Original Article

Echocardiographic Parameters of Severity in Isolated Neonatal Patent Ductus Arteriosus

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Abstract:

Background: A hemodynamically-significant patent ductus arteriosus (hsPDA) compromises the early neonatal transition. There is no general agreement on echocardiographic indicators of hsPDA that can predict clinical decompensation.

Aim of the Work: We aimed to assess echocardiographic parameters that are associated with the isolated PDA effects on hemodynamics, which could help in subsequent management decision making.

Materials and Methods: We conducted a prospective observational analytical study on 50 neonates with isolated PDA and 20 controls. They underwent clinical and echocardiographic assessment at 48 hours of age, after another 48-72 hours and prior to discharge.

Results: No correlation was found between PDA diameter and weight (p=0.72), length (p=0.11), Body surface area (BSA) (p=0.33), gestational age (p=0.13). A strong association of PDA-related hemodynamic instability was found with pulmonary hypertension (p=<0.01 & 0.05 for initial and latter studies). Left atrium diameter (LA) Z-score was higher among cases, correlated with PDA size in the 3 echocardiographic studies (p=0.001, 0.001 and 0.007 respectively), and correlated with hemodynamic instability in the initial study (p=0.03). Diameter of descending aorta at level of diaphragm and pulmonary flow/systemic flow ratio (Qp:Qs) correlated with PDA diameter in the latter 2 studies (p=0.001). Main pulmonary artery and left pulmonary artery (LPA) Z-scores were correlated with PDA size at the initial and follow-up studies as expected (p=0.001, 0.047 & 0.047; and p=0.004, 0.018 & 0.032, respectively). LPA Z-score correlated with hemodynamic instability at the follow-up study (p=0.005), which was not sustained at the subsequent study.

Conclusion: Pulmonary hypertension, larger LA Z-score and LPA Z-scores are important early (at 48 hours) associations of a hsPDA and hemodynamic instability.

Level of Evidence of Study: IIA. (*1*)

Abbreviations: Ao-isthmus: aortic isthmus; AoR: aortic root dimension; Ao VTI: aortic velocity time integral; BSA: body surface area; CW: continuous wave Doppler mode; Diaph Ao: descending aorta at the level of the diaphragm; Desc Ao: Descending thoracic aorta; hs: hemodynamically-significant; LA: left atrium; LPA: left pulmonary artery; LVEDD: Left ventricular end-diastolic dimension; LVOT: left ventricular outflow tract; MPA: main pulmonary artery; NICU: neonatal lntensive care unit; PL: parasternal long axis view; PS : parasternal short axis view; PDA: patent ductus arteriosus; PFO: Patent foramen ovale; PAP: pulmonary pressure; Pulm: pulmonary; Qp/Qs: pulmonary flow/systemic flow ratio; RPA: Right pulmonary artery; RVOT: right ventricle outflow tract SC: subcostal view; SS: Suprasternal view; VTI: velocity time integral.

Introduction

Isolated patent ductus arteriosus (PDA), albeit a very common lesion in neonates, remains a controversial issue in management. PDA is a potential cause for hemodynamic instability including pulmonary congestion and other pathologies as pulmonary hemorrhage, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, acute kidney injury, and retinopathy of prematurity. This instability has led to an aggressive approach by the many that aim to close the ductus whether pharmacologically by cyclooxygenase inhibition, surgically ductal ligation that could be performed even bed-side, or percutaneously by

coils or more recent devices. In order to balance the management based on an objective echocardiographic assessment, the hemodynamic significance and therefore relevance of the PDA has to be defined.

Others adopt a conservative approach expecting spontaneous closure of PDA especially in the premature. This is rationalized by the lack of proof of treatment response between PDA and the aforementioned morbidities, the desire to avoid adverse events that might be associated with PDA closure, and the observation that active PDA closure did not substantially reduce morbidity and mortality (*2*). There is a need for an objective measurable consistent definition of the hemodynamically-significant PDA (hsPDA) (*3*, *4*).

We aimed at finding the possible correlations between PDA size and different echocardiographic parameters. We also aimed at identifying echocardiographic associations with a hsPDA that would indicate necessity of medical closure, and direct the management to that of the PDA being the culprit lesion.

Subjects and Methods

This prospective observational analytical study included all neonates admitted to the Neonatal Intensive Care Unit (NICU) of Galaa Women and Children Specialized Military Hospital from January 1st, 2017 till August 31st, 2017, whether inborn or out-born, regardless of their gestational age.

