preoperative E/A ratio	0.90 (0.83-1.10) (35 infants)	0.83 (0.79-0.97) (37 infants)	.037
Preoperative LVFS (%)	40 (33-45) (29 infants)	38 (36-45) (33 infants)	.877
Preoperative PDA size (mm)	2.8 (2.5-3.2) (41 infants)	2.8 (2.6-3.1) (42 infants)	.993
Postoperative LVO (mL/kg/min)	212 (178-251) (42 infants)	188 (156-230) (44 infants)	.088
Postoperative IVRT (milliseconds)	58 (47-74) (35 infants)	60 (54-72) (37 infants)	.260
Postoperative E/A ratio	0.86 (0.73-1.00) (32 infants)	0.86 (0.71-1.00) (38 infants)	.925
Postoperative LVFS (%)	28 (22-36) (26 infants)	30 (25-33) (30 infants)	.711

Expressed as median (25th centiles, 75th centiles). OF, Oxygenation failure; VF, ventilation failure; LVO, left ventricular output; IVRT, isovolumic relaxation time; E/A, early-to-late-ventricular-filling velocities; LVFS, left ventricular fractional shortening; PDA, patent ductus arteriosus.

TABLE 3. Logistic regression model for risk factors for development of oxygenation failure or ventilation failure

Parameter	Odds ratio (95% confidence interval)	P value
Gestational age (w)	0.903 (0.607-1.343)	.614
Preoperative IVRT (milliseconds)	1.090 (1.031-1.153)	.002
PDA size (mm)	1.430 (0.474-4.319)	.526
Preoperative MAP (cm H ₂ O)	1.215 (0.879-1.679)	.238
Postoperative LVO at 1-h (mL/kg/min)	0.991 (0.981-1.001)	.073
Age of surgery (d)	1.137 (0.824-1.570)	.435

Omnibus likelihood ratio: $\chi^2 = 16.297$ (degree of freedom = 6); $P = .012$; Hosmer & Lemeshow test: $P = .722$. IVRT, Isovolumic relaxation time; PDA, patent ductus arteriosus; MAP, mean airway pressure; LVO, left ventricular output.

boluses, inotropic support, or hydrocortisone were required within the first 24-hour postoperative period. The incidence of PLCS in patients receiving and not receiving milrinone were 12.2% (6/43) and 2.7% (1/37), respectively. Infants receiving milrinone prophylaxis were those who were at high risk of developing PLCS (ie, LVO at 1-hour postoperative echocardiogram <200 mL/kg/min).

DISCUSSION

The introduction of early postoperative TnECHO screening and targeted milrinone treatment was followed by a reduction in the incidence of PLCS to 8.1%, which is lower than previous reports.^{11,14} Despite this practice change, the incidence of OF or VF remained high (51.2%) in this 4-year cohort. Targeted milrinone treatment has reduced the hypotension component of the syndrome, but the respiratory component is still a challenge to manage. The demographic profile of neonates who developed respiratory deterioration was discordant with the published literature. Previous evidence suggested that the most vulnerable group were neonates less than 28 days old or less than 1000 g at the time of surgery.^{10,13} Unlike previous studies, the postoperative course of neonates in our cohort was

FIGURE 1. Isovolumic relaxation time (IVRT) to predict postoperative respiratory instability. **FIGURE 2.** Isovolumic relaxation time (IVRT) to predict postoperative respiratory instability.

characterized by OF or VF without hemodynamic instability, the incidence of which is greatest with prolonged IVRT on preoperative echocardiogram.

Clinical decision-making processes related to the selection of neonates for PDA ligation and postoperative management are highly variable among neonatologists.¹ Although surgical ligation reduces the overall mortality and facilitates extubation in babies with established LV overload, recent evidence^{14,15} suggests an association with increased neurodevelopmental impairment, chronic lung disease, and severe retinopathy of prematurity after adjusting for various confounding factors. Some commentators advocate a less aggressive approach because of the association with adverse composite outcomes.¹⁶⁻¹⁸ Previous reports from our center showed that the incidence of PDA ligation among premature babies born at less than 30 weeks of gestational age decreased substantially from 10.7% in 2003 to 2005 (epoch I) to 5.3% in 2010 to 2012 (epoch II); in addition, patients in the second epoch had greater preprocedural illness severity.¹⁹ To justify a causal relationship between PDA ligation and these morbidities, it is essential to determine mechanistically how the surgery induces a profound and lasting cascade of adverse end-organ effects. An alternative explanation is that these morbidities may simply be surrogate markers for increased illness severity or may reflect higher grades of PDA shunt volume.^{15,20}

Retrospective studies have failed to identify any relationship between surgical technique, anesthetic approach, or intraoperative fluid management to the development of hypotension.^{7,12,21} Surgical ligation of a PDA leads to

significant changes in the cardiovascular physiology of preterm infants, including an acute increase in LV afterload and a decrease in the LV preload, leading to a sudden decrease in the LVO postoperatively.²² From our previous study, we showed that systolic and diastolic tissue Doppler velocities of the mitral valve and global longitudinal strain values decreased significantly over the first hour after PDA ligation.⁸ Since 2010, the standard of care has been to administer a milrinone infusion to neonates with LVO <200 mL/kg/min in an attempt to prevent the consequences of sustained exposure to increased LV afterload.⁹ Our cohort showed that only 8.1% of infants developed PLCS, which reaffirms the overall benefit of this targeted physiologic approach to postoperative hemodynamics seen previously.⁹ Milrinone, a selective phosphodiesterase III inhibitor, produces positive inotropic effects by inhibiting the hydrolysis of cyclic adenosine monophosphate in the myocardium.^{23,24} In addition, milrinone shows vasodilator and lusitropic actions.²³ Five of 7 infants who developed PLCS had 1-hour postoperative LVO around or less than 200 mL/kg/min. This may suggest that the dose of milrinone was insufficient to offload the LV and prevent late deterioration in myocardial performance. The acute volume unloading postoperatively may have further contributed to early relaxation abnormalities, leading to the evolution of low LVO after ligation.²⁵

