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ORIGINAL ARTICLE

Hemodynamic alterations recorded by electrical cardiometry during ligation of ductus arteriosus in preterm infants

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Abstract This is a prospective study using non-invasive electrical cardiometry to measure hemodynamic changes during surgical ligation of patent ductus arteriosus (PDA) in very low birth weight (VLBW, ≤1500 g) infants. The aims of this study were to examine hemodynamic aberration caused by abrupt closure of a ductal shunting and to define factors that affect hemodynamic changes. Simultaneous measurements of heart rate (HR), stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) were collected at ten time points: 1 h prior to anesthesia, at the beginning of anesthesia, starting of surgery, immediately after PDA being ligated, and 1 h followed by 6, 12, 18, 24, and 48 h after the surgery. Thirty infants with gestational age of 27.7±2.0 weeks and birth weight of 929±280 g were studied. Upon sudden termination of ductal shunting, there was a significant decline in CO to 73 % of presurgery baseline. The deterioration in CO was associated with a decreased SV rather than HR. At the same time, there was an increase of SVR following ductal ligation. Magnitude of CO and SV reduction were higher in smaller infants (≤1 kg), and recovery was to a lesser degree in infants with more severe PDA.

Conclusion: Reduced stroke volume and elevated vascular resistance contribute to the major hemodynamic aberrations in VLBW infants receiving PDA ligation surgery.

Keywords Cardiac output · Ductus arteriosus · Electrical cardiometry · Hemodynamic · Preterm

Abbreviations

CO	Cardiac output
EC	Electrical cardiometry
PDA	Patent ductus arteriosus
SV	Stroke volume
VLBW	Very low birth weight

Introduction

Patent ductus arteriosus (PDA) is common for very low birth weight (VLBW, ≤1500 g) infants. Infants who failed or are not suitable to receive pharmacological regimen for closing a hemodynamically significant PDA (hsPDA) would undergo surgical ligation. Recently, there have been increasing concerns of possible deleterious effects caused by PDA ligation, especially through the hemodynamic perturbation from the operation and post-ligation cardiac instability.

Pulse contour analysis with calibration using thermodilution technique has been widely used for assessing cardiac output (CO). However, this technique is invasive and almost impractical in preterm infants. Previous studies on hemodynamic changes following PDA ligation were based on echocardiogram and suggested a temporarily CO impairment [1, 5–7, 9, 16]. But performing an echocardiogram could

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be technically challenging, and those assessments were only obtained intermittently.

Electrical cardiometry (EC) is an impedance-based monitor that measures electrical current produced by electrodes and changes of thoracic electrical bioimpedance, which is most related to thoracic aortic flow and red blood cells (RBCs) alignment. When aortic flow stops, RBCs in the aorta are randomly orientated and impeding the conduction. Once the left ventricle contracts, the ejection flow would compel the RBCs to parallel with the flow, which results in higher conductivity and decreased bioimpedance. The magnitude and frequency of pulsatile bioimpedance changes are used to calculate varied hemodynamic measures [12].

EC has been proposed as a safe, easy, and accurate technique for hemodynamic measurement in children and infants [13, 19]. By using thermodilutional technique as gold standard, the efficacy of EC has been established in animal models [11] and in adult patients [21]. In spite of bias, analysis of CO had shown a good correlation between EC and pulmonary artery catheter thermodilution in children receiving catheterization [17]. In infants with congenital heart disease, CO measured by EC has been shown to be comparable to direct Fick-oxygen method [10] and transesophageal Doppler [15] measurement. Recent studies also demonstrated that the accuracy of EC was comparable to transthoracic echocardiogram in estimating neonatal CO [2, 8], even in VLBW preterm infants [3]. Although cardiac parameters may vary between different measuring methods (Fick's method, thermodilution, echocardiography, and cardiac MRI), the variations from those obtained using EC have been regarded as acceptable [18]. Based on these reports, we adopted EC as a tool to study hemodynamic changes in neonatal patients. We applied EC in VLBW infants who underwent surgical PDA ligation, aiming to monitor on-site hemodynamic impact caused by abrupt closure of a ductal shunting, and to define factors that may affect the hemodynamic changes during ligation in these infants.

