European Society of Medicine

ESMED
European Society of Medicine

OPEN ACCESS

Published: August 31, 2023

**Citation:** T Karim, MT Islam, et al., 2023. Correlation of Ductal size with Left Ventricular Systolic Function Changes by Echocardiography in Children after Transcatheter Closure of Patent Ductus Arteriosus in a Tertiary Care Hospital., Medical Research Archives, [online] 11(8). https://doi.org/10.18103/mra.v11i8.4253



DOI
https://doi.org/10.18103/mra.v11i8.4253

ISSN: 2375-1924

RESEARCH ARTICLE

# Correlation of Ductal size with Left Ventricular Systolic Function Changes by Echocardiography in Children after Transcatheter Closure of Patent Ductus Arteriosus in a Tertiary Care Hospital

**Karim T[1], Islam MT[2], Yadav P[3]**

1. Dr. Tahmina Karim, Associate Professor, Paediatric Cardiology, BSMMU, Shahbag, Dhaka, Bangladesh
2. Dr. Md. Tariqul Islam, Professor, Paediatric Cardiology, BSMMU, Shahbag, Dhaka, Bangladesh
3. Dr. Pratima Yadav, Resident medical officer, Paediatric Cardiology, BSMMU, Shahbag, Dhaka, Bangladesh

Contribution:
1. Article theme and data collection and write up - Dr. Tahmina Karim
2. Reviewed by - Professor Dr. Md. Tariqul Islam
3. Data analysis by- Dr. Pratima Yadav

***Correspondence author:** dr.tkarim@yahoo.com

ABSTRACT:
***Background**:* Transcatheter closure of Patent Ductus Arteriosus (PDA) is considered an excellent treatment option for children requiring PDA closure due to its low morbidity and mortality rates. Theoretically, after PDA closure, there should be a gradual improvement in left ventricular volume overload and remodeling. However, numerous studies have shown that there is a temporary decline in left ventricular function immediately following PDA closure.
***Objectives**:* To see the correlation of ductal size with changes in left ventricular systolic function by echocardiography in children undergoing transcatheter closure of PDA.
***Materials and methods**:* It was a cross sectional study. All pediatric inpatients ≥6 months of age, diagnosed as a case of PDA and planned for device closure were enrolled in the study. M-Mode, 2D, Color Doppler and 2D speckle tracking echocardiography was done by GE Echo machine Model VividS70N using probes 5MHz (5s) and 6MHz(6s). Electrocardiogram (ECG ) gated echo was done at base line (prior to closure of PDA), after 24 hour post closure and after 1 month post closure, in order to evaluate the immediate and short term changes in left ventricular systolic function from the baseline, using the following parameters: Left Ventricular Ejection Fraction (LVEF) and Left Ventricular Fractional Shortening (LVFS). The total sample size was 35. Data were collected on a pre-tested questionnaire. Data analysis was carried out by using the SPSS version 22.0 windows software. Continuous data were expressed as mean ±SD and analyzed by paired t-test. Categorical data were expressed as frequency and percentages. Correlation was seen using Pearson's correlation. P-value < 0.05 was considered statistically significant.
***Results**:* The mean age of the study subjects was 46.69 ± 41.8 months with mean body surface area of 0.56 ±0.25m² (0.32-1.3). Females were predominant with 74.3% and males were 25.7%. The mean PDA size was 3.35 ± 0.77mm and the LA: Aorta ratio was 1.45 ± 0.24. The LVEF, LVFS were reduced from 70.11±3.81 to 57.34±5.0, 39.28±3.14 to 32.0±4.54 respectively 24hours after device closure. This reduction of LVEF, LVFS were statistically significant (p<0.01). At 1 month post device follow up all the parameters returned to near baseline level. PDA size was found to be negatively correlated with early changes in left ventricular functions i.e. larger the PDA size, greater is the reduction in LV function post PDA device.
***Conclusions**:* Transcatheter closure of PDA can lead to transient reduction in left ventricular systolic function which improves gradually after a month; however, close monitoring is required. Larger the PDA size, greater is the reduction in LV function. As such moderate to large PDAs should be followed up more cautiously and immediate timely intervention is needed, if severe deterioration is found.
**Keywords***:* Patent ductus arteriosus, Transcatheter closure, Left ventricular systolic function

