Aortic stiffness index and its association with cardiovascular functions in children before and after transcatheter closure of PDA

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ABSTRACT

Background: Patent ductus arteriosus is generally associated with hyperdynamic status. Given the vascular shunt between the aorta and pulmonary artery, intrinsic aortic changes occur (aortic stiffness). In the present study, we attempted to assess the impact of PDA on aortic stiffness and its connection with cardiovascular function before and after transcatheter closure of PDA.

Patient and methods: Our study consisted of 60 children who were preparing for transcatheter closure of PDA and 60 healthy controls. All patients had clinical and echocardiographic proof of hemodynamically significant PDA.

Results: Patients with PDA exhibited significantly higher ASI than controls before closure (p-value < 0.05). After closure, ASI was significantly reduced (p-value < 0.05), but still higher than that of controls (p-value < 0.05) at the six-month follow-up assessment. Patients with PDA had significantly lower LVEF than controls before closure (p-value < 0.05). After closure, LVEF was significantly enhanced (p-value < 0.05), and no significant difference was noted amongst patients and controls (p-value < 0.05) at the six-month follow-up assessment.

Conclusion: Aortic stiffness is significantly increased in patients with PDA regardless of PDA size. Aortic stiffness is related to reduced heart function. ASI may be valuable for observing the course of patients with PDA before and after intervention.

1. Introduction

Stiffening in the large blood vessel framework, for example, the aortic tree increases the risk of cardiovascular diseases in elderly individuals and is positively associated with systolic hypertension, coronary artery disease, stroke, heart failure and atrial fibrillation, which are the main sources of mortality in developed countries and the developing world, as evaluated in 2010 by the World Health Organization. Hence, better, less obtrusive but correct measures of aortic stiffness have been created that are helpful, such as analytic records, pathophysiological markers and predictive pointers of the disease.1

PDA is normally associated with hyperdynamic status. Given the presence of a vascular shunt between the aorta and pulmonary artery, intrinsic aortic changes occur (aortic stiffness). In addition, shunt injuries might be related to an inflammatory process, and endothelial dysfunction may increase the ageing of vessels, particularly the aorta (aortic stiffness).2

In the present study, we attempted to assess the impact of PDA on the aortic stiffness index and its association with cardiovascular functions in children before and after transcatheter closure of PDA.

2. Patients and methods

This study was conducted from June 2015 to June 2016 at Aswan Heart Center and Aswan University Hospital. Our study consisted of 60 children who planned to undergo transcatheter closure of PDA and 60 healthy control children. All patients had clinical and echocardiographic proof of hemodynamically significant PDA. Patients with silent PDA, PDA not reasonable for percuta-
neous closure, or irreversible pulmonary vascular disease (pulmonary vascular resistance index (PVRI) > 7 WU m²) and individuals who had related hemodynamically significant congenital heart disease or a critical residual shunt were excluded from the study.

Control subjects were analyzed once. Controls were asymptomatic and demonstrated no variations from the normal in clinical examination, ECG, or echocardiography.

All the patients were subjected to:

A- Clinical assessment and the following parameters were particularly evaluated (Arterial blood pressure, Body weight (BWT), Oxygen saturation and Functional class (FC)). Function class was assessed in infants with PDA by using modified Ross Classification for assessment of the severity of heart failure. But in older children functional class was assessed by using New York Heart Association (NYHA) classification.

B- transthoracic 2D echocardiography and tissue doppler imaging (TDI):

ECC-gated complete 2D echocardiographic and TDI study was performed with the patient in the supine position using Philips IE 33 with S8-3 and X5-1 MHz transducers on outpatient basis, at baseline before the procedure, and at six months follow-up; and the following parameters were assessed: left ventricular dimensions, volumes, systolic and diastolic function, PDA size and types, other associated congenital anomalies and pulmonary artery pressure.

LV systolic dysfunction was defined as left ventricular ejection fraction (LVEF) of <50% or reduction in LVEF ≥ 10% from the baseline.

For diastolic function analysis, the mitral inflow signal was obtained from apical four chamber view, the E wave (early mitral inflow) and A wave (late mitral inflow) were measured, and E/A ratio was calculated. Mitral annular septal diastolic velocities in early diastole (Ea) and late diastole (Aa) were obtained by TDI and E/Ea was calculated.

