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Assessment of diastolic myocardial function in neonates with patent ductus arteriosus using tissue Doppler imaging

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***Abstract*---**Background: The present study was an analytic case control study was done and included full and preterm neonates with PDA and respiratory distress. Neonates with no PDA were also included as a control. Aim of the study: This study aimed to assess diastolic myocardial functions in neonates with different degrees of ductal patency in 1st week of life using tissue Doppler imaging. Methods: The study was conducted at neonatal intensive care unit (NICU) in Bab-Sheria hospital, pediatric department, faculty of medicine, Al Azhar University in the period from June 2018 to June 2021. The present work was conducted on fifty Neonates categorized into 3 groups as follow: Haemodynamically significant dusctus arteriosus cases: ductal diameter more than 2.5 mm and left atrium to aorta (LA: AO) ratio more than 1.5. Non haemodynamically significant ductus arteiosus cases: ductal diameter less than 2.5 mm or (LA: AO) ratio less than 1.5 and Non patent dusctus arteriosus (Control group). Results: Amount of left-to-right shunt will increase according to the size of the systemic-to-pulmonary communication, and it results in an increased pulmonary blood flow which agrees with our study, The results shows significant higher LA/AO ratio and lower E/A ratio in HD SIG Cases compared to NON-SIGNIFICANT and CONTROL group, Significantly lower septal E` velocity cm/s in both HD-SIG AND NON-HD SIG cases compared to the control group. Significantly lower lateral wall E` velocity cm/s in both HD-SIG AND NON-HD SIG cases compared to the control group. There is lower mean values of both septal E` and lateral wall E` in HD –SIG Cases compared to NON-HD SIG case, Conclusion: In neonates with HD Sig PDA have lower diastolic left ventricular velocities indicating relative

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degrees of left ventricular diastolic dysfunction in these cases compared to Non-HD Significant PDA cases and control group. Tissue Doppler echocardiography is a useful, sensitive, non-invasive technique to study the changes in myocardial structure and function.

***Keywords*---**diastolic myocardial function, neonates, patent ductus arteriosus, tissue doppler imaging.

Introduction

PDA's incidence is inversely proportional to the gestational age with the prevalence of 20% at 32 weeks gestational age and exceeding 90% at 26 weeks gestational age. [1] When the ductus arteriosus (DA) is open after birth, a left to right shunt occurs via DA.As result, the systemic blood flow is decreased, while the pulmonary blood flow is increased, the decrease in the systemic blood flow may set up congestive heart failure, cause pulmonary hemorrhage, lead to intracranial hemorrhage and exacerbate chronic lung disease. [2] Myocardial function is another important component of hemodynamic significance, but has often been forgotten in a PDA assessment and warrants further attention. Although much of the morbidity and mortality is related to the effects of the PDA on the systemic and pulmonary circulations, cardiac function is still an important driver in disease. The premature myocardium is characterized by systolic and diastolic dysfunction due to an inefficient contractile apparatus, a lack of compliant elastic and a preponderance of stiff fibrous tissue. [3] Tissue Doppler imaging (TDI) is an emerging technique that can provide measurements of movement of the myocardium and timing of myocardial events in the cardiac cycle. There is an increasing body of literature on the use of TDI in neonates. [4] The study aimed to assess diastolic myocardial functions in neonates with diffent degrees of ductal patency in 1st week of life using tissue Doppler imaging.

Patients and Methods

The current study is an analytic case-control study that included full term and preterm neonates with haemodynamically significant PDA and non-haemodynamically significant PDA at Bab-Sheria hospital, pediatric department, faculty of medicine, Al Azhar University in the period from June 2018 to June 2021. Neonates with no PDA were also included as a control group. The study population was classified into 3 groups as follows: Haemodynamically significant dusctus arteriosus cases (9 cases), Non haemodynamically significant ductus arteiosus cases (24 cases) and Non patent dusctus arteriosus (Control group) 17 neonate.

Inclusion criteria

Neonates admitted in neonatal intensive care unit with respiratory distress. (PFO is accepted with spo2 more than 95 %).

