Assessment and Treatment of Post Patent Ductus Arteriosus Ligation Syndrome

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Objective To compare differences in tissue Doppler imaging, global longitudinal strain (GLS), and cardiac troponin T (cTnT) between infants with low (<200 mL/kg/min) and high (>200 mL/kg/min) left ventricular (LV) output 1 hour after duct ligation and assess the impact of milrinone treatment on cardiac output and myocardial performance.

Study design LV function was assessed preoperatively and 1 and 18 hours postoperatively. Infants were categorized into a low-output or a normal-output group based on the echocardiographic assessment of LV output at 1 hour.

Results Thirty infants with a mean gestation of 25.3 weeks were enrolled. LV basal lateral S′, basal septal S′, and basal right ventricular S′ were lower in the low-output group (n = 19) at 1 hour postoperatively, with no significant difference in GLS (low-output −10.3% vs high-output −14.4%, $P > .05$) or cTnT between the groups. Patients in the low-output group were treated with milrinone, and by 18 hours LV performance recovered to levels comparable with the high output group. cTnT values increased at 18 hours in the whole cohort with no significant difference between the groups.

Conclusion Tissue Doppler imaging and GLS provide novel insights and further characterization of myocardial performance immediately after patent ductus arteriosus ligation. A reduction in tissue Doppler-derived LV systolic velocity may further help in monitoring cardiac performance after patent ductus arteriosus ligation and for monitoring the effects of treatment. *(J Pediatr 2014; ■: ■-■).*

The decision to undergo patent ductus arteriosus (PDA) ligation is subject to much debate and controversy, in part related to the high morbidity in survivors less than 1000 g.[1] Postligation cardiac syndrome (PLCS) complicates the postoperative course in 40%-50% of preterm infants. PLCS is a clinical entity characterized by hypotension requiring inotropic support, and/or ventilation/oxygenation failure, usually occurring 6-12 hours after ligation.[2,3] Several studies have investigated the physiologic mechanisms contributing to cardiorespiratory instability after PDA ligation and demonstrated a decrease in shortening fraction and ejection fraction associated with an increase in systemic vascular resistance (SVR) and a sudden reduction in preload.[2,4] The sudden increase in SVR is not well tolerated by the preterm myocardium.[3,5] Our group recently demonstrated that a left ventricular output (LVO) <200 mL/kg/min on echocardiography evaluation 1 hour after ligation is predictive of developing PLCS over the subsequent few hours.[6] Early administration of milrinone to infants with low LVO reduces the incidence of PLCS from 44% to 11%.[6] Conventional echocardiographic measures of left ventricular (LV) systolic performance, including fractional shortening and ejection fraction, do not predict PLCS.[4] Previously, we demonstrated that PDA ligation resulted in significant changes in myocardial tissue Doppler measures and myocardial strain imaging.

The aim of the present study was to characterize LV performance using tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) in neonates with high (>200 mL/min/kg) vs low (<200 mL/min/kg) LVO 1 hour after PDA ligation. We hypothesized that the tissue Doppler and strain measures at 1 hour postoperatively would be lower in infants with low LVO compared with those with a greater LVO. We also performed a longitudinal evaluation of TDI- and STE-derived estimates of LV systolic performance in the group with low LVO treated with milrinone.

Methods

All preterm neonates with birth weights between 500 and 1500 g and gestation between 24 and 32 weeks who were admitted to the Hospital for Sick Children

BP	Blood pressure	PDA	Patent ductus arteriosus
cTnT	Cardiac troponin T	PLCS	Postligation cardiac syndrome
FiO_2	Fraction of inspired oxygen	PWD	Pulsed-wave Doppler
GLS	Global longitudinal strain	RV	Right ventricular
LV	Left ventricular	STE	Speckle tracking echocardiography
LVEDC	LV end-diastolic circumference	SVR	Systemic vascular resistance
LVO	Left ventricular output	TDI	Tissue Doppler imaging
MAP	Mean airway pressure	VTI	Velocity time integral

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for PDA ligation were considered eligible for inclusion. Infants with major congenital abnormalities, cardiac lesions other than PDA, or a patent foramen ovale were excluded from this study. Referrals for PDA ligation are triaged according to the clinical and echocardiography findings via use of the PDA staging system.[7] All infants are anesthetized with fentanyl before the procedure at a dose ranging between 10 and 30 μg.