An informed written consent was taken from parents upon admission to the NICU prior to enrollment in the study. Data were documented in the patients' files and on special excel sheets. All candidates were subject to the standard clinical evaluation and monitoring as per NICU protocol.

Participants

The study comprised 50 neonates with isolated PDA and 20 controls. Neonates were excluded if they were subjected to perinatal asphyxia, had a primary respiratory disease (such as respiratory distress syndrome) that could affect the hemodynamics, had a concomitant congenital cardiac anomaly (excluding patent foramen ovale (PFO) and persistent left superior vena cava), sepsis, and suspected (or proven) genetic or metabolic disorders. Control group were neonates admitted to the NICU because of neonatal jaundice, hemorrhagic disease of the newborn, and due to surgical causes.

Methods

Data were collected and analyzed, including: age, gestational age, weight, length, body surface area (*5*), perinatal history and full cardiac assessment for manifestations of heart failure and pulmonary hypertension. Patients with PDA were further divided according to the grades of hemodynamic instability into 4 groups according to the local NICU protocol:
- None: No signs of hemodynamic instability;
- Mild: Tachycardia, tachypnea requiring oxygen therapy, and fluid restriction;
- Moderate: signs of low cardiac output, respiratory distress, rising oxygen demands requiring ventilatory support;
- Severe: severe dynamic instability and/or hypoperfusion requiring ant-failure measures and/or inotropes.

All patients with PDA received the standard care as per the local NICU protocol including routine medical closure by IV acetaminophen (10 mg /kg/6 hours for 5 days) or ibuprofen (10 mg/kg first day followed by 5 mg/kg for 2 days) for all PDAs diagnosed after 48 hours of life.

Echocardiography Assessment:

Serial echocardiographic studies were performed by a single operator using a GE Logiq 5 ultrasound system, probe S6 (GE Healthcare, Boston MA, USA): an initial study at 48-72 hours of life; a follow-up study after 48 hours from initial study; and a final study prior to discharge. The studies included the following dimensions: PDA narrowest diameter by 2-D derived from the parasternal short axis (PS) ductal view; main pulmonary artery (MPA) at pre- bifurcation, proximal left pulmonary artery (LPA) & right pulmonary artery (RPA) from the PS view; aortic

isthmus (Ao-isthmus) and the descending thoracic aorta (Desc Ao) from the suprasternal (SS) view; descending aorta at the level of the diaphragm (Diaph Ao) from the subcostal (SC) view; left atrium (LA), aortic root (AoR), and left ventricular end-diastolic dimension (LVEDD) from the parasternal long axis (PL) view. Z-scores for the previous measurements where calculated (*6*) with a normal range of −2 to +2 (*7*).

Flow pattern in PDA using color Doppler mode, and aorto-pulmonary pressure gradient using the continuous wave Doppler (CW) mode; pulmonary pressure (PAP) was estimated from the transductal pressure gradient and/or tricuspid regurgitant Doppler gradient; cardiac output was estimated using aortic velocity time integral (Ao VTI) for systemic cardiac output and pulmonary VTI (Pulm VTI) for pulmonary cardiac output (*8*).

Statistical Analysis

Correlation between different echocardiographic parameters were at first tested in relation to PDA diameter. The relevant parameters were further tested in relation to hemodynamic instability and pulmonary hypertension in neonates with PDA. Data were analyzed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). Continuous numerical variables were presented as mean and standard deviation (SD). Correlations were tested using the Pearson product moment correlation or Spearman rank correlation if appropriate. Changes in echocardiographic measures were analyzed using repeated measures analysis of variance (ANOVA) with application of the Bonferroni correction for multiple post pair wise comparisons. p-value <0.05 was considered statistically significant.

Results

The study included a total of 70 neonates: 50 cases and 20 control group of mean gestational age 34.2 weeks and weight 2.29 kg. The demographic characteristics of the study population are described in table (1). Case and control groups were matched regarding weight, gestational age and gender (p=0.80, 0.97, and 0.49, respectively). In the initial study, the PDA size was 0.18 ± 0.096 mm (ranging from 0.01 - 0.54 mm). Echocardiographic parameters are described in table (2).

Table (1): Demographic characteristics of the study population.

