Cardiovascular Topics

Effect of time delay of PDA closure on the aortic stiffness index and its relationship with cardiac function
Saud M Elsaughier, Ramadan Ghaleb, Hossam Mansour

Abstract

Background: Patent ductus arteriosus (PDA) causes volume overload of the left side of the heart. Stiffening in the larger central arterial system, such as the aortic tree, significantly contributes to cardiovascular diseases in older individuals and is positively associated with systolic hypertension and coronary artery disease. In this study, we evaluated the effect of time delay of PDA closure on aortic stiffness and its relationship with cardiac function before and after transcatheter closure of the PDA.

Methods: Our study population consisted of 60 children who were scheduled for transcathether closure of the PDA. They were divided into two groups as follows: group A in whom PDA closure was performed before the age of one year, and group B in whom PDA closure was performed after the age of one year.

Results: Before PDA closure, the aortic stiffness index (ASI) was significantly higher in children in group B than in those in group A (p < 0.001), and was it significantly higher in both groups than in the control group (p < 0.001).

Conclusion: Aortic stiffness was significantly elevated in patients with PDA, even small-sized PDAs, and was associated with impairment in cardiac function, particularly if PDA closure was delayed after the age of one year.

Keywords: PDA closure, aortic stiffness index, cardiac function

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Patent ductus arteriosus (PDA) causes a volume overload of the left half of the heart, which leads to pulmonary hypertension. The planning of treatment for congenital heart imperfections depends on the haemodynamic reflection of chamber renovation.1 Accordingly, it is vital to have numerous techniques accessible for development. Clinical examination, chest X-ray, electrocardiogram (ECG), blood vessel saturation (upper and lower limbs) and echocardiography are indispensable in evaluating the operability in the majority of patients with PDA.

Notwithstanding, the choice to intercede is troublesome if the outcomes are obscure. Hardening in the larger focal blood vessel framework, for example the aortic tree, essentially adds to the development of cardiovascular disorders in older individuals and is emphatically connected with systolic hypertension, coronary artery disease, stroke, heart failure and atrial fibrillation, which are the most frequent causes of mortality in low-income countries, as assessed by the World Health Organisation in 2010. Consequently, not necessarily intrusive measures, but rather more exact measures of aortic stiffness have been created, which are valuable as diagnostic indices, pathophysiological markers and predictive indicators of disease.2

In this study, we attempted to assess the impact of time postponement of PDA closure on aortic stiffness and its connection with cardiac function prior and subsequent to the transcather closure of PDA, and to utilise the aortic stiffness index (ASI) as a tool for assessing patients with PDA.

Methods

Our study population consisted of 60 children who were scheduled for transcathether closure of PDA. They were split into two groups as follows: group A in whom PDA closure was performed before the age of one year, and group B in whom PDA closure was performed after one year of age. The control group consisted of 60 healthy children. All patients had clinical and echocardiographic proof of haemodynamically notable PDA.

Patients with silent PDA, PDA not practical for percutaneous closure, irreversible pulmonary vascular disease [pulmonary vascular resistance index (PVRI) > 7 WU/m²], and individuals who had related haemodynamically notable congenital cardiovascular disease or a significant remaining shunt were excluded from the study.

Control subjects were observed once. They were asymptomatic and demonstrated no abnormalities on clinical examination, ECG or echocardiography.

Tissue Doppler imaging (TDI) and transthoracic two-dimensional echocardiography were performed on an out-patient basis with the patient in the supine position, utilising Philips IE with 88-3- and X5-1-MHz transducers at baseline, one day after the procedure and at follow up (no less than six months after the procedure).

Left ventricular (LV) systolic malfunction was characterised post-PDA closure as a LV ejection fraction (LVEF) of < 50% or a potential decline in LVEF of 10% from baseline.

For non-invasive assessment of aortic stiffness, the transverse relocation of the aortic wall was measured with available hardware.
(Philips IE 33 utilising S8-3- and X5-1-MHz transducers). The ascending aorta was recorded in two-dimensional, guided M-mode tracings. The aortic width was recorded using M-mode echocardiogram at a level of 3 cm over the aortic valve. The interior aortic widths were measured using calliper methods in systole and diastole as the separation between the trailing edge of the front aortic wall and the main edge of the back aortic wall. The aortic systolic diameter (AoSD) was measured at the time of full widening of the aortic valve, and the diastolic diameter (AoDD) was measured at the peak of the QRS complex on the electrocardiogram. The ASI was calculated from the following equation:

\[
ASI = \frac{\text{systolic blood pressure/diastolic blood pressure}}{(\text{AoSD} - \text{AoDD})/\text{AoDD}} \times 100.\]

For brain natriuretic peptide (BNP) measurement, blood samples were collected by venepuncture into ethylenediaminetetraacetic acid (EDTA) tubes within two hours of assessing the first echocardiogram for all children in the study, and six months after device closure of the PDA for children with PDA only. The samples were kept at room temperature and examined within four hours of sampling.