**Introduction:**

The ductus arteriosus is a normal fetal structure that developed by sixth week of gestation from 6th brachial arch. It maintains the communication between the aorta and pulmonary arteries. [1]

During intrauterine life, 10% of the cardiac output passes through the lungs. The remaining 90% is shunted via the ductus arteriosus to the aorta and systemic circulation. After birth, most of the right ventricular output should pass through the lungs to facilitate proper gas exchange. In order to make this possible, the ductus undergo constriction and functional closure soon after birth in term neonates. 80% of the ductus arteriosus in term infants closes in 48hours and nearly 100% by 96 hours. Failure of this normal closure results in problem in pre-term neonates [2] While ductus constriction usually leads to functional and anatomic closure, in some cases the ductus may close only or not at all.

Patent ductus arteriosus (PDA) is a common congenital heart defect resulting from the failure of the fetal ductus to close normally. It is estimated that isolated PDA occurs in approximately 0.05% of all live births, accounting for 5% to 10% of congenital heart defects[3]

The classification of PDA is based on the size of the internal ductal diameter in the lateral angiographic view, ranging from silent (less than 1 mm) to large (more than 5 mm).[4]

Clinical presentations vary depending on the size of the PDA, with small PDAs often being asymptomatic and large PDAs leading to heart failure and growth retardation.[5]

The hemodynamic impact of PDA is primarily determined by the degree of shunting.[5] Hemodynamically significant left-to-right shunting through the PDA causes pulmonary over-circulation, resulting in left ventricular volume overload and remodeling.[5] Over time, this high-pressure, large volume shunt can lead to irreversible pulmonary vascular obstructive disease.

The presentation of PDA depends upon patient age and size of the defect. Infants with moderate to large PDA may present with symptoms of CHD, including poor feeding with failure to thrive, tachypnea and diaphoresis, within few weeks of life as left to right shunt increases with the falling PVR.

The diagnosis of PDA is typically made based on clinical findings and confirmed by transthoracic echocardiography (TTE), which is the primary imaging modality. Color Doppler is highly sensitive in detecting the presence of PDA and assessing the degree of ductal shunting. Various echocardiographic techniques, including M-mode, two-dimensional (2D) echocardiography, and speckle tracking echocardiography for myocardial deformation imaging, can provide quantitative information about left ventricular function.[6] 2D biplane Simpson's method is recommended for estimation of LV volumes and ejection fraction. On the other hand, myocardial strain is a principle for quantification of left ventricular (LV) function which is now feasible with speckle tracking echocardiography.

Treatment options for PDA include surgical and transcatheter closure.[5,7,8] Regardless of age, closure is necessary to prevent bacterial endarteritis in patients with small PDAs and to manage congestive heart failure and pulmonary vascular disease in those with large PDAs.[9]

Compared to transcatheter closure, surgical ligation of PDA has disadvantages such as a higher risk of complications including bleeding, the need for general anesthesia and intubation, longer hospital stays, higher costs, and requiring a highly skilled and larger surgical team[10,11]

Transcatheter closure has emerged as the preferred treatment option for PDA since the first successful experience of transcatheter occlusion by Porstmann in 1971. It has a high closure rate exceeding 90-95%, which has improved over time due to device modifications, advancements in techniques, and increased operator expertise.[7,12] Serious complications following transcatheter PDA closure, such as embolization, infection, and vascular access thrombosis are rare.[13,14] The Amplatzer duct occluder is a widely accepted device for PDA occlusion due to its safety and effectiveness.[15]

Theoretically, PDA closure is expected to gradually improve left ventricular volume overload and remodeling.[16,17] However, several studies on children undergoing transcatheter device closure have reported an immediate decline in left ventricular performance.[9,18]

Moreover, limited studies have explored the alteration in LV hemodynamics, especially diastolic function, following transcatheter closure of PDA in pediatric population and the correlation between PDA size and post closure early changes in LV function. These forming the basis of this study.