Our institutional approach to the postoperative management of preterm infants after ligation is as follows. A routine echocardiography assessment is performed 1 hour postoperatively to assess LVO.[8] Infants with LVO less than 200 mL/kg/min are considered at high risk of developing PLCS and are started on 0.33 μg/kg/min intravenous infusion of milrinone treatment. A bolus of 10 mL/kg of 0.9% saline is coadministered for the first hour to prevent low diastolic blood pressure (BP). Infants who develop systolic hypotension (defined as a value less than the third percentile for any given gestation) in the postoperative period were treated with an intravenous infusion of 5-20 μg/kg/min dobutamine. Infants with diastolic hypotension (defined as a value less than the third percentile for any given gestation) were treated with boluses of 0.9% saline and/or intravenous infusion of 5-15 μg/kg/min dopamine. Adrenocorticotropic hormone (cosyntropin) testing was performed on all patients before surgical intervention. Intravenous hydrocortisone 0.5 mg/kg every 6 hours was administered to all neonates with intractable hypotension and postadrenocorticotropic hormone cortisol <500 mmol/L despite cardiovascular treatment.

The cohort was divided into low (LVO <200 mL/kg/min) and high (LVO >200 mL/kg/min) LVO groups based on the 1 hour postoperative echocardiogram. The study was approved by the institutional research ethics board, and written parental consent was obtained.

Neonatal birth and postnatal demographics (antenatal steroid administration, Apgar scores, gestational age and weighs at birth, respiratory distress syndrome, surfactant administration, and ventilation days) were recorded. Details of medical and surgical treatment for the PDA also were collected. Serial evaluation of hemodynamic (eg, heart rate, BP, arterial pH, and base deficit) and respiratory variables (eg, fraction of inspired oxygen [FiO_2], mean airway pressure [MAP]) was performed. Oxygenation index was calculated during the 3 time points via the following formula: oxygenation index = (MAP × FiO_2 × 100) PaO_2.

Studies were performed with the use of a Vivid 7 or E9 ultrasound scanner (GE Healthcare, Milwaukee, Wisconsin) with a 10- or 12-MHz neonatal probe, respectively. Each infant underwent 3 echocardiography assessments: 4-6 hours preoperatively (preoperatively), 1 hour postoperatively before the administration of milrinone if needed (1 hour postoperatively), and 16-18 hours postoperatively (18 hours postoperatively). All studies were conducted in accordance with our standardized functional protocol, which follows recently published guidelines[9,10] and included TDI and STE imaging methods. All studies were stored as raw data for offline analysis (EchoPAC; GE, Milwaukee, Wisconsin). Offline measurements were conducted after the infants were discharged from the unit. All infants underwent a preoperative complete echocardiographic assessment by a pediatric cardiologist to exclude congenital heart disease. We obtained the following measurements by using conventional echocardiography methods that have previously been described[10,11]:

Assessment of PDA: (1) PDA diameter measured at the pulmonary end (2D imaging); and (2) the direction and peak velocity of flow across the shunt (pulsed-wave Doppler [PWD]). Markers of volume loading: (1) left atrial to aortic root ratio (M-mode); (2) mitral valve E and A velocities and the E wave to A wave ratio (PWD); and (3) LV end-diastolic diameter (M-mode). Measures of myocardial performance: (1) LV and right ventricular (RV) outputs (PWD + 2D measurement); (2) shortening fraction (M-mode); (3) ejection fraction measured by Simpson biplane method (ejection fraction) – (2D imaging); (4) tissue Doppler velocities (S′, E′, and A′) of the mitral, septal, and tricuspid annuli; (5) isovolumic contraction and isovolumic relaxation times measured by TDI; and (6) LV global longitudinal strain (GLS).

LVO was calculated by measuring the blood velocity at the aortic valve annulus from an apical 5-chamber view via a PWD and the diameter of the aortic annulus from a parasternal long-axis view by measuring the distance between the 2 visible hinges of the aortic valve in early systole. From the PWD tracing, the velocity time integral (VTI) was calculated. The aortic cross-sectional area was calculated using the formula: π × aortic diameter^2/4. LVO was then indexed to weight as (mL/kg/min) = (aortic cross-sectional area × VTI × heart rate)/weight. The heart rate was calculated from the R-R interval obtained from electrocardiogram tracing of the aortic Doppler flow image. SVR was calculated by using the following formula: (mean systemic BP − mean tricuspid valve inflow pressure gradient)/LVO.[12] We also measured LV mean velocity of circumferential fractional shortening. It is determined by the following method[13]: velocity of circumferential fractional shortening = (LVEDC − LV end-systolic circumference)/(LVEDC × ejection time corrected for heart rate [ejection time/$\sqrt{}$RR interval]), where LVEDC = LV end-diastolic circumference.

