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Echocardiographic evaluation of Left ventricular function before and after trans-catheter patent ductus arteriosus closure

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***Abstract*---**Introduction: there are limited available studies on LV hemodynamics alteration after trans-catheter PDA closure particularly diastolic function and most of studies are with 2D echocardiography. Objective: to evaluate the effect of trans-catheter closure of PDA on LV systolic and diastolic function in children and young adults using 2D and 3D echocardiography. Materials and methods: Al-Azhar University hospitals hosted this prospective cohort study, which included 20 patients with isolated PDA who had been referred to Cath lab for trans-catheter PDA closure; LV function evaluated by 2D, 3D echocardiography and TDI before, one day after closure and on follow-up. Results: 45% of patients developed post closure LV systolic dysfunction which improved completely after 3 months of follow up, all studied patients showed significant decrease in LAD, LAD/AoD, LVEDd, LVEDs, LVEDVI and LVESVI after 3 months of trans-catheter PDA closure; (LAD/AoD, LVEDVI, LVESVI, FS and LVEF) can be used as predictors of post closure LV systolic dysfunction, diastolic function was worse in individuals with post closure LV systolic dysfunction. Conclusions: Trans-catheter closure of PDA induces a considerable reduction in LV systolic performance and function, particularly in younger patients early after closure that recovers entirely and the function is restored within 3 months, (LVEDVI, LVESVI, FS and LVEF) can be used as indictors to predict LV systolic dysfunction after trans-catheter closure of PDA and After PDA closure, worse LV diastolic function in individuals with post closure LV systolic dysfunction which showing improvement on follow up.

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***Keywords*---**2D Echocardiography, 3D Echocardiography, PDA, trans-catheter closure of PDA, left ventricular dysfunction.

Introduction

One of the most prevalent congenital heart disorders is patent ductus arteriosus (PDA) which accounts 5–10% of all congenital heart disease in term infants; PDA is more common in preterm infants and is inversely related to gestational age and weight, in 75% of cases, it is an isolated defect and it is an isolated defect in almost adult cases (Dice & Bhatia, 2007). It is an acyanotic congenital heart disease with a left to right shunt and results from failing of neonates' physiological ductus constriction (Gupta et al., 2011).

Hemodynamically significant PDA causes volume overload and remodelling of the left ventricle (LV), which in turn causes serious consequences like congestive heart failure, Eisenmenger's syndrome, atrial arrhythmias, endarteritis, and ductus aneurysm (Schneider, 2012). As with chronic aortic and mitral regurgitation, LV volume overload and compensatory remodelling change the systolic and diastolic function of the LV (Enriquez-Sarano et al., 1994). Trans-catheter closure of PDA is a safe, efficient and a well-established procedure, it is now the preferred recommended treatment (Kindler et al., 2017).

The most frequent diagnostic technique for determining PDA size and hemodynamics as well as for evaluating the size of the cardiac chambers and LV function is echocardiography (Baumgartner et al., 2010). Therefore, the goal of the research was to evaluate the effect of trans-catheter PDA closure on LV function using 2D and 3D echocardiography.

Materials and Methods

This prospective observational study included 20 patients diagnosed with PDA who had been referred to our Cath lab for trans-catheter PDA closure.

Inclusion criteria: all Patients with PDA suitable for trans catheter closure below 18 years old.

Exclusion criteria: patients with unsuitable PDA size for trans-catheter closure, Patients with significant residual shunt, Patients with associated hemodynamically significant congenital heart disease and Patients with irreversible pulmonary vascular disease.

Methods

All patients subjected to the following: Full medical history, physical exam, routine labs, basic ECG, Cardiac catheterization for closing PDA using ductal occluder by standard technique and a comprehensive 2D and 3D TTE using Philips iE33 X Matrix" ultrasound machine using "S5-1" & "X5-1" matrix array transducers (Philips Medical Systems, Andover, USA) equipped with STE technology, using a multi frequency (1 - 5 MHz) before closure, after 24 hours and on follow up (at least 3 months after closure).