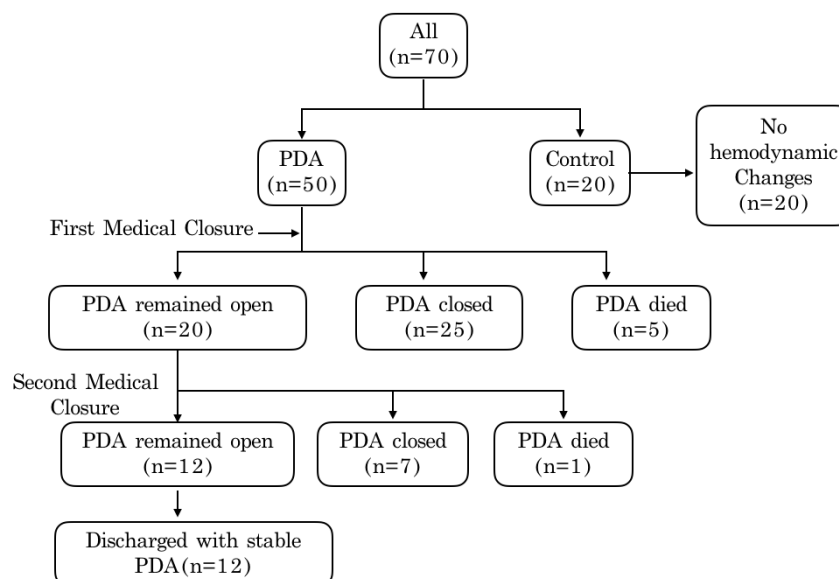|	Cases (n=50)			Controls (n=20)			Total (n=70)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Weight	2.20	0.92	0.65-4.3	2.24	0.95	0.8-3.87	2.29	0.92	0.65-4.30
Length	44.9	4.87	35-53	44	5.32	35-53	45	5	35-53
Gestational age	33.93	3.53	27-38	33.90	3.50	28-39	34.18	3.6	27-39
Gender (male/female)	26/24			11/9			37/33		

Figure (1): Outcome of cases and controls and the state of PDA. All underwent medical closure. All deaths were due to hemodynamic instability.

Table (2): Echocardiographic parameters among cases and controls in the initial study.

	Cases (number=50) mean (±SD)	Control (number=20) mean (±SD)	*P* value
Left pulmonary artery (LPA)	0.41 (±0.08)	0.34 (±0.07)	<0.001
LPA Z-score	0.03 (±0.99)	-0.58 (±1.22)	0.00007
Right pulmonary artery (RPA)	0.39 (±0.07)	0.37 (±0.08)	0.04884
RPA Z-score	0.18 (±0.96)	-0.73 (±1.18)	<0.001
Main pulmonary artery (MPA)	0.84 (±0.16)	0.74 (±0.13)	0.00005
MPA Z-score	0.85 (±0.99)	0.13 (±0.95)	<0.001
Aortic isthmus	0.40 (±0.08)	0.39 (±0.10)	0.38108
Descending Aorta	0.55 (±0.10)	0.52 (±0.10)	0.03898
Diaphragmatic Aorta	0.59 (±0.10)	0.56 (±0.12)	0.03898
Left ventricular outflow tract (LVOT)	0.69 (±0.13)	0.65 (±0.11)	0.03443
Systemic Velocity time integral (VTI)	7.75 (±2.24)	7.41 (±2.34)	0.28840
Right ventricular outflow tract (RVOT)	0.87 (±0.208)	0.75 (±0.164)	0.00017
Pulmonary velocity time integra (VTI)	8.13 (±2.167)	7.95 (±2.335)	0.55966
Pulmonary to systemic flow ratio (Qp/Qs)	1.84 (±0.846)	1.47 (±0.440)	0.00327
Left ventricular end diastolic dimension (LVEDD)	1.59 (±0.252)	1.59 (±0.281)	1
LVEDD Z-score	-0.45 (±1.395)	-0.14 (±1.491)	0.06127
Left atrial dimension (LA)	1.02 (±0.212)	0.88 (±0.175)	0.00002
LA Z-score	-1.19 (±1.335)	-1.56 (±2.298)	0.05572
Pulmonary artery pressure (PAP)	39.89 (±11.907)	31.37 (±8.294)	0.00001

Follow-up studies (after 48-72 hours from the initial study) included 65 cases (Figure 1). Among the 50 cases with PDA: 25 (55.3%) of the shunts closed; 5 patients died; and 20 cases (44.7%) continued to have a shunt: out of which, 14 cases (57.7%) had hemodynamic instability that required advanced treatment. PDA mean size at follow-up studies was 0.24 ± 0.11 mm (ranging from 0.08 - 0.5 mm). The echocardiographic findings are listed in table (3) and figure (2).

Table (3): Echocardiographic parameters among cases and controls 48-72 hours from the initial study.