Exclusion criteria

Central causes of respiratory distress (meningitis, intracranial hemorrhage), preterm neonates with respiratory distress syndrome, and other hemodynamically significant congenital heart diseases especially sever mitral regurge, Dysmorphic features suggestive of congenital anomalies and infant of diabetic (IDM) excluded

Ethical considerations

A written informed consent was obtained from patients or their legal guardians. Approval of the ethical committee in Pediatrics department and Al-Azhar faculty of medicine was obtained before the study. The data of the patients and the results of the study are confidential and the patients had the right to keep. The patient had the right to withdraw from the study at any time. The authors received no financial support for the research, authorship, and/or publication of this study**.**

Methods

All eligible neonates subjected to the following: Detailed history taking

including gestational age, sex, birth weight, mode of delivery, complete obstetric history to detect risk factors of congenital cardiac malformations as maternal fever, rash TORCH infection or Urinary tract infection, insulin dependent or gestational Diabetes.

Careful clinical examination including

Detection of clinical signs of PDA such as apneic spells, signs of heart failure , and inability to wean the infant from the ventilator or need to increase ventilator settings or O2 requirements , chest and heart examination: murmur (systolic murmur at left infra clavicular area or continuous murmur of large PDA) .

Laboratory investigations including

CBC with differential T.L.C to identify anemia, sepsis and thrombocytopenia, blood gases (pH, paco2, pao2, HCO3) and CRP to exclude sepsis.

Radiology

CXR to exclude RDS

Echocardiography 2D, M mode, conventional Doppler

will be done at second to third day of life .showing: Ductus size, Direction of flow, LA: AO ratio.

Tissue Doppler imaging

assessment of left ventricular functions. The examination was performed by the observer (pediatric cardiologist having experience in echocardiography) .The examination consisted of pulsed wave Doppler, blood flow velocity measurements of the heart valves and Tissue Doppler Imaging (TDI). Pulsed wave (PW) Doppler will be used over the mitral valve using apical four-chamber view. The following Doppler parameters were measured: peak E wave velocity and peak A wave velocity for the mitral valve and E/A ratio. The peak diastolic velocities at the LV, IVS were assessed with TDI in cases and controls. The following parameters were recorded: early diastolic velocity (E) and late diastolic velocity (A) and time intervals. In general, the higher the myocardial velocities and lower the myocardial performance index, the better the myocardial function.

Statistical analysis

All collected data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5

Results

Risk factor		Count	%
UTI	Yes (asymptomatic)	7	14.0%
	No	43	86.0%
Mother smooker	yes	1	2.0%
	No	49	98.0%
Ante partum hge	yes	2	4.0%
	No	48	96.0%
Fever	yes	0	0.0%
	No	50	100.0%
RASH	no	50	100.0%
DM	no	50	100.0%

History

Most of cases had no prenatal risk factors as DM or HTN. NO maternal rash was noted in all cases. UTI in 14 % of cases was noted, but was asympatomatic , CRP was negative in these concurant newborns.

			Count	%
CARDIAC		MURMUR	13	26.0%
		no abnormality	37	74.0%

		Control		NON SIG		HD SIG PDA		P value
		Count	%	Count	%	Count	%	
CARDIAC	MURMUR	0	0.0%	10	41.7%	3	33.3%	0.004

Cardiac examination: The table shows statistically significant difference between groups regarding presence of mumur heard clinically (p-value 0.004)

		Control		NON SIG		HD SIG PDA		P value
		Count	%	Count	%	Count	%	
DIRECTION OF FLOW	RT TO LEFT	0	0.0%	0	0.0%	0	0.0%	0.740
	LT TO RT	0	0.0%	24	100%	9	100%	
	BI DIR	0	0.0%	0	0.0%	0	0.0%	