The size, minimum diameter toward the pulmonary end, shape, and orientation of the PDA, as well as the sufficiency of the ampulla on the aortic end, all were evaluated. For systolic function, LV end-diastolic and systolic volumes (LVEDV and LVESV, respectively) were averaged over three cardiac cycles in the apical four-chamber view by the area length method and were indexed for the body surface area (BSA), LVEF and FS were obtained, Real time 3D images will be acquired by X5 1 probe, All echocardiographic images were stored digitally; LV volumes were systematically measured offline with (QLAB advanced software package (Q Lab Version 9.0 3DQAdvanced software, Philips). The acquisition of the 3D images was carried out after the 2D echocardiographic study. The 3D images were obtained in expiratory apnea with the image attached to the ECG record. The full volume data of the LV was organized into orthogonal four, two chamber, and short axis views. End diastolic and end systolic frames were selected. Mitral annular and apical points were placed on these images. Semi-automated LV endocardial border detection software on Q Lab outlines the endocardial borders in these three planes. The software then used sequence analysis to track the endocardium in all frames and then automatically calculated a true 3D EDV, ESV, and EF from the moving 3D endocardial shell.

LV systolic dysfunction was defined as a post-PDA closure LVEF less than 50% and/or a 10% drop in LVEF or more from baseline. For diastolic function, Mitral E, A, E deceleration time (EDT), E/A were assessed as per standard method. In addition, mitral E time velocity integral (E TVI), A time velocity integral (A TVI) and E TVI/A TVI were also analyzed, medial and lateral E/E' were calculated by obtaining mitral annular diastolic velocities by tissue Doppler imaging (TDI). The diameters of the left atrium and aorta were also measured simultaneously.

Ethics, Consent and Permissions

All patients or their surrogates wrote consent prior to study involvement.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were expressed as mean ±SD. Qualitative data were expressed as frequency and percentage. Mean (average): the central value of a discrete set of numbers, specifically the sum of values divided by the number of values. Standard deviation (SD): is the measure of dispersion of a set of values. A low SD indicates that the values tend to be close to the mean of the set, while a high SD indicate that the values are spread out over a wider range.

The following tests were done:

- A one-way analysis of variance (ANOVA): when comparing between more than two means (for normally distributed data).
- ROC curve (Receiver Operating Characteristic Curve): was used to detect cutoff value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

1. Sensitivity: probability that a test result will be positive when the disease is present.
2. Specificity: probability that a test result will be negative when the disease is not present.
3. Positive predictive value is the probability that the disease is present when the test is positive.
4. Negative predictive value is the probability that the disease is not present when the test is negative.

- Probability (P-value)
  1. P-value < 0.05 was considered significant.
  2. P-value < 0.001 was considered as highly significant.
  3. P-value > 0.05 was considered insignificant.

Results

Twenty patients were included in the study nine patients developed LV systolic dysfunction after trans catheter PDA closure (three patients developed LVEF less than 50% and six patients had a drop of LVEF more than 10% from the baseline). None of them had a baseline LV systolic dysfunction. Number of male patients in the research was 4 (20%). Number of female patients in the research was 16 (80%). The Age in the study population ranged from 17 to 204 months with mean ± SD = 68.3 ± 55.5 (Table I).

There was no statistical significant difference of AoD before PDA closure and after trans-catheter closure (with 24 hour and after 3 months), statistically significant decrease in LAD, LAD/AoD, LVEDd, LVEDs, LVEDVI and LVESVI after 3 months of trans-catheter PDA closure when compared with 24 hour trans-catheter PDA closure and before PDA closure and statistically significant decreased FS and LVEF after 24 hour trans-catheter PDA closure when compared with 3 months of trans-catheter PDA closure and before PDA closure. There was statistically significant decreased LVEDVI (3D) and LVESVI (3D) after 3 months of trans-catheter PDA closure when compared with 24-hour trans-catheter PDA closure and before PDA closure, highly statistically significant decreased LVEF (3D) after 24-hour trans-catheter PDA closure when compared with 3 months of trans-catheter PDA closure and before PDA closure (Table II).