Methods

Subjects

This prospective observational study was conducted in the neonatal intensive care unit (NICU) of Chang Gung Memorial Hospital between March 2012 and February 2013. In this level III nursery, infants with hsPDA who failed or were unsuitable to receive pharmacologic regimen would undergo surgical ligation. Our criteria for hsPDA included the following: (i) ductal diameter ≥2.0 mm or ≥1.5 mm/kg by echocardiogram examination, (ii) left atrium to aortic root diameter ratio (LA/Ao) ≥1.3 [20], and (iii) symptoms, including increased need for ventilatory support, pulmonary hemorrhage, or systemic hypotension. Infants with major malformations or with structural heart defects other than PDA and/or patent foramen ovale were excluded. The Institutional Review Board approved this study.

Operation procedures

All ligations were performed at patient's bedside by one of the two cardiovascular surgeons using similar technique. Anesthesia was achieved by ketamine and/or fentanyl. Cisacurium (muscle relaxant) was used exclusively. A left mid-axillary mini-thoracotomy was performed through the fourth intercostal space with the muscle-sparing method. Ductus arteriosus was ligated using pledgeted suture or a metal clip, depending on surgeon's preference.

Interventions

EC (AESCULON®, Osypka Medical GmbH, Berlin, Germany) was applied by means of four standard surface electrocardiogram electrodes over infant's forehead, right lower neck, right mid-axillary line at the level of xiphoid process, and lateral aspect of right thigh. Right-sided disposition of electrodes, instead of ordinary left-sided, was chosen to avoid the operation area. In preparation for this study, consistency and reproducibility of CO measurement using same EC on VLBW infants were tested and confirmed. We also pretested and established that there was no signal difference if the electrodes were placed on the right or left side of our patients.

Data collection

Demographic data including gender, gestational age, birth weight, body surface area (BSA), and age of surgery were recorded. BSA was computed according to Boyd formula by AESCULON®. Echocardiogram severity of PDA was expressed as size (mm), size to weight (mm/kg), and LA/Ao. All study patients were intubated and required mechanical ventilatory support. Mean airway pressure (MAP) and FiO_2 were depicted to convey degree of respiratory support. Weight at diagnosis or birth weight, whichever is heavier, was used for calculation. Patient's temperature was maintained steady at 36.7±0.3 °C.

EC was applied throughout the duration of 1 h prior and 48 h after the surgery. Physiological data including heart rate (HR), SV, CO, cardiac index (CI), and systemic vascular resistance (SVR) were automatically saved at an interval of 1 min. SVR by EC is calculated using the formula $80 \times (\textit{mean arterial pressure} - \textit{central venous pressure}\ (\textit{CVP}))/\textit{CO}$. CVP is presumed to be 3 mmHg by default. Blood pressure was recorded using Dinamap® (GE Healthcare, Little Chalfont Buckinghamshire, UK) continuous blood pressure monitor. All the measurements were serially recorded at ten time

points: 1 h prior (T_{Pre}), 1 min after beginning anesthesia (T_A), 1 min after starting of surgery (i.e., cutting the skin with a scalpel, T_S), 1 min after PDA was ligated (T_L), 1 h after closing surgery (T_{1h}), and 6th hour (T_{6h}), 12th hour (T_{12h}), 18th hour (T_{18h}), 24th hour (T_{24h}), and 48th hour (T_{48h}) after surgery. Values of five continuous measurements were averaged and adopted for each time point except at T_A, T_S, and T_L, where values of respective exact time were used. We defined condition at T_{Pre} as pre-ligation status, changes between T_S and T_{Pre} as the influence of anesthesia and changes between T_L and T_S as the immediate impact of abrupt termination of ductal shunting.

Data analysis

Since there is a lack of normal reference data for most hemodynamic measurements in preterm infants, changes were compared by percentage difference from their respective baseline instead of the absolute value. For each measurement, the value at T_{Pre} was the baseline, and values at other nine time points were divided by baseline value and recorded as dependent variables. Subgroup analyses were achieved according to body weight (at the time of surgery, <1 kg vs. ≥1 kg) and PDA severity (ductal size ≤2 mm vs. >2 mm, ≤2.5 mm/kg vs. >2.5 mm/kg, and LA/Ao <1.3 vs. ≥1.3).