Tissue Doppler velocities were obtained from the apical 4-chamber view. We used a PWD sample gate of 2 mm at the level of the annuli while always maintaining an angle of <20° between the pulsed-wave cursor and the longitudinal plane of motion. The sector width was minimized to improve the frame rate and temporal resolution. On the tissue Doppler traces we measured peak systolic (S′), early diastolic (E′), and late diastolic (A′) velocities. The isovolumic contraction and relaxation times and LV systolic time were measured (**Figure 1**; available at www.jpeds.com). For strain analysis, 2D grayscale images were recorded from the apical 4-, 3-, and 3-chamber views. GLS was calculated based on the segmental values as previously described by our group.[5]

Image acquisition was carried out by 1 of 3 investigators (A.K., A.J., and D.W.). Offline image analysis was carried

out by 2 investigators (A.K. and D.W.). The intra- and inter-observer reliability of TDI and STE in the preterm population undergoing PDA ligation was previously reported by our group using the same observers.[5] The components of the LVO calculation (heart rate, aortic VTI, aortic diameter) were entered into an electronic database, and LVO was calculated post-hoc. As a result, the observers were unaware of the LVO grouping assignment at the time of the analysis.

Cardiac troponin T (cTnT) measurements were taken immediately after the preoperative echocardiogram, 1 hour postoperatively, and after the 18-hour postoperative echocardiogram. cTnT increases in the presence of a PDA in premature infants[14] and is predictive of adverse neurodevelopmental outcomes associated with a PDA.[15] cTnT is a measurement of myocardial damage that also may be associated with the hemodynamic loading.[16] The preoperative and postoperative blood samples were performed with routine blood work and an additional 0.15 mL of blood was required per sample. The samples were tested using the Roche bedside cardiac reader (cobas h 232 POC system; Roche Diagnostics Limited, Rotkreuz, Switzerland). For low levels, the troponin reader provides a range in which the true value is: less than 0.03 μg/L or between 0.03 and 0.10 μg/L. A level greater than 0.10 μg/L is shown as an absolute value. We represented a level < 0.03 as "0" and a level between 0.03 and 0.10 as "0.065."

Statistical Analyses

We presented data as means ± SD for normally distributed variables and as medians and IQR for nonparametric data. Continuous variables between the 2 groups were compared with a Student *t* test or a Mann-Whitney *U* test as appropriate. Categorical data were compared using the χ^2 test or Fisher exact test as appropriate. We compared clinical and echo data between the 2 groups across the 3 time points using 2-way ANOVA with repeated measures. We assessed the correlation between various echocardiography measures using Pearson correlation coefficient for normally distributed data and Spearman correlation coefficient for skewed data. We accepted a P value of less than .05 as significant. The statistical analysis was performed using SPSS version 20 (SPSS Institute, Chicago, Illinois).

Results

Thirty infants were included in this study. Nineteen infants had LVO less than 200 mL/kg/min (low LVO group) and were started on an intravenous infusion of milrinone. Eleven infants had a LVO greater than 200 mL/kg/min (high LVO group) and did not require milrinone. With the exception of the 5-minute Apgar score, which differed by a single point only between the groups, there were no differences in baseline neonatal demographics, clinical or PDA characteristics between the 2 groups (Table I). None of the infants was on inotropic agents before ligation. In the low-LVO group, there was a greater proportion of infants requiring an escalation of FiO_2 >20% (10 [53%] vs 1 [9%], $P = .02$), in the postoperative period. Similarly, there was a nonsignificant trend of infants in the low LVO group needing high-frequency oscillation (8 [42%] vs 2 [27%], $P = .5$) accompanied by an increase in MAP >20% (8 [42%] vs 2 [18%], $P = .2$). Only 2 (16%) of those infants also required inotropic agents and therefore met the criteria for PLCS. Both developed a systolic BP less than the third percentile for gestation between 6 and 12 hours postoperatively and received intravenous dobutamine treatment. None of the high LVO group developed PLCS. None of the infants in our cohort received hydrocortisone. We identified an increase in median (IQR) preoperative cTnT level from 0.07 μg/L (0.07-0.18) to 0.23 μg/L (0.16-0.28) at 18 hours after surgical intervention ($P < .001$, 2-way ANOVA). There were no differences in cTnT between groups at any time point.

A decrease in LVO ($P < .001$, 1-way ANOVA) was demonstrated in the entire cohort after PDA ligation (Table II). The magnitude of the reduction from pre-operative values was greater in the low-LVO group (Table III; available at www.jpeds.com). There was, however, recovery in LVO by 18 hours in milrinone-treated patients (low-LVO group) to a level comparable with infants in the high-LVO group. An increase in SVR was seen in both groups 1 hour after PDA ligation ($P < .001$, 2-way ANOVA), although the magnitude of the increase was greater in the low-LVO group (Table II). By 18 hours, SVR decreased in milrinone-treated patients (low-LVO

Table I. Patient demographics and clinical and PDA characteristics before ligation

