RESEARCH PAPER

Echocardiographic Parameters of Patent Ductus Arteriosus in Preterm Infants

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Objective: To analyze cardiovascular parameters by echocardiography in preterm infants with patent ductus arteriosus (PDA).

Setting: Tertiary-care pediatric university hospital.

Design: Cross-sectional, hospital-based study.

Participants: 58 preterm infants, gestational age less than 33 weeks.

Measurements: A complete 2-dimension, M-mode, color doppler echocardiography was performed in each preterm infant at approximately 48 hours of life.

Results: Each preterm was categorized into hemodynamically significant PDA (hsPDA) (*n*=17, 29.3%), non-hemodynamically significant PDA (non-hsPDA) (*n* = 12, 20.7%), and no PDA (non-PDA) (*n*=29, 50%). Gestational age (29.4 ± 1.2 wk) and birth weight (1237 ± 358 g) of infants in hsPDA were significantly lower than those in non-PDA group (30.8 ±1.3 wk, 1543 ± 361 g, *P* = 0.001), as compared to those in the non-hsPDA group (29.5 ± 2.3 wk, 1296 ± 462 g). Cardiovascular parameters including left atrium/aorta ratio, left atrium volume index, left ventricular dimensions and volumes, stroke volume, and cardiac output in hs-PDA were significantly greater than those in non-hsPDA and non-PDA. LV systolic and diastolic functions were not significantly different in each group. LV global function in hsPDA (0.34 ± 0.13) was significantly lower than that in non-PDA (0.45 ± 0.13, *P* = 0.01).

Conclusions: In preterm infants with hsPDA, there was a volume load of the left heart causing increased stroke volume and cardiac output. The hsPDA could be detected by echocardiography even in the first 48 hours. The left atrial volume index may be a better indicator of the volume load of the heart.

Key words: *Diastolic function, Echocardiography, Left ventricular dimension, Patent ductus arteriosus, Preterm, Systolic function.*

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Patent ductus arteriosus (PDA) in preterm infants is common with an incidence of 34% by echocardiography on day 3 of life [1]. It is more common in preterm infants with birth weight (BW) <1000 g (58.8%) than in those with BW >1000 g (25%) and more common in those with gestational age (GA) <30 weeks (wk) (52.2%) than in those with GA >30 wk (23.7%) [1]. Although PDA can be found in normal healthy term and preterm infants up to 72 h [2], some preterm infants, especially with respiratory distress may have PDA beyond that period [3]. PDA is associated with morbidities, especially in preterm infants, resulting in pulmonary hemorrhage, pulmonary congestion, pulmonary edema, and congestive heart failure [4]. Bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis are also increased in preterm infants with PDA [5,6]. PDA can cause volume overload of the left atrium (LA) and left ventricle (LV). Our study was conducted to analyze the echocardiographic findings in preterm infants at early age with hemodynamically significant PDA (hsPDA) compared to those with non-hemodynamically significant PDA (non-hsPDA) and those without PDA.

METHODS

A cross-sectional study was conducted at the neonatal intensive care unit (NICU) and sick newborn nursery in the setting of a tertiary-care

pediatric university hospital. All preterm infants, GA <33 wk were eligible. We excluded infants with congenital heart defects (CHDs) other than PDA, major congenital anomalies, Apgar score <3 at 5 minute, clinical sepsis or septicemia, necrotizing enterocolitis, renal failure, persistent pulmonary hypertension, and those receiving indomethacin or ibuprofen. Echocardiography was performed in each patient at approximately 2 days of age. This study was approved by the Institutional Review Board, and written consent for participation was obtained from the parents or guardians.

Two-dimensional, color doppler, and M-mode echocardiography using a Sonos Helwett-Peckard 4500 echocardiography machine with curvilinear 8 MHz transducer was performed to assess the narrowest diameter of the PDA at its pulmonary end and to rule out other CHDs by a single pediatric cardiologist blinded to the clinical information.

An M-mode in the parasternal short axis view at the level of the base of the heart and papillary muscles was performed to measure the left atrium (LA) and the aortic root (Ao) ratio (LA/Ao) and left ventricle (LV) dimensions including left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) [7]. The left ventricular end-diastolic dimension index (LVEDDI) and left ventricular end-systolic dimension (LVESDI) were equal to LVEDD and LVESD divided by body surface area (BSA), respectively. The left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were calculated by Teichholz's method [8]. Left ventricular end-diastolic volume index (LVEDVI, ml/m^2) was equal to LVEDV divided by BSA.