In patients with LV systolic dysfunction after closure, there was no statistically significant differences of LAD & AoD by 2D ECHO between different states of PDA closure, there was highly statistical significant decreased LAD/AoD after 3 months of trans-catheter PDA closure when compared with 24 hour trans-catheter PDA closure and before PDA closure, statistically significant decreased LVEDd, LVEDs, LVESVI and LVEDVI after 3 months of trans-catheter PDA closure when compared with 24 hour trans-catheter PDA closure and before PDA closure and highly statistical significant decreased FS and LVEF 24 hour trans-catheter PDA closure when compared with after 3 months of trans-catheter PDA closure and before PDA closure (Table III).

In patients with LV systolic dysfunction after closure, there was statistically significant decreased LVEDVI (3D) and LVESVI (3D) after 3 months of trans-catheter PDA closure when compared with 24-hour trans-catheter PDA closure and before PDA closure, a highly statistically significant decreased LVEF (3D) 24-hour trans-catheter PDA closure when compared with after 3 months of trans-catheter PDA closure and before PDA closure. Results with 3D echocardiography are aligned with the results from 2D echocardiography without significant difference (table IV)

LAD/AoD, LVEDVI, LVESVI, FS and LVEF can be used as predictors of post closure LV systolic dysfunction as shown (Table V). LV diastolic function was worse in individuals with post closure LV systolic dysfunction than in patients with no LV systolic dysfunction post closure, LV diastolic characteristics improved but delayed behind the improvement in LV systolic performance following PDA closure. No statistically significant difference of diastolic function data between different states of PDA closure in all studied patients except E velocity which there was significant decrease after 3 months of trans-catheter PDA closure when compared with 24-hour trans-catheter PDA closure and before PDA closure. No statistically significant difference of LV diastolic function data between different states of PDA closure in patients with no LV systolic dysfunction post closure. Statistically significant decreased A, mitral A TVI and E TVI/ A TVI after 3 months of trans-catheter PDA closure when compared with 24-hour trans-catheter PDA closure and before PDA closure and no statistically significant difference of other LV diastolic function data between different states of PDA closure as shown in (Table VI)

Discussions

Trans-catheter PDA closure has now been proved to be safe and successful procedure, with short and long-term results comparable to surgical closure 6, Surgery is now reserved for patients in whom trans catheter closure is either not possible or fails (Magee, Huggon, Seed, Qureshi, & Tynan, 2001). In children and even adults, trans-catheter PDA closure has become the treatment of choice (Schneider & Moore, 2006).

Hemodynamically significant PDA causes Volume overload and remodeling in the left ventricle (Masura, Tittel, Gavora, & Podnar, 2006) and is expected to be associated with changes in ventricular filling and contractility (Bonow, Lakatos, Maron, & Epstein, 1991). Once closed, a hemodynamically significant PDA reduces LV preload by eliminating the left-to-right shunt and raises afterload 'afterload mismatch' by isolating low-resistance pulmonary circulation from LV outflow circulation. This concurrent decrease in LV preload and rise in afterload may result in LV systolic dysfunction; LV systolic dysfunction is not a ubiquitous trait in patients with PDA. In the postoperative period of mitral regurgitation procedures, similar LV systolic dysfunction has been observed (Corin et al., 1995).

The aim of this research study was to evaluate the effect of trans-catheter closure of the PDA on LV systolic and diastolic function in children and young adults using two-dimensional (2D) and three-dimensional (3D) echocardiography. Various definitions of LV systolic dysfunction have been used in prior studies. In a study by **Jeong et al,** an LVEF cutoff of 50% was utilized to determine LV systolic dysfunction 12, whereas Saurabh et al defined LV systolic dysfunction as a post-PDA closure absolute LVEF of less than 50% and/or a 10% drop in LVEF or more from baseline (Jeong et al., 2007).

Because there was no consensus on how to define LV systolic dysfunction in patients with PDA, both were considered in this research study. The evaluation of LV contractile function by EF is load dependent; however, a drop of 10% or an absolute LVEF below 50% is unusual and is considered to represent LV systolic dysfunction. Our study showed significant LV dysfunction after PDA closure in 45% of patients. Prior studies have found that the incidence of LV systolic dysfunction after PDA device closure ranged from 19% to 25%, which is substantially lower than the current study (Kim, Choi, Cho, Lee, & Hyun, 2008). At follow up, there was a large decrease in LVEDVI as well as a further decrease in LVESVI and the late drop in LVESVI was reflected in normal LV systolic function.