	Low LVO, n = 19	High LVO, n = 11	*P* value
Gestation, weeks	25.0 [24.4-25.6]	25.2 [24.9-26.6]	.39
Birth weight, g	700 [620-825]	750 [640-874]	.37
Gestation at ligation, weeks	28.7 [27.8-30.5]	29.9 [28.6-31.1]	.42
Weight at ligation, g	948 [820-1071]	990 [874-1102]	.66
Postdelivery age at ligation, days	25 [21-36]	30 [23-36]	.66
Male	9 (50%)	6 (50%)	1.0
Cesarean delivery	7 (39%)	7 (58%)	.46
5-minute Apgar score	7 [5-7]	8 [7-9]	.003
Antepartum hemorrhage	1 (6%)	2 (17%)	.55
Preeclampsia	2 (11%)	1 (8%)	1.0
Chorioamnionitis	1 (6%)	2 (17%)	.55
Antenatal steroids			.53
Partial	1 (6%)	2 (17%)	
Complete	12 (67%)	8 (67%)	
Days on invasive ventilation	23 [21-35]	24 [20-27]	.71
Necrotizing enterocolitis	1 (6%)	3 (25%)	.27
Intraventricular hemorrhage (III/IV)	3 (16%)	2 (17%)	.48
NSAIDs treatment	16 (89%)	11 (82%)	.60
Hemoglobin, g/dL	118 [109-129]	124 [91-129]	.44
pH	7.29 [7.28-7.34]	7.31 [7.29-7.39]	.79
Oxygen requirement, %	34 [30-40]	35 [26-36]	.64
MAP, cm H_2O	10 [9-10]	10 [9-10]	.71
PDA diameter before ligation, mm	3.1 [2.3-3.4]	3.3 [2.7-3.9]	.63
Maximum pressure gradient, mmHg	21 [13-26]	28 [12-39]	.26

NSAIDs, nonsteroidal anti-inflammatory drugs.
Values are expressed as median [IQR] or absolute value (%).

Table II. Conventional echocardiography markers

	Preoperative		1 hour postoperatively		18 hours postoperatively			
	Low LVO	High LVO	Low LVO	High LVO	Low LVO	High LVO	Group ANOVA	Time ANOVA
Heart rate	155 (12)	156 (18)	142 (13)	150 (18)	155 (17)	147 (14)	.19	.79
Mean BP	37 (5)	41 (7)	42 (8)	43 (9)	38 (9)	54 (8.1)*	.1	.008
Oxygenation index	10.3 (1.9)	10.0 (1.8)	9.4 (1.5)	9.5 (2.6)	11.0 (4.1)	10.4 (2.7)	.23	.66
LVO, mL/kg/min	446 (145)	407 (82)	139 (32)*,†	223 (44)*	222 (78)*	267 (48)*	.19	<.001
RVO, mL/kg/min	256 (89)	263 (105)	202 (72)	301 (92)	267 (117)	344 (139)	.04	.07
Shortening fraction (%)	37 (4)	38 (8)	24 (8)*	27 (6)*	30 (9)*	27 (6)*	.81	<.001
Ejection fraction (%)	65 (9)	63 (8)	50 (11)*	56 (9)*	54 (10)*	55 (11)*	.65	<.001
VcFs, circ/s	3.9 (0.5)	4.1 (0.8)	3.4 (1.2)	3.5 (0.9)	3.8 (1.1)	3.1 (1.0)	.06	.52
LVEDD, mm	16.5 (2.6)	17.0 (2.2)	12.5 (2.4)*	13.8 (2.4)*	13.6 (2.7)*	15.1 (1.9)*	.34	<.001
LA:Ao	2.5 (0.3)	2.5 (0.5)	1.7 (0.2)*	1.8 (0.4)*	1.8 (0.4)*	1.9 (0.4)*	.42	<.001
Mitral valve E:A ratio	0.88 (0.17)	0.89 (0.08)	0.79 (0.24)	0.86 (0.14)	0.80 (0.16)	0.88 (0.12)	.25	.27
Mitral valve E wave, cm/s	0.87 (0.25)	0.85 (0.12)	0.40 (0.07)*	0.51 (0.12)*	0.53 (0.16)*	0.57 (0.15)*	.38	<.001
Mitral valve VTI	10.8 (2.1)	11.0 (2.7)	5.7 (1.4)	6.5 (1.5)	6.9 (1.9)	7.0 (1.8)	.53	<.001
SVR, mmHg/kg/min	92 (49)	102 (27)	329 (137)*,†	198 (57)*	203 (106)*	198 (45)*	.07	<.001

E:A, E wave to A wave; *LA:Ao*, left atrial to aortic root; *LVEDD*, LV end-diastolic diameter; *NS*, not significant ($P > .05$); *VcFs*, LV mean velocity of circumferential fractional shortening (corrected for heart rate).
Values are presented as means (SD). Two-way, repeated-measures ANOVA was used to compare the difference in values across the 3 time points (ANOVA *P*). Pairwise comparisons were only performed, and the *P* value displayed, if the 2-way, repeated-measures ANOVA test yielded significant results.
*$P < .05$ vs baseline.
†$P < .05$ vs low-risk infants.

group) to levels comparable with the high-LVO group (Table II). LV systolic function and ejection fraction decreased in the entire cohort after PDA ligation, but there were no intergroup differences.