The left ventricular ejection fraction (LVEF) and the left ventricular fractional shortening (LVFS) were calculated using the previously described formula [7]. The normal values for LVEF and LVFS are ≥55% and ≥25%, respectively [7]. Predicted LVEDD was calculated according to the formula of Henry [9]. The ratio of LVEDD to predicted LVEDD expressed in percentage (%LVEDD) was calculated using the following formula: %LVEDD = [(measured LVEDD)/(predicted LVEDD)]*100. The normal value for %LVEDD is <112% [10].

Cardiac output (CO) was calculated from stroke volume (SV) multiplied by heart rate and SV was equal to LVEDV minus with LVESV. SV and CO were represented as mL/kg and mL/min/kg, respectively. A measurement of left atrial volume (LAV) was obtained from the prolate ellipse method using apical 4-chamber and parasternal long-axis views at ventricular end systole (maximum LA size). All 3 dimensions (D1, D2, and D3) were measured and to calculate LAV by using formula: [D1 × D2 × D3] × [0.523] [11]. Left atrium volume index (LAVI) was equal to LAV divided by BSA.

Left ventricular diastolic function was assessed by pulse-wave Doppler at the tip of the mitral valve inflow to measure E, A, E/A ratio, and deceleration time (DT). Left ventricular myocardial performance index (LV MPI) or Tei index has been devised to incorporate both systolic and diastolic time intervals in expressing global ventricular performance [12].

A hsPDA was diagnosed by findings of ≥2 of these 3 echocardiographic findings: PDA narrowest diameter >1.4 mm, the percentage of the ratio of the time velocity interval (TVI) of the diastolic retrograde flow to the TVI of the systolic anterograde flow along the descending aorta ≥30%, and LA/Ao ≥1.5 [4], whereas non-hsPDA was the presence of PDA, but not meet the above criteria. The non-PDA group had no PDA.

Clinical diagnosis of hsPDA was defined as an infant with at least two of the following findings namely heart murmur, persistent tachycardia (heart rate >160/ min.), active precordium, bounding pulse or pulse pressure >25 mmHg, hepatomegaly, pulmonary hemorrhage or increasing ventilatory support, and cardiomegaly or pulmonary congestion.

Student's *t* test was used for continuous variables or Mann-Whitney U test if data were not normal distribution. Pearson correlation was used to demonstrate correlation. *P* value <0.05 was considered to be statistically significant.

RESULTS

Of 58 preterm infants (31 males), those whose GA were 30.1 ± 1.7 wk and BW 1402 ± 403 g; 17 (29%) had hsPDA whereas 12 (21%) had non-hsPDA, and

29 (50%) had no PDA (non-PDA). Overall, GA, BW, and BSA in PDA group were significantly less than those in non-PDA group (30.8±1.3 wk, 1543 ± 361 g, 0.13 m^2; $P<0.001$, $P<0.007$, $P=0.006$). GA, BW, and BSA in hsPDA group were not significantly different from those in non-hsPDA group and those in non-hsPDA were also not significantly different from those in non-PDA group, however, those in hsPDA group were significantly lower than those is non-PDA group (***Table* I**). Mean heart rate in all patients was 149±10/min and not significantly different in each group. Only 4 patients were clinically diagnosed as having hsPDA. Echocardio-graphy was performed in hsPDA, non-hsPDA, and non-PDA groups at mean age of 44.2 ± 10.7, 41.7 ± 10.9, 45.4 ± 9.1 h, respectively ($P>0.05$). As expected, mean PDA diameter in hsPDA (2.4 ± 0.8 mm) was significantly larger than in non-hsPDA (1.1 ± 0.3 mm), $P<0.0001$. Cardiovascular parameters assessed by echocardiography were summarized in ***Table* II**. Overall, LA/AO ratio, LAVI, LVESDI, LVEDDI, %LVEDD, LVEDVI, LVESVI, SV, and CO in hsPDA group were significantly greater than those in non-hsPDA and non-PDA groups whereas those parameters in non-hsPDA and non-PDA were not significantly different. LV systolic function and diastolic function were not significant different in all three groups. LV global function in hsPDA group (0.34 ± 0.13) was significantly lower than that in non-PDA group (0.45 ± 0.13). However, LV MPI in hsPDA and non-hsPDA (0.39 ± 0.12) were not significantly different and LV MPI in non-hsPDA and non-PDA were also not significantly different.

LVEDVI was represented as volume load of the left ventricle. LA/AO ratio was correlated fairly with LVEDVI (r = 0.361, $P<0.01$); however, LAVI was correlated more with LVEDVI (r = 0.633, $P<0.001$).