Statistical analysis was performed using IBM SPSS Statistics version 20. Continuous within-factor (measurements of ten time points) and between-factor (measurements between subgroups) variables were analyzed using repeated measure analysis of variance with Bonferroni correction. Multiple regression analysis was applied to adjust correlation between variables. Variables at specific time point of each subgroup were further compared with independent *t* test. Statistical significance was defined as *p* value of less than 0.05.

Results

A total of 30 VLBW infants were studied (Table 1). All of them fulfilled at least one echocardiographic criterion for the diagnosis of hsPDA defined in this study. Hemodynamic variables at baseline and respective changes as percentage are depicted in Table 2.

CO and CI

Both CO and CI changed significantly during the study course (Table 2). Comparing to baseline, CO had a non-significant decrease to 91 % at T_S but later continues to decrease to 73 % of baseline at T_L. Immediate impact of ligation, reflected by CO decrease from T_S to T_L (91 to 73 % of baseline, $p<0.001$), was seen in both metal clip and suture ligation. Afterward, CO returned to 92 and 94 % of baseline at 24th and 48th hour post surgery, respectively.

Reduction of CO was more obvious among infants weighing <1 kg, and the difference was of a marginal statistical significance ($p=0.049$). At T_S and T_L, CO declined to 83 and 72 % in infants weighing <1 kg, compared to 98 % at T_S and 81 % at T_L in larger infants. The difference of CO at T_S between weight subgroups (83 vs. 98 %, $p=0.03$) was significant. Furthermore, the recovery was to a lesser degree among infants with LA/Ao ≥1.3 at T_{12h} (77 vs. 100 %) (Fig. 1a, b).

HR and SV

HR dropped to 86 % of baseline at T_L, otherwise remained constant throughout the course. Although HR drop was noted at T_L, none of the patients had bradycardia <100 beats/min. CO was best correlated to SV ($r^2=0.62$), comparing to HR ($r^2=0.05$), and the reduction of SV at T_L was more obvious among infants weighing <1 kg (83 vs. 99 %) and infants with more severe PDA (Fig. 1c–e).

SVR

SVR was significantly elevated after ligation. It rose to the highest level of 142 % at T_L and remained increased after surgery. The degree of SVR elevation was more significant among infants with larger PDA, especially for infants with PDA >2 mm and LA/Ao ≥1.3 at T_{1h} (Fig. 2). It was not related to body weight.

Discussion

This is the first study using EC to record on-site hemodynamic change in preterm infants undergoing PDA ligation. None of the prior studies were able to measure CO and attributing factors at the critical point of sudden termination of a ductal shunting. We took advantage of the non-invasive EC to accomplish our investigation, whereas previous studies were all based on echocardiogram.

Our patients demonstrated a non-significant decrease in CO following general anesthesia to 91 % of the baseline. However, in the subgroup analysis, we found both CO and contractility showed significant reduction following general anesthesia in infants <1 kg. The hemodynamic effect of general anesthesia was independent of the severity of PDA. It seems that the smaller the infants are, the more likely for them to have cardiovascular impact by general anesthesia.

We observed that upon ductal ligation, CO, HR, and SV declined simultaneously to 73, 86, and 91 % of the baseline measurement, respectively. The immediate post-ligation CO change showed close correlation to the changes in SV

Table 1 Demographic and clinical features of 30 VLBW preterm infants receiving PDA ligation