Direction of the flow

Tables shows All cases with PDA has left to right shunt across PDA

	Control					NON SIG					HD SIG PDA					Overall P value	P1 value	P2	P3
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum				
DUCT SIZE						2.384	0.9	2.45	0.818	3.1	4.34	1.03	3.2	2.5	4.47	0.157			
LA/AO RATIO	0.94	0.18	0.94	0.56	1.29	0.90	0.29	0.98	0.05	1.30	2.11	0.78	1.77	1.50	3.80	<0.001	1.000	<0.001	<0.001
E/A RATIO	1.38	0.38	1.20	0.99	2.40	1.15	0.47	1.07	0.40	2.40	0.69	0.09	0.70	0.50	0.80	<0.001	0.143	<0.001	0.004
septal `e	7.60	1.50	8.00	4.28	9.00	4.92	1.94	4.76	0.05	9.05	4.41	1.10	4.23	3.00	7.00	<0.001	< 0.001	< 0.001	1.000
septal `e -`a ratio	1.00	0.31	0.98	0.66	1.75	0.93	0.32	0.88	0.40	1.78	0.89	0.19	0.98	0.55	1.19	0.682			
lateral `e	9.14	2.44	8.06	5.37	13.00	5.73	2.57	5.79	1.60	12.00	4.57	1.23	5.00	2.00	6.00	<0.001	< 0.001	< 0.001	0.866
lateral `e -`a ratio	1.21	0.37	1.30	0.10	1.70	0.96	0.34	0.88	0.37	1.55	0.67	0.19	0.60	0.37	0.98	0.001	0.073	0.001	0.101

Table compares echocardiography and TDI parameters: P1 control with NON SIG PDA, P2 control VS HD SIG PDA, P3 NON SIG VS HD SIG PDA. The results shows significant higher LA/AO ratio and lower E/A ratio in HD SIG Cases compared to NON-SIGNIFICANT and CONTROL group, Significantly lower septal E` velocity cm/s in both HD-SIG AND NON-HD SIG cases compared to the control group. Significantly lower lateral wall E` velocity cm/s in both HD-SIG AND NON-HD SIG cases compared to the control group. There is lower mean values of both septal E` and lateral wall E` in HD –SIG Cases compared to NON-HD SIG cases

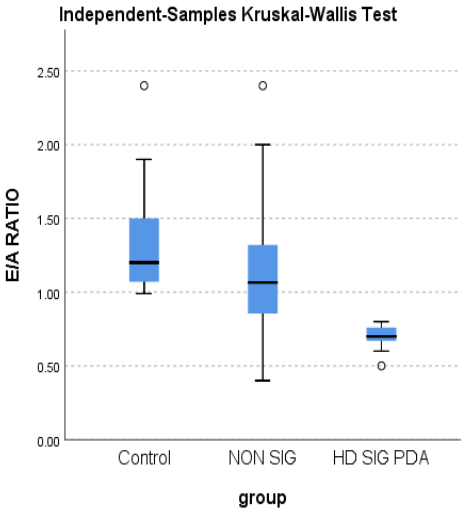

Figure 1. Post hoc pair wise comparison between E/A RATIO among different groups

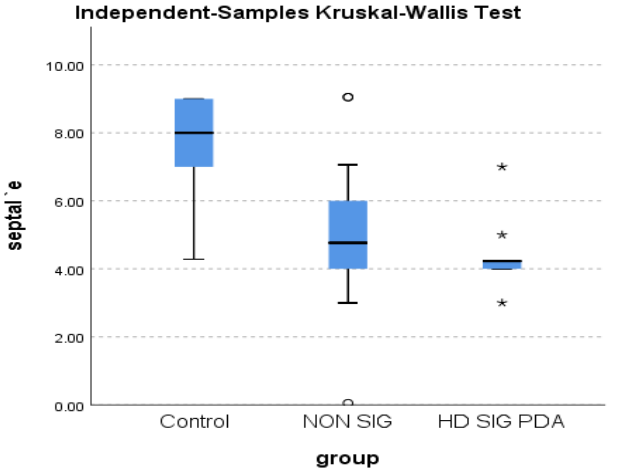

Figure 2. shows significantly lower septal E` velocity cm/s in both HD-SIG AND NON-HD SIG cases compared to the control group

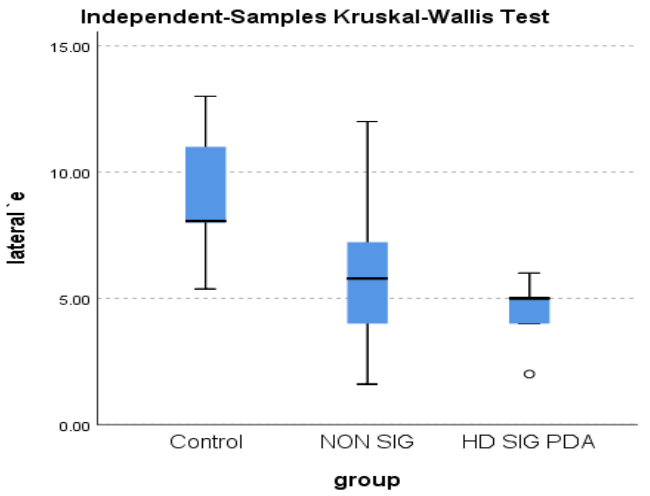

Figure 3. show significantly lower lateral wall E` velocity cm/s in both HD-SIG AND NON-HD SIG cases compared to the control group