DISCUSSION

In this study, the incidence of PDA in preterm infants <33wk gestation on the second day of life was 50%. However, only 29% had hsPDA while 21% had non-hsPDA. Mean GA and BW in hsPDA group were significantly lower than in non-PDA group whereas those in non-hsPDA group were not significantly different from the other two groups. These findings demonstrated that hsPDA was found to be more common in those with lower GA and BW. Clinical diagnosis of hsPDA in the early age of neonates was not sensitive and specific.

Systolic and diastolic LV dimensions, the LA dimension, and the LA volume in hsPDA were significantly increased. These findings confirmed that in hsPDA, when compared to non-hsPDA and non-PDA, there was volume load to the left side of the heart as a result of left to right shunt from the descending aorta across the PDA into the pulmonary artery, which then returned to LA and LV. The SV and CO were also significantly increased in hsPDA when compared to those in non-hsPDA or non-PDA. There was significant higher SV and CO in hsPDA group when compared to non-hsPDA and non-PDA groups which were consistent with the previous reports [13,14]. Walther, *et al*. [14] reported 25 preterm

TABLE I PATIENT CHARACTERISTICS OF THE STUDY POPULATION

Patient characteristics	PDA		No PDA(n = 29)	P value
	hsPDA(n = 17)	non-hsPDA(n = 12)		
Gestational age (wk)	29.4 ± 1.2	29.5 ± 2.3	30.8 ± 1.3	0.001†
Birthweight (g)	1.237 ± 358	1.296 ± 462	1.543 ± 361	0.008†
Age at echo (h)	44.2 ± 10.7	41.7 ± 10.9	45.4 ± 9.1	NS
PDA size (mm)	2.4 ± 0.8	1.1 ± 0.3	0	<0.001*†‡
Body surface araq (m^2)	0.11	0.12	0.13	0.007†
Heart rate (/min)	151 ± 11	148 ± 13	147 ± 9	NS

NS: No significant difference between the three groups; Significance of difference between hsPDA group and non-hsPDA group‡, non-hsPDA group and no PDA group, and hsPDA and no PDA group†; echo echocardiography; hsPDA: hemodynamically significant patent ductus arteriosus; M: male; non-hsPDA: non hemodynamically significant patent ductus arteriosus; PDA: patent ductus arteriosus*

TABLE II ECHOCARDIOGRAPHIC PARAMETERS OF THE STUDY POPULATION

Cardiovascular Parameters	PDA		No PDA(n = 29)	P value
	hsPDA(n = 17)	non-hsPDA(n = 12)		
LA/AO	$^{\dagger}1.5 \pm 0.3^{\ddagger}$	$^{*}1.2 \pm 0.2^{\ddagger}$	$^{\dagger}1.2 \pm 0.2^{*}$	$^{\dagger}0.001$, $^{\ddagger}0.02$
LAVI (mL/m^2)	$^{\dagger}9.1 \pm 4.2^{\ddagger}$	$^{*}6.1 \pm 2.0^{\ddagger}$	$^{\dagger}5.4 \pm 2.0^{*}$	$^{\dagger}0.003$, $^{\ddagger}0.03$
LVOT (mm)	5.3 ± 0.7	5.2 ± 0.6	5.3 ± 0.5	NS
LVESDI (mm/m^2)	$^{\dagger}9.2 \pm 1.6^{\ddagger}$	$^{*}7.6 \pm 2.1^{\ddagger}$	$^{\dagger}7.4 \pm 1.3^{*}$	$^{\dagger}0.0001$, $^{\ddagger}0.03$
LVEDDI (mm/m^2)	$^{\dagger}13.2 \pm 2.0^{\ddagger}$	$^{*}11.7 \pm 1.6^{\ddagger}$	$^{\dagger}11.0 \pm 1.3^{*}$	$^{\dagger}0.001$, $^{\ddagger}0.03$
%LVEDD (%)	$^{\dagger}109.2 \pm 14.5^{\ddagger}$	$^{*}97.5 \pm 13.7^{\ddagger}$	$^{\dagger}97.1 \pm 11.1^{*}$	$^{\dagger}0.003$, $^{\ddagger}0.04$
LVEDVI (mL/m^2)	$^{\dagger}52.6 \pm 18.6^{\ddagger}$	$^{*}40.2 \pm 14.0^{\ddagger}$	$^{\dagger}40.4 \pm 12.1^{*}$	$^{\dagger}0.009$, $^{\ddagger}0.04$
LVESVI (mL/m^2)	$^{\dagger}19.9 \pm 7.0^{\ddagger}$	$^{*}13.9 \pm 7.2^{\ddagger}$	$^{\dagger}14.0 \pm 5.8^{*}$	$^{\dagger}0.004$, $^{\ddagger}0.04$
SV (mL/kg)	$^{\dagger}3.1 \pm 1.1^{\ddagger}$	$^{*}2.4 \pm 0.6^{\ddagger}$	$^{\dagger}2.2 \pm 0.5^{*}$	$^{\dagger}0.005$, $^{\ddagger}0.04$
SVI (mL/m^2)	33.1 ± 12.8	26.3 ± 8.1	26.3 ± 7.2	NS
CO (mL/kg)	$^{\dagger}462 \pm 154^{\ddagger}$	$^{*}352 \pm 101^{\ddagger}$	$^{\dagger}323 \pm 78^{*}$	$^{\dagger}0.002$, $^{\ddagger}0.04$
CI (mL/min/m^2)	$^{\#}4.9 \pm 1.8^{\ddagger}$	$^{*}3.9 \pm 1.2^{\ddagger}$	$^{\#}3.9 \pm 1.0^{*}$	$^{\dagger}0.04$, ‡NS
LV EF (%)	62 ± 5	68 ± 12	66 ± 8	NS
LV FS (%)	31 ± 4	36 ± 13	34 ± 6	NS
E/A ratio	0.9 ± 0.2	1.0 ± 0.4	0.9 ± 0.2	NS
DT (ms)	81 ± 43	97 ± 42	103 ± 25	NS
LV MPI	$^{\dagger}0.34 \pm 0.13^{\ddagger}$	$^{*}0.39 \pm 0.12^{\ddagger}$	$^{\dagger}0.45 \pm 0.13^{*}$	$^{\dagger}0.01$