Birth data				
Gestational age (week)		27.7±2.0		
Birth weight (g)		929±280		
Male (%)		11 (37 %)		
Echocardiographic PDA severity			Subgroup	
PDA diameter (mm)		2.71±0.85	≤2.0 mm	6 (20 %)
			>2.0 mm	24 (80 %)
PDA diameter/weight (mm/kg)		2.95±1.01	≤2.5 mm/kg	7 (23 %)
			>2.5 mm/kg	23 (77 %)
LA/Ao		1.54±0.29	<1.3	5 (17 %)
			≥1.3	25 (83 %)
Surgical ligation			Subgroup	
Postnatal age (day)		13.8±7.2		
Postmenstrual age (week)		29.7±2.2		
Weight (g)		963±288	<1 kg	15 (50 %)
			≥1 kg	15 (50 %)
Body surface area (m^2)		0.1±0.02		
Ventilation setting	MAP (cmH_2O)	8.0±0.8		
	FiO_2 (%)	28.8±10.5		
Ligation methods			Suture	14 (47 %)
			Metal clip	16 (53 %)
Anesthetics	Ketamine (mg/kg)	2.08±1.13		20 (67 %)
	Fentanyl (mcg/kg)	1.96±1.07		10 (33 %)
Muscle relaxant	Cisacurium (mg/kg)	0.53±0.36		30 (100 %)

VLBW very low birth weight, *PDA* patent ductus arteriosus, *LA/Ao* left atrium to aortic diameter ratio, *MAP* mean airway pressure, *FiO_2* fraction of inspired oxygen

Values are mean ± standard deviation or *n* (%)

(r^2=0.20, p=0.02), which in turn was associated with contractility. After surgery, CO returned gradually to pre-ligation level at T_{24h} and remained through 48 h post ligation. The transient decrease in HR might be caused by an increased vagal tone from stimulation of the recurrent laryngeal nerve during surgical procedure. These changes in EC were comparable to clinical measurement of hemodynamic variables. Though their blood pressure could be maintained during the course, we saw nine of the study infants required inotropes for systemic hypotension at T_{Pre} and another one developed transient hypotension after ductal ligation. Following surgery, five of the infants were off pressor support at T_{24h}, and one infant remained hypotensive and pressor dependent even after 48 h. Obviously, some of these infants experienced acute hemodynamic decompensation following ligation: a condition known now as "post-ligation cardiac syndrome" (PLCS) [4]. With a preexisting left-to-right shunt and overstressed myocardium, sudden closure of the ductus may result in a decrease in the left atrial filling pressure, and following Frank-Starling's law diminished myocardial contractility as well. Moreover, closure of ductal shunting also leads to an instant elevation in SVR. In lieu of a failing myocardium, such afterload increase may further compromise contractility and cardiac output. PLCS is a potentially lethal complication following ductal ligation in preterm infants, and the effects of cardiopulmonary failure usually peak at 6–12 h after operation. Although smaller infants and larger presurgery ductal shunt might predict the development of post-ligation cardiac syndrome, close monitoring and appropriate management according to various pathophysiology, such as myocardial decompensation or load-dependent collapse, are pivotal to the optimal care of these patients. Our findings reiterated the importance of close monitoring for hemodynamic changes during ligation, and usually the alteration would recover after 24 to 48 h. In our study, post-ligation SVR remained elevated from the baseline could be explained by an originally lower vascular resistance due to ductal shunting, and its elevation may indicate the returning of normal level. However, it would be helpful to verify our speculation if we had normal hemodynamic reference data of preterm infants.

Our findings are in agreement with the previous results based on echocardiographic study in that left ventricular (LV)