Anatomic properties of the ductus were surveyed for extent, smallest thickness near the pulmonary end, shape, PDA orientation, and vessel function on the aortic end. PDA size was measured at the pulmonary end in the parasternal short axis and ductal views.

C- Non-invasive evaluation of aortic stiffness:

After routine conventional echocardiography examination, patients were placed in a left mild recumbent position and the ascending aorta was recorded in the two-dimensional-guided M-mode tracings. The aortic diameter was recorded by M-mode echocardiogram at a level of 3 cm above the aortic valve. Aortic Systolic (AoS) diameter was measured at the time of full opening of the aortic Valve, and diastolic (AoD) diameter was measured at the peak of QRS complex of the electrocardiogram. Aortic stiffness index (ASI) was calculated from the following equation:

\[
ASI = \frac{(SBP/DBP)((AoSD - AoDD)/AoDD) \times 100.7
\]

D- BNP measurement:

All samples were collected by venipuncture into Ethylenediaminetetraacetic Acid (EDTA) tubes within two hours of obtaining the baseline echocardiogram for all children in the study and six months after device closure of PDA (for children with PDA only). The blood samples were kept at room temperature and analyzed within four hours of sampling. In some cases, the sample was centrifuged and the plasma was frozen for one to two days at 700 C. Before analysis, each tube was inverted several times to ensure homogeneity. The BNP assay was a sandwich immunoassay that consisted of a disposable device to which 250 mL of EDTA-anticoagulated whole blood or plasma was added. The Triage meter was used to measure BNP concentration by detecting a fluorescent signal that reflected the amount of BNP in the sample. The upper limit of the normal lab reference for BNP was 30 pg/ml.

E- Cardiac catheterization:

Cardiac catheterization was performed for assessment of pulmonary artery pressure and shunt quantification. Arterial and venous access was obtained during the study. PAH was defined as mean PA pressure >25 mmHg. Calculation of Qp/Qs was done to estimate the magnitude of the shunt using the following equation: 

\[
Qp/Qs = (pulmonary saturation – mixed venous saturation)/pulmonary saturation – PA saturation,
\]

Mixed venous saturation = (3 * SVC saturation + IVC saturation)/4. A Qp/Qs between 1 and 1.5 were considered a small left to right shunt. A Qp/Qs > 1.8 indicate a large left to right shunt, while Qp/Qs < 1 indicate a net right to left shunt. Angiographic assessment was performed by placing a pigtail catheter in the descending thoracic aorta. Angiograms were performed in standard lateral view for PDA sizing. In selected cases, right anterior oblique (RAO) view was used also for better visualization of PDA for insertion of Amplatzer duct occluder or coil in some cases with small PDA. The PDA was crossed from the pulmonary end in all patients. Amplatzer delivery sheath (AGA Medical, Plymouth, MN) was introduced from the venous route over Amplatzer super stiff guide wire (Boston Scientific, Natick, MA, USA) and was parked in the descending thoracic aorta. Device was delivered as per the standard technique described earlier. Aortogram was done at 10 min after the release to confirm device position and rule out residual shunt. After device deployment, echocardiographic assessment was performed for the device position, descending thoracic aortic and left pulmonary artery velocity. The ductal occluder device was released after excluding the significant residual shunt and obstruction in aorta and/or left pulmonary artery.

F- Follow up (clinically and by echocardiography)

All cases were followed at six months thereafter and the following parameters were assessed: FC, weight gain, Position of the device and residual shunt, Pulmonary artery pressure, LV systolic and diastolic function, Aortic stiffness and BNP.

3. Statistical analysis

Statistical analysis was performed using version 16.1 of the Statistical Package for Social Science version 16.01 for Windows (SPSS Inc., Chicago, IL). The correlation and association between aortic stiffness and different parameters were assessed.

4. Results

At the beginning of this investigation, the average age of PDA patients was 23.7 ± 34.6 months. All PDA patients experienced percutaneous closure by device or coil. In these patients, additional heart defects were not identified. All patients were followed up for a 6-month period. The average age of controls was 31.8 ± 34.4 months.

Before closure, patients with PDA exhibited significantly increased ASI compared with controls (p-value < 0.05), but the levels were significantly reduced (p-value < 0.05) after closure. These values were higher than those of the controls (p-value < 0.05) at the six-month follow-up assessment (Table 1).