AO, aorta; CI, cardiac index; CO, cardiac output; DT, deceleration time; LA, left atrium; LAVI, left atrial volume index; LVEDDI, left ventricular end-diastolic dimension index; LVEDVI, left ventricular end-diastolic volume index; LV EF, left ventricular ejection fraction; LV FS, left ventricular fractional shortening; LV MPI, left ventricular myocardial performance index; LVOT, left ventricular outflow tract; LVESDI, left ventricular end-systolic dimension index; LVESVI, left ventricular end-systolic volume index; SV, stroke volume; SVI, stroke volume index; %LVEDD, the percentage of the ratio of left ventricular end-diastolic dimension to predicted left ventricular end-diastolic dimension. Significance of difference between hsPDA group and non-hsPDA group‡, non-hsPDA group and no PDA group, and hsPDA and no PDA group†; hsPDA: hemodynamically significant patent ductus arteriosus; M: male; non-hsPDA: non hemodynamically significant patent ductus arteriosus: PDA, patent ductus arteriosus.*

infants with BW <1250 g and found that 11 preterm infants who had CO between 190 and 310 mL/min/kg which was within the normal range never developed symptomatic PDA when compared to 14 preterm infants developing symptomatic PDA had an increase in left ventricular output from their baseline more than 60 mL/min/kg at least 24 h before symptoms developed. Lindner, *et al*. [13] reported that neonates with symptomatic PDA had high SV (2.69, 1.98-4.10 mL/kg) and CO (419, 305-562 mL/min/kg), which later decreased to 1.63 (1.22-1.98) mL/kg and 246 (191-292) mL/min/kg after PDA ligation. One of the echocardiographic parameters which was found to be sensitive for detecting sign of volume load to the left ventricle was LAVI. In this study, LAVI in hsPDA group was significantly higher when compared to LAVI in non-hsPDA and non-PDA groups. Moreover, LAVI was more correlated to LVEDVI (r =0.633) than LA/AO ratio (r = 0.363). Previous reports suggesting LA/AO ratio as a sensitive and specific parameter in detecting PDA may be limited since the aorta was probably enlarged due to the high SV and CO, leading to no change in LA/AO [1]. We suggest that LAVI should be considered when performing the echocardiography to detect hsPDA which had hemodynamic significance. In early neonatal life (within 2 days), hsPDA could be diagnosed by echocardiography even without clinical symptoms. Heart rate in each group was not significantly difference. Afilune, *et al*. [1] also found that on the third day of life, only 52% of preterm neonates with PDA had clinical symptoms.

WHAT IS ALREADY KNOWN?