Table 2 Hemodynamic measurements of different parameter during the study course

	T_{Pre}	T_A	T_S	T_L	T_{1h}	T_{6h}	T_{12h}	T_{18h}	T_{24h}	T_{48h}	Repeated measure ANOVA
MBP (mmHg)	36.8±8.0	36.1±6.7	37.9±8.4	38.4±8.9	38.2±8.3	39.0±8.6	39.0±8.6	39.5±8.2	40.6±7.5	41.2±7.5	NS
CO[a] (L/min)	0.26±0.08	0.93 (0.89–0.98)	0.91 (0.83–1.00)	0.73** (0.67–0.80)	0.83 (0.74–0.92)	0.83 (0.77–0.89)	0.82 (0.73–0.91)	0.87 (0.80–0.95)	0.92 (0.84–1.00)	0.94 (0.85–1.02)	$p<0.001$*
CI[a] (L/min/m^2)	2.82±0.56	0.93 (0.89–0.98)	0.91 (0.83–1.00)	0.74** (0.68–0.81)	0.82 (0.75–0.89)	0.82 (0.75–0.89)	0.80 (0.73–0.87)	0.88 (0.80–0.95)	0.92 (0.84–1.00)	0.93 (0.84–1.02)	$p<0.001$*
HR[a] (beats/min)	163±12	1.00 (0.97–1.03)	0.98 (.93–1.02)	0.86** (0.78–0.93)	0.99 (0.94–1.04)	0.99 (0.96–1.02)	0.98 (0.95–1.01)	0.95 (0.92–0.97)	0.95 (0.92–0.98)	0.96 (0.93–1.00)	$p=0.002$*
SV[a] (mL)	1.63±0.48	0.94 (0.86–1.01)	0.94 (0.85–1.03)	0.91 (0.81–1.02)	0.85 (0.75–0.95)	0.85 (0.77–0.92)	0.83 (0.75–0.90)	0.94 (0.85–1.03)	0.98 (0.88–1.08)	0.99 (0.89–1.10)	$p=0.011$*
SVR[a] (dyns/m^5)	10,485±3197	1.06 (0.97–1.14)	1.24 (1.08–1.40)	1.42** (1.29–1.55)	1.27 (1.11–1.43)	1.28 (1.15–1.40)	1.32 (1.16–1.48)	1.22 (1.08–1.35)	1.17 (1.03–1.30)	1.25 (1.09–1.41)	$p<0.001$*

MBP mean blood pressure, *CO* cardiac output, *CI* cardiac index, *HR* heart rate, *SV* stroke volume, *SVR* systemic vascular resistance, *ANOVA* analysis of variance, *NS* not significant

Values are mean±standard deviation or mean (95 % confidence interval)

[a] Each measurement was divided by corresponding T_{Pre} value and depicted as percentage at ten time points: 1 h prior to surgery (T_{Pre}), 1 min after beginning anesthesia (T_A), 1 min after starting of surgery (T_S), 1 min immediately after ductus was ligated (T_L), 1 h after closing the surgery (T_{1h}), 6th hour (T_{6h}), 12th hour (T_{12h}), 18th hour (T_{18h}), 24th hour (T_{24h}), and 48th hour ($T_{48\ h}$) after the surgery

*$p<0.05$ indicates statistically significant within-factor difference

**Indicates significant within-factor difference between T_S and T_L, which represents immediately impact of closure of a ductal shunting