	Cases (number=50) mean (±SD)	Control (number=20) mean (±SD)	*P* value
Left pulmonary artery (LPA)	0.39 (±0.08)	0.37 (±0.08)	0
LPA Z-score	-0.13 (±0.95)	-0.36 (±1.07)	0.00007
Right pulmonary artery (RPA)	0.37 (±0.07)	0.39 (±0.08)	0.04884
RPA Z-score	-0.72 (±0.81)	-0.41 (±1.05)	0
Main pulmonary artery (MPA)	0.78 (±0.15)	0.77 (±0.15)	0.00005
MPA Z-score	0.42 (±0.87)	0.29 (±1.15)	0
Aortic isthmus	0.42 (±0.10)	0.40 (±0.08)	0.38108
Descending Aorta	0.55 (±0.11)	0.55 (±0.13)	0.03898
Diaphragmatic Aorta	0.59 (±0.12)	0.57 (±0.10)	0.03898
Left ventricular outflow tract (LVOT)	0.66 (±0.14)	0.70 (±0.09)	0.03443
Systemic Velocity time integral (VTI)	12.98 (±2.37)	7.09 (±1.82)	0.2884
Right ventricular outflow tract (RVOT)	0.82 (±0.17)	0.81 (±0.16)	0.00017
Pulmonary velocity time integra (VTI)	8.55 (±3.01)	7.46 (±1.95)	0.55966
Pulmonary to systemic flow ratio (Qp/Qs)	1.83 (±0.51)	1.57 (±0.50)	0.00327
Left ventricular end diastolic dimension (LVEDD)	1.53 (±0.31)	1.51 (±0.24)	1
LVEDD Z-score	-0.78 (±1.57)	-0.07 (±1.28)	0.06127
Left atrial dimension (LA)	0.90 (±0.28)	0.91 (±0.19)	0.00002
LA Z-score	-1.70 (±1.98)	-1.39 (±1.41)	0.05572
Pulmonary artery pressure (PAP)	37.78 (±11.76)	28.13 (±8.65)	0.00001

Pre-discharge studies were performed in 44 out of the 50 followed-up cases: 32 neonates were discharged with no PDA; 12 with a non-hemodynamically-significant PDA; and 1 passed away. The mean age at discharge was 10 days, ranging from 6 -30 days. Upon discharge, the PDA mean size was 0.22 (± 0.125 mm) ranging from 0.01 - 0.4 mm. The echocardiographic parameters are listed in table (4) and figure (2).

No significant correlation was found between PDA diameter and: weight (p = 0.72); BSA (p = 0.33); or gestational age (p=0.13). PDA and the various echocardiographic parameters were chronologically followed-up. Table (5) summarizes the correlation between PDA diameter and different echocardiographic measurements.

Table (4): Echocardiographic parameters among cases and controls in the pre-discharge study.

	Cases (number=50) mean (±SD)	Control (number=20) mean (±SD)	*P* value
Left pulmonary artery (LPA)	0.27 (±0.50)	0.37 (±0.08)	0.50
LPA Z-score	-0.15 (±0.78)	-0.46 (±1.02)	0.20
Right pulmonary artery (RPA)	0.25 (±0.72)	0.39 (±0.08)	0.51
RPA Z-score	-0.33 (±1.05)	-0.53 (±1.03)	0.52
Main pulmonary artery (MPA)	0.94 (±0.75)	0.77 (±0.15)	0.45
MPA Z-score	0.12 (±0.81)	0.27 (±1.07)	0.53
Aortic isthmus	0.50 (±0.16)	0.41 (±0.08)	0.08
Descending Aorta	0.57 (±0.12)	0.55 (±0.12)	0.58
Diaphragmatic Aorta	0.62 (±0.13)	0.57 (±0.10)	0.21
Left ventricular outflow tract (LVOT)	2.64 (±3.05)	0.69 (±0.10)	0.05
Systemic Velocity time integral (VTI)	5.46 (±4.04)	6.95 (±1.87)	0.23
Right ventricular outflow tract (RVOT)	3.51 (±4.02)	0.83 (±0.17)	0.04
Pulmonary velocity time integra (VTI)	6.77 (±4.31)	7.44 (±2.06)	0.60
Pulmonary to systemic flow ratio (Qp/Qs)	1.76 (±0.44)	1.66 (±0.57)	0.45
Left ventricular end diastolic dimension (LVEDD)	1.31 (±0.95)	1.64 (±0.23)	0.25
LVEDD Z-score	0.43 (±0.91)	-0.09 (±1.23)	0.96
Left atrial dimension (LA)	0.50 (±0.83)	0.91 (±0.19)	0.12
LA Z-score	-1.42 (±1.357)	-1.42 (±1.40)	1.00
Pulmonary artery pressure (PAP)	31.25 (±8.54)	28.67 (±9.25)	0.32

Table (5): Correlation between PDA diameter and echocardiographic measurements.