The results obtained will give an idea about opting for timely intervention as and when necessary, after clinical correlation.

Furthermore, it will also prompt clinicians to be more cautious when dealing with follow up of PDA device closure.

*Objectives of the study:*

*General Objective:*

- To determine the immediate and short-term changes in Left ventricular systolic function in children undergoing transcatheter closure of Patent ductus arteriosus.

*Specific Objectives:*

- To see the baseline left ventricular systolic function in children with PDA prior to transcatheter closure.
- To see the immediate (after 24hours) and short term (1 months) after echocardiographic changes in LV systolic function in children after transcatheter closure of patent ductus arteriosus.
- To see the correlation of ductal size with LV functional changes.

**Materials and Methods**

*Study population:*

This cross-sectional study was conducted in Department of Pediatric Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka from November, 2019 to October, 2020. A total of 35 Pediatric inpatients ≥ 6months of age, admitted in the Department of Pediatric Cardiology, BSMMU for transcatheter closure of PDA were selected by consecutive purposive sampling. Written informed consent was obtained from the parents of study subjects after proper explanation.

Selection of patients:

Inclusion criteria: All pediatric patients≥6months of age with hemodynamically significant PDA causing left ventricular volume overload (left atrial to aortic diameter ratio in long axis transthoracic echocardiography >1.2:1 and exclusive left to right blood shunt through PDA) undergoing transcatheter device closure were enrolled in the study.

*Exclusion criteria:*

- Patients having other associated congenital heart disease like ASD, VSD, PS, CoA, etc.
- Patients not suitable for transcatheter closure, PVR > 8wU/m2, or anatomy other than Krichenko type A and B,
- Critically ill patients.
- Parents unwilling to enroll their child in the study were excluded from the study.

Study Procedure:

All pediatric inpatients ≥6 months of age who got admitted in department of Pediatric Cardiology following inclusion and exclusion criteria were included in the study. Meticulous history taking and clinical examination was done. CBC, CRP, blood grouping, serum ALT, serum creatinine, chest x-ray, ECG, HBsAg, VDRL, PT, APTT, BT, CT were done as part of routine pre-procedure investigation.

*Echocardiography:*

ECG gated echocardiography was done with GE Echo machine Model VividS70N after sedation by oral Chloral hydrate (50mg/kg), as prescribed by the pediatric cardiologist for some patients as per need. Patients were examined in supine and lateral positions. All standard echocardiographic views: apical 4 chamber and 5 chamber, parasternal long axis and short axis, ductal view and suprasternal views, subcostal, were recorded in all patients. Probes 5Hz (5s) and 6MHz (6s) were used. M-mode, 2D, Color Doppler were the echo modalities used. The PDA was visualized and measured in high left parasternal short axis and suprasternal views by 2D echo and confirmed by Color Doppler. M-Mode was used to obtain the LA: Aorta ratio and fractional shortening in parasternal long axis view, measured in systole. LVEF was computed automatically from LV end-diastolic and end-systolic volumes according to the Simpson's modified biplane method in apical 4 and 2 chamber views.

Echocardiography was done in single machine by single pediatric cardiologist and measurements were taken in 3 cardiac cycles to avoid intra observer variability and recorded at baseline.

Cardiac Catherization:

Suitable patients underwent transcatheter device closure using dissociative anesthesia with ketamine. The procedure involved cardiac catheterization through the femoral route. Heparin was administered to prevent coagulation after vascular access, with a dosage of 100 units/kg. Various catheters, including NIH, Pigtail, RCA, and multipurpose catheters, were utilized. Angiographic assessment was performed by crossing the PDA and positioning the catheter in the descending thoracic aorta. Standard lateral view angiograms were taken to determine PDA size, while the right anterior oblique (RAO) view provided better visualization of the PDA. Following sizing, skilled pediatric cardiologists closed the PDA using a ductal occluder device (Amplatzer type). Successful deployment of the device was confirmed with a repeat angiogram to assess device positioning and identify any residual leakage. After 24 hours, repeat echocardiography was conducted to evaluate immediate changes in left ventricular systolic function compared to baseline. Patients were discharged on Day 7, in accordance with institutional protocol, after completing the antibiotic course. Follow-up appointments were scheduled for 1 month after PDA device closure to reassess echocardiographic changes in left ventricular function and compare them to baseline findings.