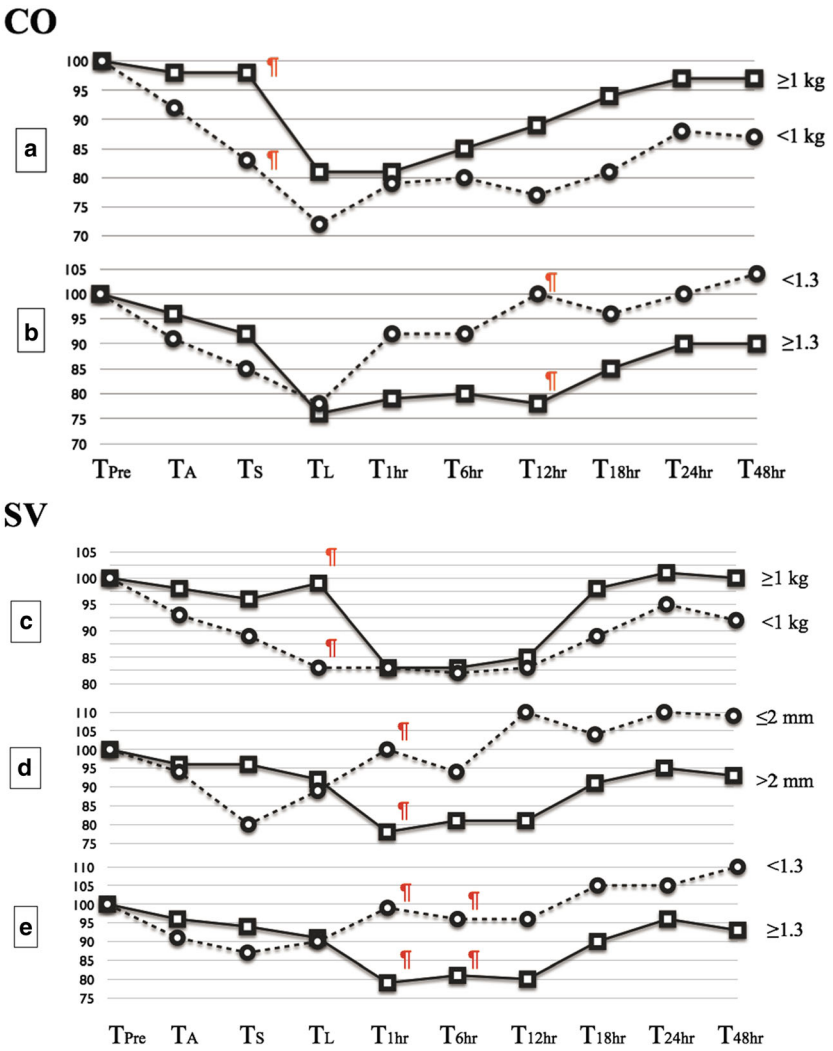

Fig. 1 Comparisons of PDA ligation-related hemodynamic alterations of CO between infants **a** weighing <1 kg and ≥1 kg and **b** LA/Ao <1.3 and ≥1.3 and SV alterations between infants **c** weighing <1 kg and ≥1 kg, **d** PDA size ≤2 mm and >2 mm, and **e** LA/Ao <1.3 and ≥1.3, at ten respective time points. Magnitude of hemodynamic instability was more obvious in smaller infants, especially for significantly impaired CO at T_S (*red pilcrow sign*). Hemodynamic recovery was postponed in infants with severer PDA, especially for whose LA/Ao ≥1.3 at T_{12h} (*red pilcrow sign*). In likely situation, magnitude of SV instability increased in smaller infants weighing <1 kg, especially at T_L (*red pilcrow sign*). Recovery of SV was to a lesser degree in infants with more severe PDA, especially for whose PDA >2 mm at T_{1h} (*red pilcrow sign*) and LA/Ao ≥1.3 at T_{1h} and T_{6h} (*red pilcrow sign*), respectively

performance deteriorated after ductal ligation. Linder compared VLBW preterm infants' hemodynamic before and 2 days after PDA ligation and concluded a decrease in LV output and SV [6]. Kimball reported a reduction of preload and non-significant change of LV performance immediately after ligation in preterm infants [5]. Noori observed that the

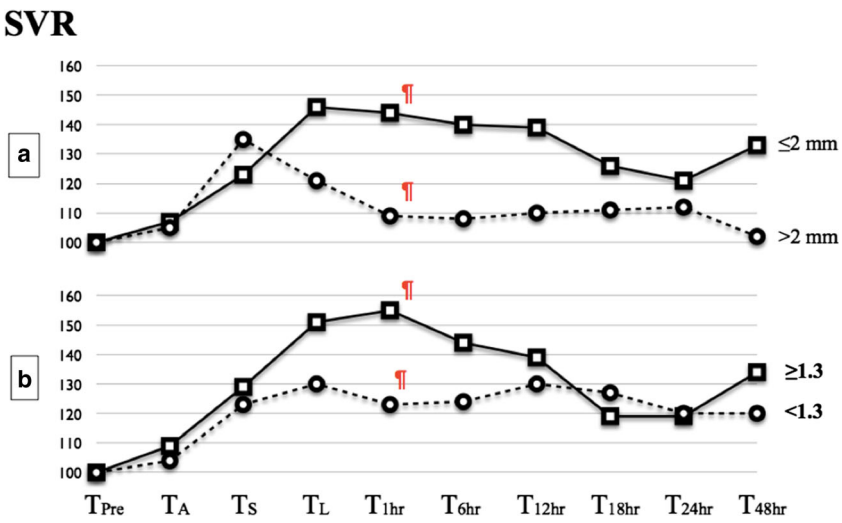

Fig. 2 Comparisons of PDA ligation-related SVR change between infants with different PDA severity **a** size ≤2 mm and >2 mm and **b** LA/Ao <1.3 and ≥1.3. Degree of SVR elevation was particularly more significant in infants with PDA >2 mm and LA/Ao ≥1.3 at T_{1h} (*red pilcrow sign*), respectively