	P value		
	Initial	**Follow-up**	**Pre-discharge**
Left pulmonary artery (LPA)	<0.001	0.016	0.032
LPA Z-score	0.004	0.018	0.032
Right pulmonary artery (RPA)	0.087	0.472	0.386
RPA Z-score	0.128	0.671	0.645
Main pulmonary artery (MPA)	0.002	0.002	0.047
MPA Z-score	0.001	0.047	0.047
Aortic isthmus	0.355	0.112	0.256
Descending Aorta	0.130	0.001	0.001
Diaphragmatic Aorta	0.233	0.001	0.042
Left ventricular outflow tract (LVOT)	0.383	0.704	0.248
Systemic Velocity time integral (VTI)	0.002	0.043	0.178
Right ventricular outflow tract (RVOT)	0.133	0.309	0.113
Pulmonary velocity time integra (VTI)	0.010	0.044	0.022
Pulmonary to systemic flow ratio (Qp/Qs)	0.488	0.001	0.001
Left ventricular end diastolic dimension (LVEDD)	0.001	0.001	0.007
LVEDD Z-score	0.001	0.001	0.019
Left atrial dimension (LA)	0.171	0.001	0.013
LA Z-score	0.185	0.001	0.015
Pulmonary artery pressure (PAP)	<0.001	<0.001	<0.001

PDA size correlated in the 3 sets of studies with LPA dimension (p <0.001, 0.016 and 0.032, respectively), LPA Z-score (p=0.004, 0.018 and 0.032 respectively), MPA (p=0.002, 0.002, and 0.044 respectively) and MPA Z-score (p=0.001, 0.047 and 0.047, respectively).

The Desc Ao correlated with PDA size in the follow-up study and pre-discharge studies (p=0.001) but not the initial study. Similarly the Diaph-Ao showed a correlation in the follow-up (p=0.001) and pre-discharge studies (p=0.001 and 0.042, respectively) but not in the initial study.

Systemic VTI showed a strong correlation with PDA size in the initial and follow up studies (p=0.002 and 0.043 respectively), but not in the pre-discharge study; also the pulmonary VTI showed significant correlation with PDA size in all studies (p=0.010, 0.044 and 0.022, respectively). Qp:Qs showed a significant correlation in the follow-up and pre-discharge studies (p=0.001) but not in the initial study.