*Statistical analysis*

Data analysis was carried out by using the Statistical Package for Social Science (SPSS) version 22.0 windows software. Continuous data were expressed as mean ±SD and analyzed by paired t-test. Categorical data were expressed as frequency and percentages. Correlation was seen using Pearson's correlation. P-value < 0.05 was considered statistically significant

**Results:**

A total of 35 patients were selected for the study.

**Demographics**

The mean age of the study subjects was 46.69±41.8 months (7-156 months). The anthropometric measurements revealed mean BSA was 0.56±0.25m² (range-0.32-1.3), with the mean weight being 12.9±7.28kg (6-36kg) and height 94.2 ±19.7cm (65-154cm)(Table 1).

**Table-I: Distribution of study subjects based on anthropometric characteristics (N=35)**

| Variables | Mean ±SD | Range |
|---|---|---|
| **Age (months)** | **46.69 ± 41.8** | **7-156** |
| **Weight (kg)** | **12.91 ± 7.28** | **6-36** |
| **Height (cm)** | **94.20 ±19.79** | **65-154** |
| **Body surface area (m²)** | **0.56 ±0.25** | **0.32-1.3** |

The study population had female predominance with 26 (74.3%). Males were 9 (25.7%) (Fig 1)

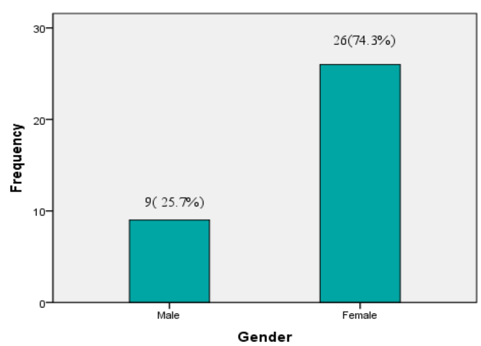


**Fig 1:** Bar diagram showing distribution of study subjects based on gender.

Clinical parameters showed that the most common presenting complaints in this study group was recurrent RTI (100%), followed by dyspnea (94.3%) and history of poor feeding with suck pause suck cycle (54.3%).

**Table-II: Distribution of study participants based on presenting complaints (N=35)**

| Variables | Frequency | Percentage (%) |
|---|---|---|
| History of suck pause suck cycles | 19 | (54.3) |
| History of poor feeding | 18 | (51.4) |
| History of recurrent RTI | 35 | (100) |
| Dyspnea (Ross classification) | | |
| Class –I | 33 | (94.3) |
| Class- II | 2 | (5.7) |
| Class –III | 0 | 0 |

**Table-III: Echocardiographic parameters of study subjects at baseline (N=35)**

| Variables | Mean ±SD | Range |
|---|---|---|
| Ductal size (mm) | 3.35 ± 0.77 | 2-5.4 |
| LA: Aorta ratio | 1.45 ± 0.24 | 1.23-2.18 |
| LV Systolic function | | |
| LVEF (%) | 70.48±4.79 | 61-77 |
| LVFS (%) | 39.74±3.76 | 34-46 |

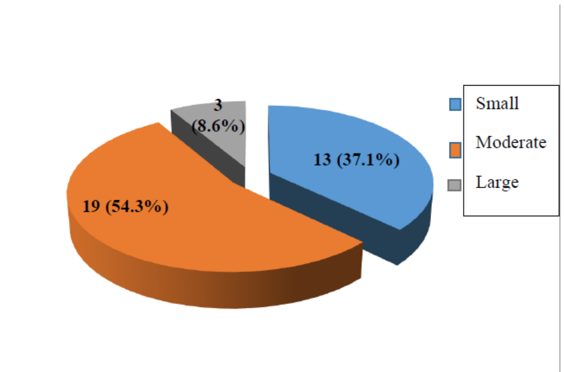


**Figure-2: Pie chart showing distribution of study subjects based on size of PDA**The figure 2 represents most of the patients had moderate size PDA i.e. 54.3%, 37.15% had small size and 8.6% had large size PDA