At follow-up, our findings showed complete spontaneous recovery of LV systolic dysfunction, which is similar with **Eerola et al.** (Eerola, Jokinen, Boldt, & Pihkala, 2006), **Kim et al.** (Kim et al., 2008) and **Galal et al.** (Galal et al., 2005) However, Persistent LV systolic dysfunction was documented in 11% of adult patients who underwent PDA closure, according to **Jeong et al** (Jeong et al., 2007). This disparity is likely attributed to the longer duration of volume overload in adults compared to children, resulting in more profound and irreversible alterations in LV. There has yet to be a definitive demonstration of pre-closure predictors of LV systolic failure after PDA closure (Sharma et al., 2021). Our study showed that LVESVI, LVEDVI, FS and LVEF may be used as predictors of immediate LV systolic dysfunction post PDA closure. Because there were no definite criteria for diastolic dysfunction in children with PDA descriptive analysis was used in this research study.

The changes in E velocity in all patients without change in EDT are consequent to decreased preload to LV, Late reductions in mitral A velocity and A TVI, along with a considerable increase in the E/A TVI ratio in patients with post closure LV systolic dysfunction and no additional change in E velocity at follow-up, indicating that the diastolic characteristics of LV have improved, lowering the relative contribution of late diastolic filling to total LV filling. These findings support the expectation of a delayed reversal of the altered diastolic characteristics of LV following PDA closure.

Diastolic characteristics of LV in Patients with post-closure LV systolic dysfunction improved slower and to a lesser extent, indicating significantly changed myocardial characteristics due to volume overload. Our study's larger number of females is aligned with the higher prevalence of PDA in females.

Limitations of the study

Small sample size is one of the limitations of this study so minor differences impacting LV dysfunction may have been missed in the variables, short term follow-up of the patients and the parameters utilized to assess LV function were load dependent, which could affect the interpretations in the post closure condition. So, for further evaluation of the LV function characteristics, further studies with long-term follow up are required, more research with a greater number of patients, more PDA variants, and other parameters could be beneficial and parameters which are load independent as isovolumic acceleration can be used and that may enhance the specificity.

Conclusions

Trans-catheter closure of PDA induces a considerable reduction in left ventricular systolic performance and function, particularly in younger patients early after closure that recovers entirely and the function is restored within 3 months, LVEDVI, LVESVI, FS and LVEF can be used as indictors to predict left ventricular systolic dysfunction after trans catheter closure of PDA and After PDA closure, worse LV diastolic function in individuals with post closure LV systolic dysfunction which showing improvement on follow up; however, the improvement in LV diastolic function lagged behind the improvement in LV systolic performance.

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Tables:

Table (I): The research patient's demographic characteristics

	Study population (n = 20)	
	N	%
Sex		
Male		
n (%)	4	20%
Female		
n (%)	16	80%
Age (months)		
Mean ± SD.	68.3 ± 55. 5	
Range (Min-Max)	17 - 204	

SD: standard deviation

Table (II): assessment of LV systolic function by 2D ECHO and 3D ECHO in all studied patients

		LV systolic function (2D echo)			F	P-value
		Before closure (n = 20)	Within 24H of closure (n = 20)	After 3 months of closure (n = 20)		
LAD (mm)	Mean	25.8	23.9	22.4	3.6	0.033 S
	±SD	4.1	4.0	4.1		
AoD (mm)	Mean	19.9	19.2	19.2	0.2	0.816 NS
	±SD	4.0	3.7	3.4		
LAD/AoD	Mean	1.3	1.3	1.2	5.3	0.007 S
	±SD	0.2	0.1	0.1		
LVEDd (mm)	Mean	40.4	36.9	35.2	4.6	0.014 S
	±SD	5.4	5.6	5.5		
LVEDs (mm)	Mean	25.8	25.2	22.5	4.2	0.018 S
	±SD	3.8	4.0	3.6		
LVEDVI (ml/m^2)	Mean	97.2	77.3	71.3	7.06	0.002 S
	±SD	28.8	20.2	17.8		
LVESVI (ml/m^2)	Mean	33.3	31.2	24.0	4.2	0.02 S
	±SD	12.3	11.3	7.6		
FS (%)	Mean	36.2	31.9	36.1	6.4	0.003 S
	±SD	4.0	5.4	3.5		
LVEF (%)	Mean	65.9	59.6	66.7	8.02	0.001 S
	±SD	5.4	7.9	4.7		
	LV systolic function (3D echo)					
		Before closure (n = 20)	Within 24H of closure (n = 20)	After 3 months of closure (n = 20)		