Tissue Doppler velocities were measurable in all infants across the 3 evaluation time points. Isovolumic timing measurements were not possible in 5 (6%) studies because of the difficulty in identifying the start and end of systolic and diastolic waves. GLS measurements were not possible in 8 (9%) scans because of poor image quality. There were early postoperative intergroup differences in tissue Doppler-derived systolic velocities. At 1 hour, LV S′, septal S′, and RV S′ were lower in low-LVO group compared with the high-LVO group (Table IV and Figure 2). The magnitude of change in systolic velocity from preoperative to 1 hour after intervention was only significant for LV lateral S′ and septal S′ (Table III). There was complete recovery by 18 hours in LV systolic velocities in the low-LVO group who received milrinone to levels comparable with the high-LVO group. GLS decreased in both groups after surgical intervention, with a nonsignificant trend towards lower values in the low-LVO group (-10.6 ± 3.2 % vs -14.4 ± 1.9%, $P > .05$). By 18 hours, GLS in the low-LVO group who received milrinone returned to a level comparable with the high-LVO group (Tables III, IV, and Figure 2).

A negative correlation between SVR and tissue Doppler systolic velocities of the LV and septal walls ($r = -0.6$,

Table IV. GLS and TDI estimates of myocardial performance

	Preoperative		1 hour post postoperativley		18 hours postoperativley			
	Low LVO	High LVO	Low LVO	High LVO	Low LVO	High LVO	Group ANOVA	Time ANOVA
LV lateral TDI, cm/s								
S′	5.1 (1.0)	4.8 (0.7)	3.1 (1.0)*,†	3.8 (0.9)†	4.3 (1.0)†	3.9 (0.8)†	.87	<.001
E′	8.0 (4.4)	6.3 (2.7)	3.2 (1.5)†	4.2 (1.7)†	4.2 (1.2)†	4.7 (1.7)†	.85	<.001
A′	9.7 (3.0)	8.1 (2.9)	4.6 (2.0)†	5.8 (3.0)†	5.5 (2.1)†	5.8 (1.8)†	.94	<.001
Septal TDI, cm/s								
S′	4.9 (1.0)	4.8 (0.6)	3.0 (0.7)*,†	4.2 (0.6)†	4.1 (0.8)†	4.1 (0.3)†	.14	<.001
E′	5.9 (2.0)	5.5 (1.6)	3.3 (1.2)†	5.0 (1.8)†	4.8 (1.9)†	4.8 (1.3)†	.22	<.001
A′	7.0 (1.4)	6.8 (1.3)	4.6 (1.1)†	5.6 (1.5)†	5.8 (1.5)†	5.9 (1.1)†	.20	<.001
RV TDI, cm/s								
S′	7.1 (1.7)	8.2 (1.6)	5.6 (1.7)*,†	7.8 (1.9)	6.2 (1.5)	6.8 (0.9)	.007	.02
E′	8.5 (3.5)	8.5 (2.1)	5.4 (2.1)†	7.3 (2.9)†	6.2 (2.7)†	7.7 (3.1)†	.08	<.001
A′	9.8 (3.0)	8.9 (2.0)	7.3 (1.6)	9.1 (2.1)	8.5 (2.3)	9.2 (2.6)	.78	.81
LV GLS, %	−18.9 (2.6)	−20.2 (5.4)	−10.6 (3.2)†	−14.3 (1.9)	−15.0 (3.3)†	−14.9 (2.5)	.6	<.001
LV event times								
LV systolic time, ms	169 (23)	172 (33)	145 (14)†	153 (18)†	147 (18)†	151 (22)†	.48	<.001
IVCT, ms	38 (14)	35 (6)	54 (16)†	52 (9)†	40 (13)†	47 (8)†	1.0	<.001
IVRT, ms	46 (14)	41 (8)	69 (13)*,†	56 (13)†	54 (11)†	58 (11)†	.07	<.001

IVCT, isovolumic contraction time; *IVRT*, isovolumic relaxation time; *LVET*, LV ejection time.
Values are presented as means (SD). Repeated-measures ANOVA was used to compare the difference in values across the 3 time points (ANOVA *P*). Pairwise comparisons were only performed, and the *P* value displayed, if the 2-way, repeated-measures ANOVA test yielded significant results.
*$P < .05$ vs low-risk infants.
†$P < .05$ vs baseline.