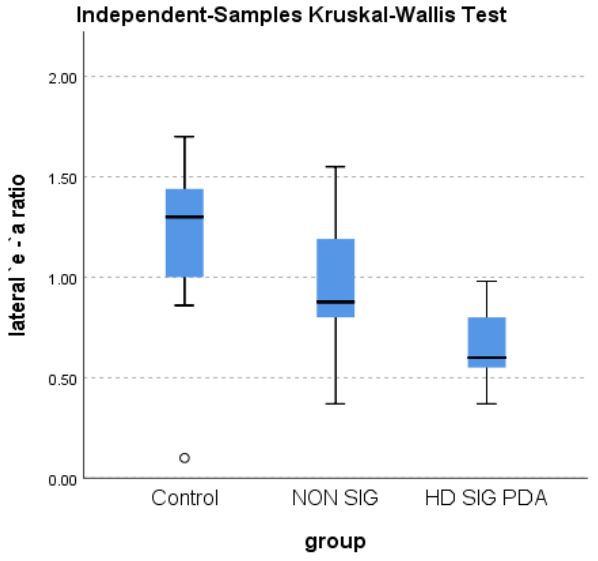

Figure 4. compares lateral e` a` ratio between different groups

Discussion

Ductus arteriosus is a necessary structure for the fetus. It allows communication between the pulmonary artery and descending aorta during fetal life. [5] Hemodynamically significant patent ductus arteriosus (hsPDA) is a common problem in the first week of life in the preterm infants. PDA may lead to clinical

problems in the preterm and term newborn. [6] This study is an analytic case-control study conducted at Bab-Sheria Hospital, Pediatric Department, Faculty of Medicine, Al Azhar University within three years in the period from June 2018 to June 2021. Our study included three groups; the first group involved haemodynamically significant dusctus arteriosus cases (n=9); the second group involved non haemodynamically significant dusctus arteriosus cases (n=24); and the third group involved non patent dusctus arteriosus or (Control group) (n=17). We aimed to assess diastolic myocardial functions in neonates with different degrees of ductal patency in 1st week of life using tissue Doppler imaging. This study is one of very few investigations which discussed myocardial diastolic functions in patients with PDA, and their role in assessment of HD- significance.

Comparable results were obtained previously, One hundred fifty-two preterm babies ≤ 34 weeks gestation were included in Soliman et al., [7] study, 87 babies (57.2%) had PDA, 33 (37.9%) of them had hemodynamically significant PDA, while 54 (62.1%) babies had hemodynamically non-significant PDA and 65 babies (42.8%) did not have PDA. Danfang et al., [8] studied 105 neonates ≤ 34 weeks gestational age and found 34 (43.5%) having hsPDA, 44 (56.5%) having non-hsPDA and 27 (25.7%) having no PDA. Many other studies proved gestational age and weight are intimately linked to PDA in preterm neonates. Specifically, PDA is present in 80% of infants weighing less than 1,200g at birth, compared to 40% of infants weighing less than 2,000g at birth. [9]

Preterm babies having hsPDA had more RDS, pneumonia and pneumothorax evidenced by X-ray findings compared to non-hsPDA group (P = 0.007) in the study of Soliman et al., [7]. Also, it was found that longer duration of significant PDA is associated with the higher risk for bronchopulmonary dysplasia (BPD)/death in extremely preterm infants. [10] Regarding echocardiography and Tissue Doppler imaging (TDI) parameters in our study, it was found that all cases with PDA had left to right shunt across PDA. The left to right shunting through hemodynamically significant patent ductus arteriosus (PDA) causes pulmonary over circulation with resultant left ventricle (LV) volume overload and remodeling. [11] Preterm infants with hemodynamically significant patent ductus arteriosus (hsPDA) have left-to-right shunt across PDA causing less blood flow to the lower legs. [12] Amount of left-to-right shunt will increase according to the size of the systemic-to-pulmonary communication, and it results in an increased pulmonary blood flow which agrees with our study. Early identification of preterm infants who subsequently fail to achieve ductal closure allows early initiation of intervention and reduced treatment failure. The diagnosis of hemodynamically significant ductal patency requires echocardiographic assessment. However, the definition of hemodynamically significant patent ductus arteriosus remains controversial. [13] Lee, [14] considered PDA was hemodynamically significant according to the following echocardiographic criteria; PDA diameter>3 mm, LA:Ao >1.5. Yoo et al., [15] defined HSPDA if PDA had a transductal diameter ≥1.4 mm/kg with significant left to right shunt confirmed by echocardiography.