LA diameter was strongly correlated with PDA size in the 3 studies (p=0.001, 0.001 and 0.007, respectively); so was LA Z-scores (p=0.001, 0.001 and 0.007, respectively). LVEED showed no correlation at the initial study, then a significant correlation was found at the follow-up and pre-discharge studies (p=0.013 and 0.001, respectively); and a similar pattern with LVEDD Z-score (p=0.001 and 0.015, respectively). PAP showed a strong correlation with PDA size (p<0.001) in all studies. No correlation was found with RPA and RPA Z-score; LVOT; and Ao isthmus.
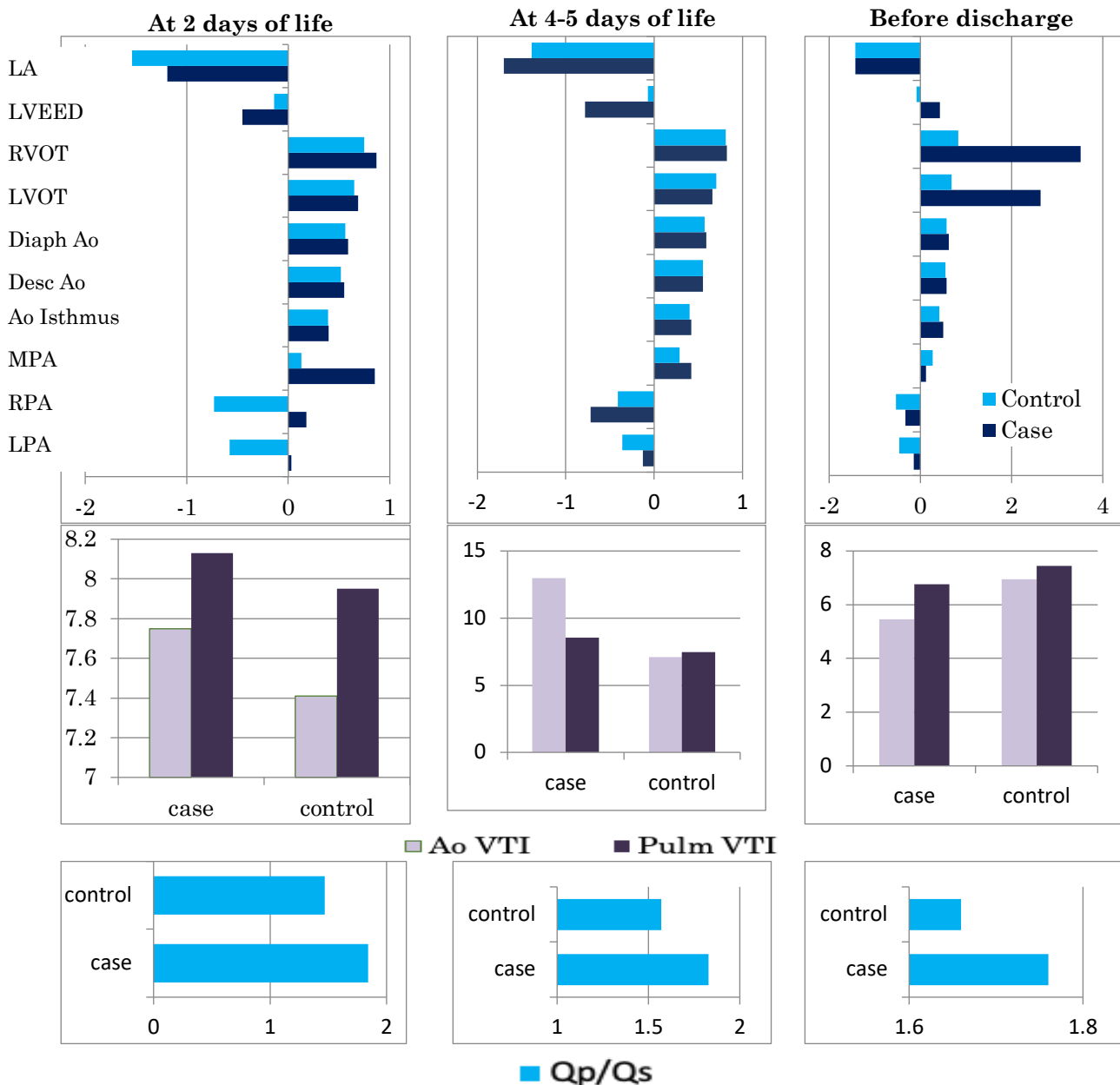

Figure (2): Echocardiographic findings at at 48 hours of age, after another 48-72 hours and prior to discharge of cases and controls and the state of PDA. All underwent medical closure.

Ao Isthmus: aortic isthmus; Desc Ao: Descending thoracic aorta; Diaph Ao: descending aorta at the level of the diaphragm; LA: left atrium Z-score; LPA: left pulmonary artery Z-score; LVEED: Left ventricular end-diastolic dimension Z-score; LVOT: left ventricle outflow tract; MPA: main pulmonary artery Z- score; RPA Z: Right pulmonary artery ; RVOT: right ventricle outflow tract.

The echocardiographic parameters were further investigated to correlate with the degree of hemodynamic instability at the initial and follow-up studies (tables 6 & 7): PDA size showed a significant correlation with hemodynamic instability in the initial and follow-up studies (p<0.001). In addition, a strong association was found between pulmonary hypertension and hemodynamic instability in the initial and follow-up studies (p <0.01 and 0.05, respectively).

Among all the echocardiographic parameters that were correlated with PDA diameter, the LA Z-score was the most significantly associated with hemodynamic instability in the initial study (p=0.03), while the LPA Z-score was the most associated with hemodynamic instability at the follow-up study (p=0.005).

Table (6): Class of hemodynamic instability among initial and final assessment.

	Hemodynamic instability	
	Initial study	Follow-up study
None	11	6
Mild	7	3
Moderate	20	7
Severe	12	4

Table (7): Correlation between echocardiographic parameters and the severity of hemodynamic instability.

	P value	
	Initial study	Follow-up study
Patent ductus arteriosus size	≤0.001	≤0.001
Left pulmonary artery (LPA)	0.893	0.262
LPA Z-score	0.668	0.009
Main pulmonary artery (MPA)	0.799	0.826
MPA Z-score	0.416	0.630
Descending Aorta	0.840	0.630
Systemic Velocity time integral (VTI)	0.148	0.727
Right ventricular outflow tract (RVOT)	0.774	0.633
Pulmonary velocity time integral (VTI)	0.624	0.789
Pulmonary to systemic flow ratio (Qp:Qs)	0.591	0.616
Left atrium (LA)	0.091	0.629
LA Z-score	0.031	0.217
Pulmonary artery pressure (PAP)	<0.001	0.005

*All significant correlations were positive.