Patients with PDA had significantly lower LVEF than controls before closure (p-value < 0.05). After closure, LVEF significantly improved (p-value < 0.05), and no significant difference was noted between patients and controls (p-value < 0.02) at the 6-month follow-up evaluation (Table 1).

A significant difference was noted between patients and controls with regard to LVEDD and LVESE before closure (p-value < 0.05). After closure, LVEDD was significantly reduced (p-value < 0.05) but remained slightly higher than that of controls (p-value < 0.05) at the six-month follow-up evaluation (Table 1).
Patients with PDA exhibited significant impairment in LV diastolic function compared with controls before closure (p-value < 0.05). After closure, LV diastolic function significantly improved (p-value < 0.05) but was still lower than that of controls (p-value = 0.007) at the 6-month follow-up evaluation (Table 1).

BNP levels were significantly higher in children with PDA than in controls before closure (p-value < 0.05). The levels decreased significantly six months after closure (p-value < 0.05) and became non-significant compared with those of the controls (p-value = 0.88) (Table 2).

PAP was significantly higher in children with PDA before closure (p-value < 0.05). After closure, PAP significantly decreased (p-value < 0.05) and ultimately became non-significant compared with controls (p-value = 0.67) (Table 2).

Patients with PDA had significantly lower functional class than controls before closure (p-value < 0.05). After closure, the functional class improved significantly (p-value < 0.05) but remained significantly lower than that of controls (p-value 0.01) at the 6-month follow-up (Table 2).

PDA size was positively correlated with ASI (r = 0.75), p-value < 0.001, (Fig. 1). Before PDA closure, ASI was negatively correlated with LVEF (r = 0.66), p-value < 0.0001, (Fig. 2) and positively correlated with LVDD before closure (r = 0.58), p-value < 0.0001, (Fig. 3). BNP (r = 0.303), p-value 0.01, (Fig. 4), E/Ea ratio (r = 0.50), p-value < 0.0001, (Fig. 5) and PAP (r = 0.68), p-value < 0.0001, (Fig. 6). ASI was positively correlated with the age at which PDA closure was done (r = 0.9457), p value < 0.0001, (Fig. 7).

5. Discussion

PDA alters the volume and weight of the left side of the heart and increases pulmonary vascular resistance. Thus, it is vital to have different strategies accessible for follow-up. In the present investigation, we attempted to assess the impact of PDA on aortic stiffness and its connection with heart function before and after transcatheter closure of PDA to be employed as a method for observing the course of PDA patients.

The hypothesis of this study is that the biophysical characteristics of the aorta are irregular in children with PDA, and elevated arterial stiffness is an additional factor that causes the advancement of late ventricular failure in these patients. Given that confirmation of PDA is typically connected with hyperdynamic status and the presence of a vascular shunt between the aorta and pulmonary arteries, essential aortic changes occur. In addition, shunt lesions might be related to increased inflammation, and endothelial cell dysfunction may quicken the ageing of vessels, particularly the aorta (aortic stiffness).

Pulmonary artery pressure, being an indicator of fluid accumulation, can be utilized as a marker of heart failure. In this study, we observed a significant reduction in pulmonary artery pressure following PDA closure. This finding is consistent with previous studies reporting a decrease in pulmonary artery pressure after PDA closure.

BNP plasma levels are associated with systolic right ventricle (RV) pressure in patients with volume overburden in the RV. BNP plasma levels are connected with right atrial and ventricular pressure in patients with various loading disorders and a wide range of ages.

Effects after the closure of a large PDA are mainly influenced by the age at repair and pre-operative pulmonary vascular disease. Ages is a crucial indicator of pulmonary vascular disease. In gen-

| Table 1 | Comparison between patients and controls as regard ASI and cardiac functions before and after PDA closure. |
|----------|-------------------------------------------------------------------------------------------------------------------|
| Variables | Patients with PDA (n = 60) | Controls (n = 60) | P | P* | p* |
|----------|----------|-----------------|---|---|---|
| ASI | Mean ± SD | 8.3 ± 2.7 | 4.3 ± 1.4 | 1.6 ± 0.74 | <0.05 | <0.05 | 0.05 |
| LVEF% | Mean ± SD | 59.4 ± 5.3 | 66 ± 4.2 | 66.7 ± 3.4 | <0.05 | <0.05 | 0.2 |
| LVDD mm | Mean ± SD | 3.4 ± 0.85 | 3 ± 0.82 | 2.8 ± 0.55 | <0.05 | <0.05 | 0.5 |
| LVESD (mm) | Mean ± SD | 2.2 ± 0.37 | 2.0 ± 0.32 | 1.9 ± 0.54 | <0.05 | <0.05 | 0.5 |
| E/Ea | Mean ± SD | 1.2 ± 1.9 | 6.9 ± 0.88 | 6.5 ± 1.06 | <0.05 | <0.05 | 0.007 |