LVEDVI (ml/m^2)	Mean	97.9	78.2	71.5	7.2	0.002 S
	±SD	29.1	19.8	17.9		
LVESVI (ml/m^2)	Mean	33.8	32.0	23.8	5.6	0.006 S
	±SD	11.9	10.9	6.6		
LVEF %	Mean	65.4	59.1	66.7	10.1	< 0.001 HS
	±SD	4.9	7.6	4.0		

S: p-value < 0.05 is considered non-significant. HS: p-value < 0.001 is considered highly significant. NS: p-value > 0.05 is considered non-significant .F: F value of ANOVA test. LV: left ventricle. LAD: left anterior descending artery. AoD: aortic root diameter. LVEDd: Left Ventricular End Diastolic Diameter. LVEDVI: Left Ventricular End-Diastolic Volume Index. LVESVI: Left Ventricular End-Systolic Volume Index. FS: Fractional shortening. LVEF: Left Ventricular Ejection Fraction

Table (III): assessment of LV systolic function by 2D ECHO in patients with post closure LV systolic dysfunction.

		LV systolic function in patients with LV systolic dysfunction after closure(2D)			F	P-value
		Before closure (n = 9)	Within 24H of closure (n = 9)	After 3 months of closure (n = 9)		
LAD (mm)	Mean	26.3	23.8	21.8	2.05	0.150 NS
	±SD	4.7	4.7	4.9		
AoD (mm)	Mean	18.4	18.2	18.4	0.01	0.991 NS
	±SD	4.2	4.1	3.5		
LAD/AoD	Mean	1.4	1.3	1.2	11.9	< 0.001 HS
	±SD	0.1	0.1	0.1		
LVEDd (mm)	Mean	40.7	35.8	33.7	9.1	0.001 S
	±SD	4.0	3.6	3.0		
LVEDs (mm)	Mean	26.9	26.1	22.3	10.5	0.001 S
	±SD	2.2	2.6	1.9		
LVEDVI (ml/m^2)	Mean	114.4	83.9	75.5	6.2	0.007 S
	±SD	30.7	22.8	18.9		
LVESVI (ml/m^2)	Mean	42.9	39.6	28.1	5.6	0.01 S
	±SD	11.0	10.5	7.8		
FS (%)	Mean	33.2	27.0	33.7	15.4	< 0.001 HS
	±SD	2.9	2.7	2.9		
LVEF (%)	Mean	62.0	52.2	63.4	21.9	< 0.001 HS
	±SD	4.2	3.7	3.8		

S: p-value < 0.05 is considered non-significant. HS: p-value < 0.001 is considered highly significant. NS: p-value > 0.05 is considered non-significant. F: F value of ANOVA test. LV: left ventricle. LAD: left anterior descending artery. AoD: aortic root diameter. LVEDd: Left Ventricular End Diastolic Diameter. LVEDVI: Left Ventricular End-Diastolic Volume Index. LVESVI: Left Ventricular End-Systolic Volume Index. FS: Fractional shortening. LVEF: Left Ventricular Ejection Fraction

Table (IV): assessment of LV systolic function by 3D ECHO in patients with post closure LV systolic dysfunction

		LV systolic function in patients with LV systolic dysfunction after closure(3D)			F	P-value
		Before closure (n = 9)	Within 24H of closure (n = 9)	After 3 months of closure (n = 9)		
LVEDVI (ml/m^2)	Mean	115.8	85.2	76.8	6.6	0.005 S
	±SD	29.6	22.1	18.6		
LVESVI (ml/m^2)	Mean	42.9	40.6	27.0	7.8	0.002 S
	±SD	11.2	9.8	5.7		
LVEF %	Mean	62.3	52.0	64.4	25.7	< 0.001 HS
	±SD	3.8	4.3	3.6		

S: p-value < 0.05 is considered non-significant. HS: p-value < 0.001 is considered highly significant. NS: p-value > 0.05 is considered non-significant. F: F value of ANOVA test. LV: left ventricle. LVEDVI: Left Ventricular End-Diastolic Volume Index. LVESVI: Left Ventricular End-Systolic Volume Index. LVEF: Left Ventricular Ejection Fraction.