Discussion

There is no general agreement on the echocardiographic predictors of a hsPDA. Several predictors have been developed, the most widely used is left atrium/aortic root ratio (LA/Ao ratio), however it lacks powerful statistical correlation with the possible complications. The most sensitive indicator used currently is the presence of retrograde diastolic flow in superior mesenteric artery. Though sensitive and specific, the reliability and repeatability of this index when performed by trained neonatologists is low, with a Kappa coefficient not exceeding 0.2 (*9*). In view of these facts, this study assessed echocardiographic parameters that are associated with a hsPDA, and therefore would predict the need for subsequent treatment and decision for closure of this PDA; and help in identifying whether the PDA is the culprit disorder causing hemodynamic instability or not. We used Z-scores to interpret the results accurately, taking into consideration the effect imposed by the subject's BSA and gestational age (*10, 11*).

In this study; no correlation was found between PDA diameter, and gestational age and weight; that was opposed by many studies that proved gestational age and weight are intimately linked in an inverse relationship to PDA in preterm neonates (*12*), and the same for a symptomatic PDA (*13*). As a matter of fact, our study did not include wide weight and gestational age ranges, including the extreme premature and the low birth weight.

The echocardiographic parameters used in this research were based on the known hemodynamic sequelae of a PDA: if the pulmonary vascular resistance allows significant left-to-right shunting, left sided volume overload can occur and therefore left-sided structures dilate,

and measurements associated with LA, LV, and aorta are therefore enlarged (*14*). Our results show that the mean LA value & LA Z-score were higher among neonates with isolated PDA than that of controls, which was also synchronous with the finding that both correlated with the PDA size in the 3 successive studies. However, the LA Z-score correlated the most with a hsPDA in the initial study, indicating its value as a potential early marker for a hsPDA. LA measurements, although easy to perform, is debated as the entrance of the pulmonary veins into it might interfere with accurate delineation; and the large patent foramen ovale might allow the engorged left atrium to empty into the RA (*15*). In response to this, PFOs are seldom large enough to decompress the LA and equalize atrial pressures. We suggest that the increase of LA Z-score ≥2 is an indicator for hsPDA. To our knowledge, this work is one of very few studies that study the role of LA Z-score in assessment of PDAs and its hemodynamic significance. It should be investigated more whether this parameter can be the marker of physiological closure of PDA.

LV dilatation occurred later in the course of our study: where LVEED and LVEED Z-score correlated only with the PDA diameter only at the latter studies. The enhanced pulmonary blood flow from the significant PDA results in an increase in LV preload, with LA and LV dilatation, increase in LV output and ejection fraction, all resulting in an overall hyperdynamic LV as supported by a systemic review including 34 studies (*16*). The echocardiographic markers achieve statistical significance later on reflecting the late LV dispensability, and time interval needed for myocardial adaptation to compensate for pulmonary over-circulation and left heart overfilling (*17*).

Our results show that systemic VTI was significantly higher in cases throughout serial measurements, with a significant correlation with PDA diameter in the initial two studies, caused by the hyperdynamic state previously described. The changes in systemic VTI are synchronous to the physiologic changes posed by PDA, and could reflect the hemodynamic PDA closure (*18*). On the contrary the aortic isthmus did not show such correlation in our study. According to literature, less blood flows across the Ao isthmus in the fetus compared to the newborn and therefore its diameter is smaller in relation to the Desc- Ao in normal newborns. In children beyond three months of age, the isthmus is usually the same size or larger than the Desc Ao (*19*). Literature on the relation between Ao isthmus size and existence of a PDA in newborns is scarce, however, there is an agreement that there is no significant relation to the existence of a PDA (*20*), or observed with surgical closure (*21*). Desc Ao diameter showed a similar pattern, which is, being correlated with PDA diameter in the latter studies. A significant ductal shunt results in diastolic run-off to the pulmonary circulation (*22*), causing a hyperdynamic circulatory effect. However, a study on flow velocities in the Asc and Dec Ao showed no difference between preterm infants with and without PDA. The lack of influence of PDA on flow velocity thus indicates that the diameter of the aortic lumen might not be significantly altered by the existence of PDA (*23*).