- Left atrium to aorta ratio is increased in hemodynamically significant patent ductus in preterm infants.

WHAT THIS STUDY ADDS?

- Left atrial volume index is more sensitive than left atrium to aorta ratio in determining volume load of the left heart.
- Cardiac functions including systolic and diastolic function are normal even volume load of the left heart.

Systolic function and diastolic function of the left ventricle were not significantly different in each group even in hsPDA which had left ventricular volume overload and higher SV and CO. Interestingly, LV MPI in hsPDA group was significantly lower than LV MPI in non-PDA group. Murase, *et al*. [15] reported that LV MPI at 48 h was not significantly different in preterm neonates with PDA and without PDA (0.35 ± 0.16 *vs* 0.36 ± 0.16). However, in that report they did not categorize hs-PDA and non-hsPDA. LV MPI represents the ratio of the sum of isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT) to the left ventricular ejection time (ET). Systolic dysfunction results in a prolongation of the IVCT and a shortening of ET [12]. Both systolic and diastolic dysfunction cause abnormality in myocardial relaxation resulting inprolongation of the IVRT. Murase, *et al*. [15] reported the effect of PDA on LV MPI in very low birth weight infants and found that there was no significant relationship between LV MPI and echocardiographically detectable PDA. The LV MPI of infants with PDA and without PDA at any age since birth (12, 24, 36, 48, 72, and 96 h) were not significant different. LV MPI at 48 h, the same period of time as that of our study, was 0.35 ± 0.22 and 0.36 ± 0.16. However, in this study, we found that LV MPI in hsPDA group was significantly lower than in non-PDA group. Although there was no statistically significant time-course difference in LV MPI of neonates at any GA, however, at postnatal age from 48 to 96 h, the LV MPI tended to be higher in preterm who had higher GA and BW [15]. This may explain why in this study, the LV MPI in non-PDA was higher than LV MPI in hsPDA group, since GA and BW in non-PDA group were significantly higher than those in hsPDA group.

We conclude that in preterm infants with hsPDA, there was a volume load of the left heart causing increased stroke volume and cardiac output. Echocardiography was more sensitive in detecting hsPDA as early as within 48 hours of age. The left atrial volume index was found to be the better indicator of the volume load of the heart than the left atrium to the aorta ratio.

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REFERENCES

1. Afiune JY, Singer JM, Leone CR. Echocardiographic post-neonatal progress of preterm neonates with patent ductus arteriosus. J Pediatr. 2005;81:454-60.
2. Reller MD, Ziegler ML, Rice MJ, Solin RC, McDonald RW. Duration of ductal shunting in healthy preterm infants: an echocardiographic color flow Doppler study. J Pediatr. 1988;112:441-6.
3. Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr. 1995;127:774-9.
4. Skinner J. Diagnosis of patent ductus arteriosus. Semin Neonatol. 2001;6:49-61.
5. Agarwal R, Deorari AK, Paul VK. Patent ductus arteriosus in preterm neonates. Indian J Pediatr. 2008;75:277-80.
6. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol. 2006;26:S14-8.
7. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440-63.
8. Teichholz LE, Kreulen T, Herman MV, Gorlin R.

Problems in echocardiographic volume determinations: echocardio-graphic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol. 1976;37:7-11.
9. Henry WL, Ware J, Gardin JM, Hepner SI, McKay J, Weiner M. Echocardiographic measurements in normal subjects. Growth-related changes that occur between infancy and early adulthood. Circulation. 1978;57:278-85.
10. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. Circulation. 1980;62:1054-61.
11. Jiamsripong P, Honda T, Reuss CS, Hurst RT, Chaliki HP, Grill DE, *et al*. Three methods for evaluation of left atrial volume. Eur J Echocardiogr. 2008;9:351-5.
12. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, *et al*. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function–a study in normals and dilated cardiomyopathy. J Cardiol. 1995;26:357-66.
13. Lindner W, Seidel M, Versmold HT, Dohlemann C, Riegel KP. Stroke volume and left ventricular output in preterm infants with patent ductus arteriosus. Pediatr Res. 1990;27:278-81.
14. Walther FJ, Kim DH, Ebrahimi M, Siassi B. Pulsed doppler measurement of left ventricular output as early predictor of symptomatic patent ductus arteriosus in very preterm infants. Biol Neonate. 1989;56:121-8.
15. Murase M, Ishida A, Morisawa T. Left and right ventricular myocardial performance index (Tei index) in very-low-birth-weight infants. Pediatr Cardiol. 2009;30:928-35.