**Table-IV: Echocardiographic parameters of left ventricular systolic function before and after PDA device closure at 24 hours and 1 month (N=35)**

| LV systolic function parameters | Before closure | 24hours after closure | $p^a$ | 1month after closure | $p^b$ |
|---|---|---|---|---|---|
| | Mean ±SD | | | Mean ±SD | |
| LVEF (%) | 70.11±3.81 | 57.34±5.0 | <0.001$^s$ | 68.26±6.78 | 0.139$^{ns}$ |
| LVFS (%) | 39.28±3.14 | 32.0±4.54 | <0.001$^s$ | 38.91±3.91 | 0.662$^{ns}$ |

In the study, after 24 hours of device closure, LVEF, LVFS were significantly reduced from 70.11±3.81 to 57.34±5.0, 39.28±3.14 to 32.0±4.54 respectively (p<0.01). At 1 month post device follow up all the parameters returned to near baseline level.

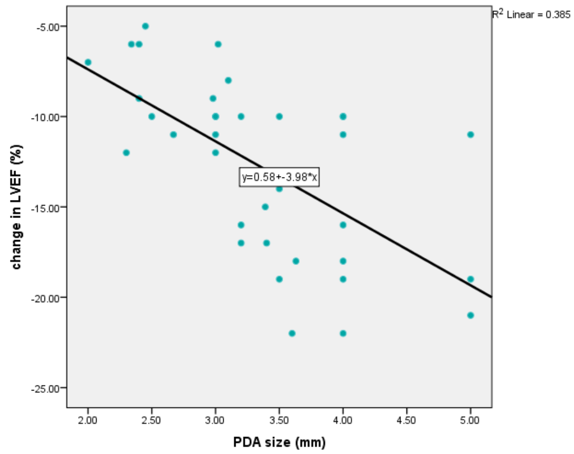


**Figure-3:** Scatter plot diagram showing correlation between ductal size with early changes in LVEF (early post closure LVEF-pre closure LVEF).

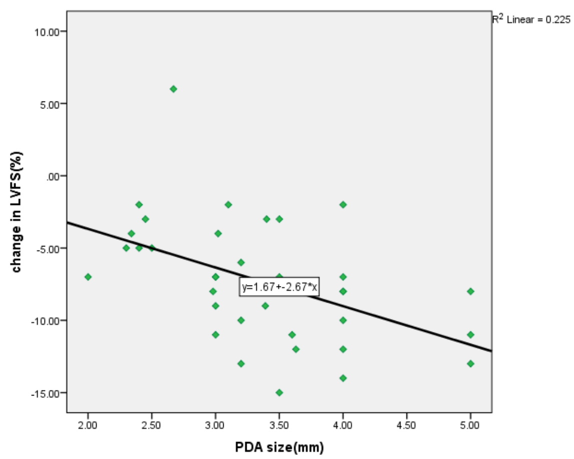


**Figure-4:** Scatter plot diagram showing correlation between ductal size with early changes in LVFS (early post closure LVFS-pre closure LVFS)

PDA size was found to be strongly negatively correlated with early changes in LVEF and LVFS as shown in Fig 3 and 4, i.e. larger the PDA, greater the reduction in LVEF and LVFS.

**Discussion:**

Our study aimed to find out if echocardiographic changes occur in LV function after transcatheter closure of PDA and to investigate the correlation between PDA size and changes in left ventricular systolic function as assessed by echocardiography after transcatheter closure of PDA.