change of blood pressure was not significant but LV output decreased immediately after and at 23.5-h post ligation in VLBW infants [9]. In Noori's study, the degree of LV output impairment was positively correlated to PDA size and was associated with a decreased preload and an increased SVR. Immediate deterioration of myocardial function after ligation was also observed in extremely preterm infants by various researchers [1, 7].

The magnitude of impaction on CO following PDA ligation was more profound in smaller infants. This is in accordance with study results by McNamara et al. who reported post-ligation LV impairment in infants <1 kg. They also suggested a decreased tolerance of immature myocardium to an altered loading condition [7]. Such body weight or maturity-related differential compromise was also seen in SV and contractility. However, when compared to Noori and McNamara's results, the magnitude of CO decline shortly following PDA ligation was smaller in our study (66 and 48 % decrease from baseline, respectively, vs. our 17 % decrease at T_{1h}), and the recovery of CO 24 h after the surgery was better. This could well be caused by the difference in our patient population. Both Noori and McNamara's patients were less mature (gestational age of 26.2 and 25.3 weeks, respectively, vs. ours 27.7 weeks) and smaller (birth weight of 845 and 777 g, respectively, vs. ours 929 g). As shown above, LV adaptation to such physical and/or physiological aberration is maturation dependent. The difference in our studies might have just attested to it.

As Rowland previously suggested, immature myocardium is more sensitive to an increased afterload [14], we clearly demonstrated that magnitude of hemodynamic alteration was bigger in both smaller infants and in infants with more severe PDA shunting. It was also noted that infants with larger PDA shunting needed longer time to recover from this hemodynamic perturbation.

There are limitations of current study. Firstly, there is a lack of a gold standard to which we can compare and validate the results of our measurement. While echocardiogram-derived estimates are often used as surrogates, the design of this study emphasized real-time intra-operative measurements, which so far could only be achieved by using EC. However, there is still insufficient evidence for EC to replace echocardiogram as gold standard for assessment of cardiac function in preterm patients. Furthermore, EC has not been widely used in preterm infants, and there is no reference of normal values for infants with various degree of maturity. Secondly, the preciseness of preload and afterload estimation by EC is inconclusive. Preload is the end volumetric pressure that stretches the ventricles, which is usually measured as end-diastolic volume in echocardiogram. There is no similar measurement to be achieved by EC. Also, SVR provided by EC is calculated based on a presumed 3 mmHg CVP by default. However, under the pathological condition of our study patients, a CVP might vary significantly with regard to the multiple changes of fluid and left and right ventricular function. Hence, derived hemodynamic measurements by EC based on a constant CVP might be biased, even though we believe that the bias could be reduced if the calculation is raised on the same assumption. Thirdly, there is no convincing measurement to represent ventricular contractility by EC. Although EC gives a reading of index of contractility (ICON), which is derived from the maximum rate of change of thoracic electrical impedance and as an index of peak aortic acceleration [12], the accuracy of using ICON as a measurement of ventricular contractility warrants further validation. Lastly, although general anesthesia is undoubtedly important for hemodynamic alterations, due to obvious ethical reason, there was no sham control to exam the effect of anesthesia and/or thoracotomy in our study.

Conclusion

Our current study demonstrated that abrupt diversion of a ductal shunting contributes to hemodynamic aberrations in VLBW infants undergoing PDA ligation, and decreased preload, increased vascular resistance, and impaired LV performance might be the principal causes. Anesthesia for the surgery may magnify the alteration, particularly in infants weighing <1 kg. Infants with smaller weight and larger PDA are at risk for more severe hemodynamic perturbation following surgery.

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Conflict of interest The authors declare that there are no conflicts of interest in this study.

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