Table (V): echo parameters that can be used as predictors of post closure LV systolic dysfunction (ROC curve (Receiver Operating Characteristic Curve) was used to detect cutoff value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
LAD/AoD	> 1.31	0.93	88.9%	81.8%	83%	88.1%	0.001
LVEDVI	> 102.7	0.81	66.7%	90.9%	88%	73.2%	0.018
LVESVI	> 33.8	0.92	77.8%	90.9%	89.5%	80.4%	0.001
FS	< 36.5	0.91	88.9%	81.8%	83%	88.1%	0.001
LVEF	< 67.5	0.9	88.9%	72.7%	76.5%	86.8%	0.002
LVEDVI 3D	> 114.6	0.84	55.6%	90.9%	85.9%	67.2%	0.008
LVESVI 3D	> 33.3	0.92	77.8%	90.9%	89.5%	80.4%	0.001
LVEF 3D	< 67	0.85	88.9%	72.7%	76.5%	86.8%	0.007

PPV: positive predictive value. AUC: Area under curve. NPV: negative predictive value. LV: left ventricle. LAD: left anterior descending artery. AoD: aortic root diameter. LVEDVI: Left Ventricular End-Diastolic Volume Index. LVESVI: Left Ventricular End-Systolic Volume Index. FS: Fractional shortening. LVEF: Left Ventricular Ejection Fraction.

Table (VI): assessment of LV diastolic function in patients with post closure LV systolic dysfunction

		LV diastolic function in patients with LV systolic dysfunction after closure(2D)			F	P-value
		Before closure (n = 9)	Within 24H of closure (n = 9)	After 3 months of closure (n = 9)		
E (cm/s)	Mean	127.7	115.8	115.8	2.8	0.079 NS
	±SD	7.9	11.5	16.0		
A (cm/s)	Mean	99.6	84.8	76.6	3.5	0.044 S
	±SD	23.4	15.3	15.5		
E/A	Mean	1.3	1.4	1.5	1.3	0.290 NS
	±SD	0.3	0.2	0.2		
EDT (m/s)	Mean	182.2	179.4	176.8	1.69	0.204 NS
	±SD	5.8	6.4	6.6		
Mitral E TVI (cm)	Mean	16.4	16.3	16.0	1.47	0.250 NS
	±SD	0.5	0.5	0.6		
Mitral A TVI (cm)	Mean	7.4	7.2	5.3	6.2	0.006 S
	±SD	1.6	1.6	1.0		
E TVI / A TVI	Mean	2.3	2.3	3.1	10	0.001 S
	±SD	0.4	0.3	0.6		
Mitral E´ (medial)	Mean	8.9	9.1	9.1	0.027	0.973 NS
	±SD	2.0	1.9	1.9		
Mitral E´ (lateral)	Mean	10.2	9.9	9.7	0.24	0.783 NS
	±SD	1.7	1.8	1.4		
Medial E/E´	Mean	14.8	13.2	13.2	0.97	0.390 NS
	±SD	2.4	2.7	3.0		
Lateral E/E´	Mean	12.8	12.1	12.3	0.21	0.810 NS
	±SD	1.8	2.3	2.5		

S: p-value < 0.05 is considered non-significant. HS: p-value < 0.001 is considered highly significant. NS: p-value > 0.05 is considered non-significant. F: F value of ANOVA test. LV: left ventricle. EDT: E-wave Deceleration Time. TVI: Time-velocity Integral. E/A: early to atrial filling velocity ratio. E/e': early mitral inflow velocity to early diastolic mitral annulus velocity ratio