The relaxation properties of the LV are impaired in myocytes of preterm infants, characterized by prolongation of IVRT and lower diastolic flow with predominant ventricular filling in late diastole with atrial contraction.²⁶ In contrast to the relatively more mature infants, those born at less than 28 weeks of gestation did not show an increase in diastolic function over the first 4 weeks of life.²⁷ Applying tissue Doppler techniques, preterm infants with hsPDA had been shown to have lower myocardial velocities and higher myocardial performance index, suggesting relative systolic and diastolic myocardial dysfunction.²⁸ Chronic myocardial hypoperfusion secondary to low coronary perfusion pressure in neonates with hsPDA might increase the likelihood of impaired myocardial performance when subjected to the stressor of PDA ligation, as shown by serial echocardiograms and biochemical markers of ischemic myocardial damage.^{29,30} These indices are also affected by shunt volume, which may mask underlying impairment in diastolic performance. In the presence of a high-volume shunt with pulmonary overcirculation, the passive component increases secondary to left heart pressure loading, leading to shortened IVRT as well as pseudonormalization of the E/A ratio.^{29,31} The association between respiratory instability and longer preoperative IVRT or lower E/A ratio is more likely to reflect diastolic dysfunction preoperatively than lower volume shunt. The prolongation in IVRT, to comparable levels in both groups, after surgical intervention most likely reflects

impairment in diastolic performance secondary to the acute increase in LV afterload. The median postoperative increases in IVRT were 14 milliseconds (IQR, 7-24) and 27 milliseconds (IQR, 8-41), in the OF and non-OF groups, respectively. This difference was not statistically significant ($P = .107$, Mann-Whitney U test), although that may reflect low sample size. The smaller degree of change in IVRT in the OF group may reflect a priori diastolic dysfunction or may relate to more unloading of the left heart with removal of a higher volume shunt. We postulate that the nature of OF may relate to inability of the LV with a priori diastolic dysfunction to adapt to increased LV afterload, leading to further augmentation in LV filling pressures and pulmonary venous hypertension, and thus provide a contextual explanation for the residual OF. The magnitude of the changes in oxygenation and ventilation was clinically significant in many infants, but not all, which emphasizes the need for close monitoring. In addition, these data highlight that postoperative changes in respiratory well-being may be cardiovascular, which requires an alternative treatment approach.

The relationship of OF or VF to advanced postnatal age may be partly explained by the prolonged exposure to the high-volume shunting through the hsPDA, resulting in chronic myocardial ischemia secondary to coronary artery steal and thus more significant diastolic dysfunction compared with those operated earlier. Moreover, the advanced postnatal age at surgery implies that we selected older infants who had poorer lung compliance with more severe evolving bronchopulmonary dysplasia (BPD). Attributed to chronic inflammation and impaired pulmonary alveolar and vascular development in premature infants, BPD is also known to be associated with ventricular dysfunction.^{32,33} Abnormal LV myocardial performance index has been noted to correlate with the grade of BPD.³² Assuming pulmonary venous hypertension plays a causative role, it is plausible that this subpopulation may benefit from a higher dose of milrinone, but this requires prospective evaluation.

In contrast to our earlier study,⁵ we did not identify any association between post-ACTH cortisol and clinical indices of postoperative OF or VF in our cohort (Table 1). This can be related to the relatively small sample sizes in both studies. Prospective studies in a larger sample are needed to explore the relative contribution of adrenal insufficiency in the pathogenesis of postligation respiratory instability.

Our study has several limitations. First, this was a descriptive observational study in a single center over an approximately 4-year period. Because of its nonrandomized nature and the small number of individual components of primary outcomes, our study could be underpowered to identify the risk factors associated with respiratory instability among preterm infants undergoing PDA ligation.

Second, because we inserted peripheral arterial catheters only in infants considered to be at high risk of developing cardiorespiratory instability, we did not have oxygen indices of all our patients postoperatively, which are more objective to quantify the degree of respiratory support. Also, many of our images were taken per our standard of clinical care. Images from multiple echocardiogram operators of echocardiogram may potentially be subjected to interobserver differences. Parameters of diastolic function were measured in only two thirds of infants, and tissue Doppler imaging techniques were not applied in half of our patients, which limited our investigations of the risk factors contributing to postoperative instability. Nevertheless, we were able to show a low incidence of PLCS among preterm infants managed with targeted milrinone treatment, although the high incidence of respiratory instability without hemodynamic disturbance necessitates further study.

CONCLUSIONS

Selective use of milrinone after PDA ligation improves hemodynamic stability, but the incidence of respiratory instability after surgical intervention remains high. The phenotypic nature of the clinical deterioration in this modified population differs, and longer IVRT on preoperative echocardiogram was associated with an adverse postoperative respiratory course. The physiologic nature of the latter finding requires prospective investigation.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: patent ductus arteriosus, neonates, oxygenation failure, ventilation failure, milrinone