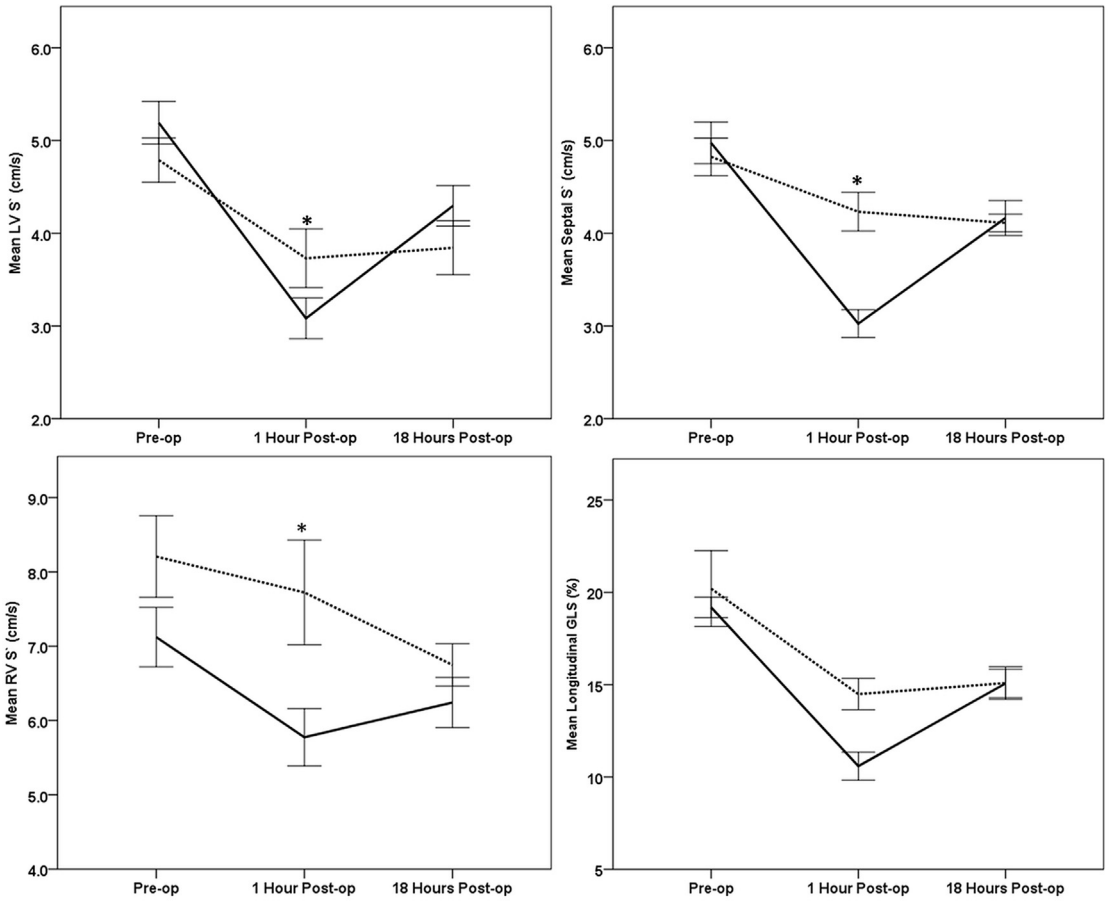

Figure 2. LV, septal, and RV S′ velocities and LV GLS in the 2 groups across the 3 time points. Strain values are represented as a positive value for the purposes of graphical representation. The *solid line* represents the low-LVO group, and the *dotted line* represents the high-LVO group. The *error bars* represent the SE. *Depicts a significant difference between the groups at that time point (2-way ANOVA with repeated measures).

$P < .001$ and $r = -0.7$, $P < .001$, respectively) was present at the preoperative and 1-hour evaluation. There was a weaker negative correlation between SVR and tissue Doppler diastolic velocities of the LV and septum: LV E′ ($r = -0.4$, $P = .001$), LV A′ ($r = -0.4$, $P = .002$), and septal E′ ($r = -0.6$, $P < .001$). There was no correlation between SVR and septal A′ ($r = -0.2$, $P = .1$). There was a negative correlation between SVR and GLS ($r = -0.6$, $P < .001$). There was a positive correlation between LVO and LV S′ ($r = 0.6$, $P < .001$), septal S′ ($r = 0.7$, $P < .001$), and GLS ($r = 0.7$, $P < .001$). There was a weak positive correlation between RV S′ and LVO ($r = 0.3$, $P = .02$). Similarly, there was a positive correlation between LVO and LV E′ ($r = 0.6$, $P < .001$), LV A′ ($r = 0.6$, $P < .001$), septal E′ ($r = 0.6$, $P < .001$), and septal A′ ($r = 0.4$, $P = .004$).