The mean age of the study subjects was 46.69± 41.8 months (7- 154 months) with majority of the patient being female 26(74%). Male comprised 25.7% Of the total study population. The exact reason of female preponderance is not clear, but the phenomenon was observed that female are more commonly affected by PDA than males, by ratio of around 2:1 [19]

The anthropometric measurements revealed mean BSA was 0.56±0.25 $m^2$ (range 0.32 to 1.3), with the mean weight being 12 .9±7.28kg (6-36kg) and height 94.2± 19.7cm(65-159cm). These parameters were similar to the characteristics of the patients in the study conducted by Indian researcher [9] Clinical parameters showed that the most common presenting complaints in this study group was recurrent RTI (100%), followed by dyspnea (94.3%) and history of poor feeding with suck pause suck cycle (54.3%). This observation reflects that clinical history of patient with hemodynamically significant PDA invariably have features of failure to thrive, poor feeding, dyspnea depending on the ductal size and quantity of left to right shunt (Schneider and Moore 2006). The mean ductal size at pulmonary end was 3.35±0.77mm(2-5.4mm). Most of the patient ,54.3% in this study had moderate PDA and only large PDA which was similar to study conducted in Indian population [9]

In this study, we observed a significant reduction in ejection fraction (LVEF) and fractional shortening (LVFS) immediately after PDA closure ($p<0.001$), which improved after 1 month. The assessment of left ventricular systolic function at the 1-month follow-up showed no significant difference compared to the pre-closure status ($p>0.05$). These findings are consistent with previous studies conducted in children.[9,20,21]

The observed immediate reduction in LVEF and LVFS can be explained by the association of PDA with left-to-right shunting, which increases left ventricular preload. According to Frank-Starling's Law, increased preload leads to enhanced contractility (SF and EF). However, PDA closure results in a sudden decrease in left ventricular preload, resulting in decreased systolic performance. Another possible explanation for this observation is the sudden increase in afterload due to the termination of blood flow through the PDA and the transition from low-resistance pulmonary circulation, which contributes to systolic dysfunction.[9,21]

Additionally, our study demonstrated a negative correlation between PDA size and changes in left ventricular systolic function, indicating that larger PDA size is associated with greater deterioration of LV function. This finding is consistent with studies conducted among the Egyptian, Iranian, and Saudi Arabian pediatric populations, which have shown that PDA size can serve as a useful predictor for early reduction of LV function following closure.[12,14,17]

Overall, our findings contribute to the existing body of knowledge on the impact of PDA closure on left ventricular systolic function, emphasizing the importance of considering PDA size in assessing post-closure outcomes. However, further research with a larger sample size and diverse populations is warranted to confirm and expand upon these findings.

However, correlation of ductal size with diastolic function was not analyzed separately in any of the studies. Hence, the present study provides a basis for research in this area.

**Conclusion:**

In conclusion, our study revealed a transient reduction in left ventricular systolic function following PDA closure, with subsequent recovery towards baseline levels within one month. The findings also support the notion that larger PDA size is associated with a greater decline in LV function. However, given the limitations of our study, including its single-center nature and relatively short follow-up period, further investigation involving longer-term and multi-center studies with more extensive monitoring is warranted. Such studies will provide a more comprehensive understanding of the impact of PDA closure on left ventricular function and help guide clinical decision-making.

**Limitation:**

Shorter duration of follow up Single center study

Difficulties in the visualization of certain parts of the left heart because of restricted acoustic windows and challenges in the quantitative assessment of left ventricle function.

**Conflict of interest:**

Authors declare no conflict of interest.