The interaction between the systemic and pulmonary vascular resistances via the PDA are quite complex in the neonate, and might be labile as well (*24*). The RV output reflects the pulmonary blood flow whereas the LVO reflects the systemic blood flow. The shunt across the PFO influences the RV output, and the shunt across the PDA influences the LV output. Thus, ventricular output measurements in a newborn infant with a PDA and foramen ovale are not very accurate. In the case of a hsPDA, the pulmonary blood flow increases due to the amount of blood running back from the Desc Ao into the lung circulation through PDA; at the same time, the systemic blood flow decreases, known as the steal phenomenon. The pulmonary-to-systemic flow (Qp:Qs) ratio therefore increases (*15*). Our work proved the same correlation with PDA diameter in the follow-up and pre-discharge studies. The amount of left-to-right shunt increased according to the size of the systemic-to-pulmonary communication, and it results in an increased pulmonary blood flow (*25*). A less significant correlation between PDA and pulmonary-VTI was found across our serial studies. Pulmonary VTI can generally reflect an increase in pulmonary blood flow (*26*), especially with the increase of pulmonary vascular resistance (*27*). However, the setting of shunting across a septal defect might differ than that of a ductal shunt with interplay of different hemodynamic factors, as well as some difficulty with the assessment of RV outflow pulsed wave Doppler.

Anatomically, the DA connects to the LPA near its origin from the MPA, therefore with a significant PDA an increase in MPA and LPA sizes may occur (*24*). In our study, the MPA, MPA

Z-score, LPA and LPA Z-scores were correlated with PDA size at the initial and follow-up studies as expected. The LPA Z-score is correlated with hemodynamic instability at the follow-up study, however this significance was not sustained at the pre-discharge study. We relate this to the fact that infants that were discharged with a PDA were symptom-free: their PDAs being of small size and of a low hemodynamic impact. LPA Z-score therefore might be an indicator of the hsPDA only.

The various echocardiographic parameters were correlated with hemodynamic instability, to investigate their value as early predictors of hemodynamic instability. The PDA size, as agreed in many studies, had a high predictive value of hemodynamic instability (*25*). In addition, a strong association of PDA-related hemodynamic instability with pulmonary hypertension was found: which may be either a consequence or a cause to the PDA shunt. In primary pulmonary hypertension, it may play a role to decrease the pulmonary blood flow in exchange for systemic perfusion by deoxygenated blood leading to hypoxemia and further hemodynamic instability (*28*). On the other hand, pulmonary arterial hypertension may be a result of a large left-to-right PDA shunt that leads to significant hemodynamic changes, that is, systemic hypoperfusion and pulmonary hyperperfusion (*15*). The key feature is an increased pulmonary venous return resulting in high PAP, this leads to (1) RV systolic and diastolic failure secondary to increased afterload; (2) decrease in RV stroke volume and RV filling; (3) decrease in pulmonary blood flow with ventilation-perfusion mismatch; (4) RV dilatation causing a D-shaped left ventricle with decreased LV preload; and, (5) decreased LV stroke volume (*29*). In view of these facts, our results of a high association of pulmonary hypertension in cases with PDA with hemodynamic instability is so much supported.

Our work emphasizes the need for a diagnostic scoring system to identify whether the decompensation is due to the PDA or other factors and to identify the severity of hemodynamic effect of an isolated PDA. How small is small and how big is a big PDA in terms of clinical effect? a question that we need to answer. Future incorporation of the LA & LPA Z-scores might prove to be basis of classification, indicators for treatment and predictors of outcome. There is a need to validate an objective scoring system to identify those who are in need of closure: among those where the PDA is the underlying cause of hemodynamic decompensation.

Our work is limited by being a single-center study that included neonates admitted to the NICU, the sample lacks the geographical and clinical diversity. Also, the sample size did not allow the separate study of preterm and term neonates.

Conclusion

Our study assessed the echocardiographic parameters associated with PDA size and severity, that could be used as markers for identifying a hsPDA and guide the management accordingly. LA Z-score appeared to be a significant early parameter (at 48-72 hours of age); and LPA Z-score was a useful parameter associated with hemodynamic instability. Left heart parameters including LV diameter, Ao VTI, and Desc Ao were later markers (96 hours of age onwards). We recommend that LA Z-score be considered in the evaluation of PDA regarding its significance and need for closure. Validation studies are required to test these parameters as indicators and predictors, and define cut-off values that could be used. Also a replica study in premature neonates would be valuable.

Author Contributions:

All authors shared in conceiving the work, data collection and analysis, revision of literature, revision of final version of the manuscript. B.M.H. submitted the manuscript and corresponded until publication. All authors have read and agreed to the published version of the manuscript.

FUNDING

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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