Discussion

Reference ranges for tissue Doppler velocities in extremely low birth weight infants are emerging.[17-19] It is difficult to perform a direct comparison between preoperative TDI velocities in this cohort and previously published data, because most neonatal studies of TDI were performed in the infant's first week of life. Nevertheless, the preoperative TDI systolic and diastolic velocities in this cohort were all generally greater than those presented in the literature for similar gestational-age infants. This finding may relate to the impact of a high-volume shunt present in our population increasing preload. It is also worth noting that after PDA ligation, infants in the low-LVO group had TDI velocities that were lower than the previously published values.

We also observed significant changes in LV GLS in both groups. Although the magnitude of the change was larger in the lower output group, it did not reach statistical significance. This may relate, at least in part, to the greater variability of the strain measurements compared with the tissue Doppler measurements or to the small study sample size. The effect of the acute changes on tissue Doppler velocities is likely attributable to the load-dependency of the measures rather than a true decrease in LV contractility (intrinsic myocardial function). Evaluation of true myocardial contractility is not feasible with current echocardiography techniques, which

provide information on myocardial systolic/diastolic performance alone.[20] Longitudinal changes in LV function measured by tissue Doppler and strain measurements appear to be influenced by the acute changes in loading conditions. There was a significant negative linear relationship between peak systolic tissue Doppler velocities and SVR measurements. The same negative correlation was observed between the absolute value of GLS and SVR, suggesting that those markers of myocardial performance are strongly influenced by afterload changes. Although we accepted the limitations of the SVR calculation based on echocardiography, it was interesting to note that the low-LVO group had a much greater SVR than the high-LVO group. In a study in animals, researchers demonstrated that strain was sensitive to acute changes in afterload and that strain rate measurements seem to be less affected.[20] Strain rate measurements are, however, technically more difficult and are highly frame rate dependent. In preterm infants with greater heart rates, assessment of strain rate is technically challenging.

LV diastolic velocities (E′ and A′) were lower after PDA ligation, but an intergroup difference was not seen. Early tissue Doppler velocities are influenced by different factors, including early relaxation, restoring forces determined by the amount of shortening during systole, and lengthening load which represents preload.[21] Only LV isovolumic relaxation time at 1 hour was different with longer interval duration in the low-LVO group, which may relate to the acute volume unloading causing early relaxation abnormalities or may be a consequence of increased afterload.[22] Diastolic function may contribute to the evolution of low LVO after ligation. The lack of intergroup differences in most measures of diastolic function suggests that the magnitude of the change in diastolic function (and preload) play a lesser role in the etiology of low LVO. The weak correlation between LVO, SVR, and the diastolic TDI variables further supports this reasoning. RV diastolic velocities were less influenced by ligation.

It has been suggested that the reduction in LV systolic function post duct closure may relate to myocardial injury related to ischemia.[23] For this reason, we included the use of biomarkers in the current project. cTnT levels were unchanged 1 hour after PDA ligation but increased at 18 hours. The levels were not different between the 2 groups. The lack of intergroup differences at 1 and 18 hours suggests that myocardial ischemia is not a contributory factor in the etiology of low LVO. However, it is possible that the delayed increase in cTnT at 18 hours is a consequence of its sudden exposure to increased SVR, analogous to the increase in plasma troponin that occurs in the transitional period.[24,25] The nature of the elevation in cTnT may relate to the release of cytosolic cTnT not bound to the myofibril.[26]

Administration of milrinone to patients with low LVO was associated with recovery in LVO, LV lateral, and septal S′ velocities to levels comparable with the high-LVO group. Milrinone, a phosphodiesterase III inhibitor, increases tissue bioavailability of cyclic adenosine monophosphate, resulting in vasodilation, positive inotropy, and afterload reduction. We previously demonstrated that the immediate postoperative administration of intravenous milrinone to infants with low LVO results in a reduction in the risk of development of PLCS.[6] The presumed benefits of milrinone treatment were thought to relate predominantly to its vasodilator and afterload-reducing effects. In this study, we found that intravenous milrinone was associated with longitudinal improvement in TDI- and STE-derived indicators of systolic function by 18 hours. Although milrinone is known to possess a lusitropic effect, with the exception of septal E′, treatment was not associated with recovery in diastolic velocities in the low LVO group by 18 hours of life. This finding suggests that the predominant effect of milrinone is afterload reduction coupled with an improvement in systolic function rather than lusitropy. There were, however, 2 infants in the low-output group who developed PLCS despite treatment with milrinone. It was not possible to further investigate factors contributing to the development of PLCS in these patients because of the low event rate. The physiologic nature of disease and causal factors in neonates with PLCS, despite milrinone treatment, requires further evaluation in larger groups. There were no obvious differences in any echocardiography markers of systolic performance between these 2 infants and the rest of treatment cohort.