This agrees with our study

That showed that the cut-off value for PDA diameter in HSPDA is 2.5 mm or larger, the mean in HSPDA cases was 4.34 mm, and the median was 2.3 mm

compared to the NON HDSIG PDA cases , the mean was 2.384 mm and median was 2.1mm , that confirms that HSPDA are associated in most cases with PDA larger than 2.45 mm and mode was 2mm and 2.3 mm . Lee et al., [16] results showed that at 5 h, babies with haemodynamically significant patent ductus arteriosus (PDA) had significantly higher systolic and diastolic velocities in both ventricles than those with non-significant PDA. There was significantly higher LA/AO ratio and lower E/A ratio in haemodynamically significant dusctus arteriosus cases compared to non haemodynamically significant dusctus arteriosus cases and control group.

The left atrial-to-aortic ratio (LA/Ao), the early passive filling to late active phase ratio (E/A), the interval between closure of the aortic valve and mitral valve (isovolumic relaxation time, IVRT), and LVO are quantifiable indices of pulmonary over-circulation that can aid the delineation of hemodynamic significance of the DA. [15] The presence of haemodynamically significant dusctus arteriosus increases diastolic TDI velocities according to Breatnach et al., [17] study. Agha et al., [11], also found a significant reduction of LA/AO compared with preclosure values ($p < 0.001$). This reduction was observed at 48 hours, which continued to decrease further at 1 month and 6 months. At 6 months. In the study of Kluckow and Evans, [18] PDA diameter ≥1.5 mm has 81 % sensitivity and 85 % specificity in identifying haemodynamically significant dusctus arteriosus, and LA :Ao ≥1.5 has 91 % specificity in identifying haemodynamically significant dusctus arteriosus, which totally agree with our study , as from results the p value is significant in comparing LA: AO ratio between haemodynamically significant dusctus arteriosus and control ($P2 < 0.001$) and comparing haemodynamically significant dusctus arteriosus to non haemodynamically significant dusctus arteriosus cases($p3 < 0.001$) and 100 % in both sensitivity and specificity .

The mean LA/Ao increased systematically, from a minimum of 0.94 in the control group, through 1.66 in the –HS group and 1.86 in the +HS group, to a maximum of 1.98 in cases that needed ligation (L-HS) in the study of Guthrie, [19]. E/Ea values in infants with patent ductus arteriosus (PDA) appeared to be greater than those in non-PDA infants in the study of Murase et al., [20]. There was significantly lower septal E` velocity cm/s and lower lateral wall E` velocity cm/s in both haemodynamically significant dusctus arteriosus cases and non haemodynamically significant dusctus arteriosus cases compared to the control group. There was lower mean values of both septal E` and lateral wall E` in haemodynamically significant dusctus arteriosus cases compared to non haemodynamically significant dusctus arteriosus cases. Patients with a PDA and reversed diastolic aortic flow showed marked discordance in each marker compared to control patients; specifically, the pulmonary vein D-wave peak velocity, mitral E-wave peak velocity, LA: Ao ratio, LVEDD, and LVO were higher, and the IVRT was shorter in the PDA with holodiastolic flow reversal in the descending aorta (PDAr) group. [23] Initial myocardial velocities of preterm infants in Parikh et al., [25] study were significantly lower and myocardial performance index significantly higher in the haemodynamically significant ductus arteriosus group compared with other groups.

Conclusion

In neonates with HD Sig PDA have lower diastolic left ventricular velocities indicating relative degrees of left ventricular diastolic dysfunction in these cases compared to Non-HD Significant PDA cases and control group. Tissue Doppler echocardiography is a useful, sensitive, non-invasive technique to study the changes in myocardial structure and function.

Conflict of interest: no conflicts of interest.

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