P (Significance between patients before and after closure), P* (Significance between patients before closure and controls), p* (significance between patients after closure and controls), LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; E/Ea: the ratio of early mitral flow velocity to early mitral anular velocity.

| Table 2 | Comparison between patients and controls as regard BNP, PAP and FC before and after PDA closure. |
|----------|-----------------------------------------------------------------------------------------------------|
| Variables | Patients with PDA (n = 60) | Controls (n = 60) | P | P* | p* |
|----------|----------|-----------------|---|---|---|
| BNP | Mean ± SD | 59.6 ± 16.1 | 19.9 ± 5.5 | 19.8 ± 5.1 | <0.05 | <0.05 | 0.88 |
| PAP | Mean ± SD | 43.3 ± 7.3 | 23 ± 4.7 | 23.2 ± 5.1 | <0.05 | <0.05 | 0.67 |
| FC | Mean ± SD | 3.5 ± 0.5 | 1.1 ± 0.3 | 1.0 ± 0.0 | <0.05 | <0.05 | 0.01 |

P (Significance between patients before and after closure), P* (Significance between patients before closure and controls), FC: function class.
eral, patients less than one year of age will likely not exhibit irreversible PAH, and it is generally accepted that irreversible changes appear at one to two years of age. This hypothesis has a few restrictions on the pathogenesis of irreversible PAH, and its development is multifactorial and erratic.

Blount and Vogel demonstrated that a PDA may exhibit a greater impact on pulmonary blood flow than on a ventricular septal deformity and that irreversible pulmonary vascular alteration may occur in patients less than two years old. This finding is presumably the consequence of the high-pressure pulsatile...
Fig. 4. Correlation between ASI and BNP before PDA closure.

Fig. 5. Correlation between ASI and LV diastolic function.

Fig. 6. Correlation between ASI and PAP before PDA closure.
bloodstream transmitted from the aorta to the PA throughout the cardiovascular cycle in PDA.21

Note that a few patients with marginal hemodynamic information with PDA and PAH can worsen after PDA closure due to resistant pulmonary hypertension, advanced PVD and right heart failure after PDA closure. The patient's normal history is subsequently similar to primary or idiopathic PAH. These patients will recover if PDA is untreated. An examination to recognize who may benefit from PDA closure after a long period of PAH recession and who may exhibit exacerbation with progressive pulmonary vascular disease and right heart failure is not currently available.

Future research on the nature and degree of morphological changes in pulmonary vessels, individual variability, and connections with hereditary and epigenetic variables may provide some insight into this difficult issue. According to recent researches, the patient who does not experience benefits upon the closure of a large PDA may exhibit poor outcomes compared with other patients without closure.

Aortic stiffening prompts rapid PWV, and an earlier pulse wave reflection causing an increase in focal SBP and a reduction in DBP with an increase in pulse pressure are consistent with these findings. An increased SBP may increase the LV after load with an increase in oxygen demand, LV hypertrophy, fibrosis, and subsequently reduced in LV ejection fraction.22

In agreement with previously published data,23 which have shown that increasing age is associated with increasing aortic stiffness as assessed by both aortic PWV and regional aortic distensibility, in our study ASI was measured in patients with same PDA size but with different ages, and we found positive significant correlation between ASI and time delay to PDA closure ($r = 0.9457$), $p$ value < 0.0001 (Fig. 7).

6. Conclusions

Aortic stiffness is fundamentally noted in patients with PDA, even those with small-sized PDA, and is related to debilitation in cardiovascular function. After device closure, ASI is significantly reduced and associated with a significant change in heart function and the functional class of patients months after device closure. ASI may be valuable for observing the course of patients with PDA before and after intervention.

Conflict of interest

Authors declare that there is no conflict of interest.

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