There are several limitations to the study design. First, because the study is not randomized and lacks a control group of high-risk infants that did not receive milrinone, it is not possible to be certain that the changes seen were related to treatment and not independent temporal changes. Second, the sample size is small, which prohibits making any meaningful statements of treatment effect. Third, as mentioned previously, it is not possible to accurately measure LV afterload in these patients. Also, the calculation of SVR is dependent on LVO, and thus may not represent true vascular resistance in this population.

TDI and STE provide novel insights and further characterization of LV systolic performance immediately after PDA ligation. Treatment with milrinone appears to have a positive influence on LV systolic function, although this needs confirmation in a prospective randomized controlled trial. ■

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Table III. Comparison of the change in LVO, SVR, and function parameters between the groups

	1 hour postoperatively − preoperatively			18 hour postoperatively − 1 hour postoperatively		
	Low LVO	High LVO	*P* value	Low LVO	High LVO	*P* value
LVO, mL/kg/min	−307 (138)	−183 (85)	.01	+83 (66)	+ 43 (69)	.13
SVR, mmHg/kg/min	+237 (130)	+96 (62)	.003	−125 (140)	0 (80)	.01
Shortening fraction, %	−12 (7)	−11 (8)	.4	+5 (8)	0 (5)	.1
Ejection fraction, %	−15 (8)	−6 (9)	.009	+4 (13)	−1 (14)	.3
VcFs, circ/s	−0.5 (0.9)	−0.6 (1.0)	.8	+0.4 (1.1)	−0.5 (1.2)	.06
LV S′, cm/s	−2.1 (1.7)	−1.0 (0.7)	.03	+1.2 (1.4)	0.1 (0.7)	.008
LV E′, cm/s	−4.7 (3.6)	−2.7 (2.1)	.2	1.0 (1.7)	0.5 (0.8)	.4
LV A′, cm/s	−5.1 (3.5)	−2.5 (2.5)	.06	1.0 (3.3)	−0.1 (3.8)	.5
Septal S′, cm/s	−1.9 (1.1)	−0.6 (1.1)	.004	+1.1 (0.7)	−0.1 (0.6)	<.001
Septal E′, cm/s	−2.6 (2.2)	−1.1 (1.9)	.09	+1.4 (1.7)	0 (1.5)	.01
Septal A′, cm/s	−2.3 (2.0)	−1.6 (1.0)	.3	+1.2 (1.8)	0 (1.5)	.2
GLS, %	−8.6 (3.9)	−5.7 (6.4)	.2	+4.5 (3.5)	0.5 (3.0)	.006

Comparisons are made between preoperative to 1 hour postoperative and between 1 hour postoperative to 18 hours postoperative. A positive sign (+) depicts an increase in the parameter between the compared time points. A negative sign (−) depicts a reduction in the value of the parameter between the compared time points.

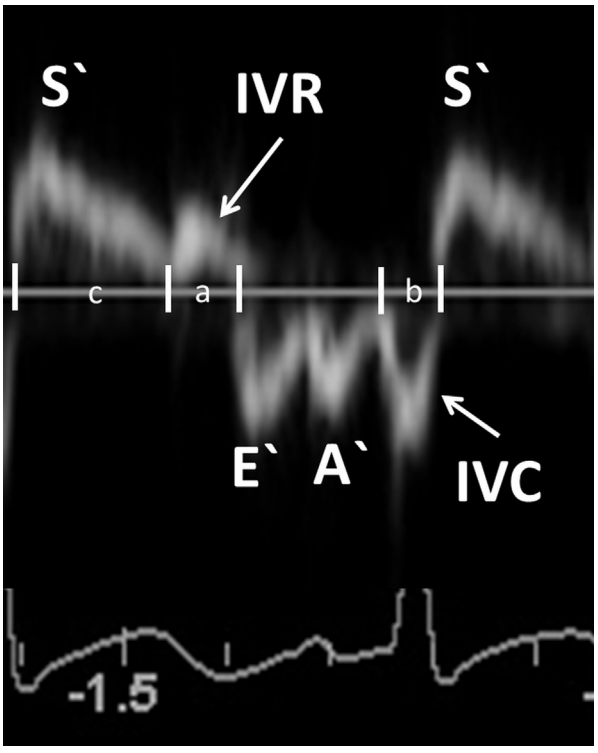

Figure 1. Tissue Doppler velocities of the LV in a preterm infant after PDA ligation. The different phases of the cardiac cycle are clearly identified. The systolic velocity (S′) and early (E′) and late (A′) diastolic velocities can easily be measured. Isovolumic relaxation time (IVR and a) time and isovolumic contraction (IVC and b) time in addition to systolic time (c) can also be measured.