**References**


1. Finenemore. A, Grove. A. Year. Physiology of the fetal and transitional circulation. In: Seminars in fetal and neonatal medicine, 2015.Elsevier :210-216.
2. Agarwal, R. Deorari, A.K, Paul, V.K. Patent ductus arteriosus in preterm neonates. The Indian Journal of pediatrics. 2008, 75(3), pp. 277-280.
3. Fortescue E.B, Lock J.E, Galvin T, McElhinney D.B. To close or not to close: the very small patent ductus arteriosus. Congenital heart disease. 2010 Jul;5(4):354-65.
4. Arora. R, Vijaylakshmi .IB. Rao P.S, Chugh R. A, Patent ductus arteriosus. Comprehensive Approach to Congenital Heart Diseases. New Delhi, India: Jaypee Brothers Medical Publishers. 2013 Feb: 28:307-1.
5. Schneider D.J, The patent ductus arteriosus in term infants, children, and adults. In Seminars in perinatology 2012 Apr; 36(2):146-153.
6. Dragulescu. A, Mertens L.L, Developments in echocardiographic techniques for the evaluation of ventricular function in children. Archives of cardiovascular diseases. 2010 Nov 1;103(11-12):603-14.
7. Kori M.I, Hemodynamic Effect of Patent Ductus Asteriosus (PDA) (Doctoral dissertation, University Teknologi Malaysia). 2015: 56.
8. Clyman R.I, Couto J, Murphy G.M, Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? In: Seminars in perinatology 2012 Apr;36(2):123-129.
9. Gupta S.K, Krishnamoorthy K.M, Tharakan JA, Sivasankaran S, Sanjay G, Bijulal S, Anees T. Percutaneous closure of patent ductus arteriosus in children: Immediate and short-term changes in left ventricular systolic and diastolic function. Annals of pediatric cardiology. 2011 Jul;4(2):139.
10. Zulqarnain A, Younas M, Waqar T, Beg A, Asma T, Baig M.A. Comparison of effectiveness and cost of patent ductus arteriosus device occlusion versus surgical ligation of patent ductus arteriosus. Pakistan Journal of Medical Sciences. 2016 Jul;32(4):974.
11. Animasahun B.A, Adekunle M.O, Falase O, Gidado M.T, Kusimo O.Y, Sanusi M.O, Johnson A. Is transcatheter closure superior to surgical ligation of patent ductus arteriosus among Nigerian Children? African Journal of Paediatric Surgery: AJPS. 2018 Apr;15(2):100.
12. Ali S, El Sisi A. Transcatheter closure of patent ductus arteriosus in children weighing 10 kg or less: Initial experience at Sohag University Hospital. Journal of the Saudi Heart Association. 2016 Apr 1;28(2):95-100.
13. Masura J, Tittel P, Gavora P, Podnar T. Long-term outcome of transcatheter patent ductus arteriosus closure using Amplatzer duct occluders. American heart journal. 2006 Mar 1;151(3):755-e7.
14. Elmarsafawy H, Matter M, Abo-Haded H.M, Rakha S, Hafez M.M, Alsawah G.A, Abuelkheir M.M. Transcatheter closure of patent ductus arteriosus, evaluating the outcome: single center experience in Mansoura, Egypt. Progress in Pediatric Cardiology. 2019 Mar 1; 52:33-8
15. Baruteau A.E, Hascoët S, Baruteau J, Boudjemline Y, Lambert V, Angel C.Y, Belli E, Petit J, Pass R. Transcatheter closure of patent ductus arteriosus: past, present and future. Archives of cardiovascular diseases. 2014 Feb 1;107(2):122-32.
16. Agouba R, Alghamdi M.H, Alhabshan F. Left ventricular dysfunction after patent ductus arteriosus (PDA) closure. Journal of the Saudi Heart Association. 2015 Oct 1;27(4):311-2.
17. Agha H.M, Hamza H.S, Kotby A, Ganzoury M.E, Soliman N. Predictors of transient left ventricular dysfunction following transcatheter patent ductus arteriosus closure in pediatric age. Journal of the Saudi Heart Association. 2017 Oct 1;29(4):244-51.
18. Tilahun B, Tefera E. Transient left ventricular systolic dysfunction following surgical closure of large patent ductus arteriosus among children and adolescents operated at the cardiac centre, Ethiopia. Journal of cardiothoracic surgery. 2013 Dec;8(1):1-5.
19. Schneider, D.J Year. Moore, J.W. Patent ductus arteriosus. Circulation.2006 ,114(17):1873-1882.
20. Amoogzar H, Shakiba A.M, Derakhshan D, Ajami G, Cheriki S, Borzouee M, Edraki M.R, Mehdizadegan N. Evaluation of left ventricular function by tissue Doppler and speckle-derived strain rate echocardiography after percutaneous ductus closure. Pediatr Cardiol. 2015 Jan;36(1):219-25
21. Kim Y.H, Choi H.J, Cho Y, Lee S.B, Hyun M.C. Transient left ventricular dysfunction after percutaneous patent ductus arteriosus closure in children. Korean Circulation Journal. 2008 Nov 1;38(11):596-600.