Blood samples were centrifuged and the plasma was frozen for one to two days at −70°C. Before the examination, each tube was shaken a few times to guarantee homogeneity. The BNP assay is a sandwich immunoassay in which 250 ml EDTA-anticoagulated blood or plasma had been added. The triage metre was used to measure the BNP concentration by detecting a fluorescent signal that reflected the amount of BNP in the sample. The upper limit of the normal laboratory reference for BNP was 30 pg/ml.

Cardiovascular catheterisation was performed for the evaluation of pulmonary artery pressure (PAP) and shunt measurement. Pulmonary artery hypertension (PAH) was characterised as PAP > 25 mmHg. Angiograms were performed in the standard horizontal view for PDA estimation. The PDA was crossed from the pulmonary end in all patients. An Amplatzer delivery sheath (AGA Medical, Plymouth, MN) was placed in the venous route over an Amplatzer super-stiff guidewire (Boston Scientific, Natick, MA, USA) and was left in the descending thoracic aorta.

The device was delivered according to the standard method. The aortogram was performed 10 minutes after withdrawal to confirm device position and rule out the remaining shunt. After device placement, echocardiographic examination was performed to assess the device location and the descending thoracic aortic and left pulmonary arterial velocity. The ductal occluder device was withdrawn after eliminating the residual shunt and obstruction in the aorta and/or left pulmonary artery.

**Statistical analysis**

Analyses were performed using the Statistical Package for Social Sciences, version 16.01 for Windows (SPSS Inc, Chicago, IL). Correlation between aortic stiffness and different parameters was determined via univariate analysis and correlation coefficients.

**Results**

At the time of the examination, the mean age in group A was 6.8 ± 3.4 months and 70% were female. In group B, the mean age was 51.1 ± 43 months and 83% were female. Demographic data are shown in Table 1. All study patients with PDA experienced percutaneous closure with either a device or a coil. In these children, no other heart deformities were detected.

Follow up was possible for all patients over a period of six months. During the subsequent period, none of the patients had any progression in their peak velocities or gradients across the left pulmonary artery or the aortic isthmus, and no residual shunt was detected.

There was no significant difference between groups A and B with regard to duct size, as determined using echocardiography or during the intervention. The mean PDA measurement in group A was 4.0 ± 0.97 mm, and 4.7 ± 1.7 mm in group B (p = 0.1). Prior to PDA closure, the ASI was significantly higher in group B than in group A (p < 0.05) (Table 2), and was significantly higher in both groups than in the control group (p < 0.05) (Tables 3, 4). However, the ASI was significantly higher in group B than in group A at the six-month follow-up assessment (p < 0.05) (Table 2).

Prior to PDA intervention, the LVEF of group B was significantly lower than that of group A (52.6 ± 2.2 vs 59.4 ± 5.3%) (p < 0.05) (Table 2), and was significantly lower in both groups than in the control group (66.7 ± 3.4) (p < 0.05) (Tables 3, 4). After PDA closure, the LVEF improved significantly in both groups (p < 0.05).

In group A, there was no significant difference between patients and controls regarding LVEF (p = 0.6) at the six-month follow-up assessment (Table 3). It was still significantly lower in

**Table 1. Demographic characteristics of patients with PDA and the control group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 60)</th>
<th>Control group (n = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months) mean ± SD</td>
<td>28.9 ± 38.0</td>
<td>29.2 ± 34.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>25 (42)</td>
<td>20 (33)</td>
<td>0.8</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>35 (58)</td>
<td>40 (77)</td>
<td></td>
</tr>
<tr>
<td>BWT (kg) mean ± SD</td>
<td>12.8 ± 11.4</td>
<td>11.2 ± 4.1</td>
<td>0.3</td>
</tr>
<tr>
<td>SBP (mmHg) mean ± SD</td>
<td>94.8 ± 9.4</td>
<td>96 ± 8.4</td>
<td>0.4</td>
</tr>
<tr>
<td>DBP (mmHg) mean ± SD</td>
<td>61 ± 6.9</td>
<td>62 ± 6.8</td>
<td>0.3</td>
</tr>
<tr>
<td>HR (b/m) mean ± SD</td>
<td>99 ± 12</td>
<td>90 ± 11</td>
<td>0.6</td>
</tr>
</tbody>
</table>

p ≤ 0.05 was considered statistically significant; SD: standard deviation; BWT: body weight; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR (b/m): heart rate (beats per minute).

**Table 2. Comparison between group A and B with regard to ASI, BNP, PAP and cardiac function before and after PDA closure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (n = 30)</th>
<th>Group B (n = 30)</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASI, mean ± SD</td>
<td>6.7 ± 2.8</td>
<td>3.8 ± 1.4</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.4 ± 5.3</td>
<td>66.4 ± 4.2</td>
<td>0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>3.4 ± 0.85</td>
<td>3 ± 0.82</td>
<td>0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>BNP, mean ± SD</td>
<td>57.7 ± 15.1</td>
<td>18.9 ± 5</td>
<td>&lt;0.05</td>
<td>0.3</td>
</tr>
<tr>
<td>PAP, mean ± SD</td>
<td>40.3 ± 6.2</td>
<td>23.9 ± 4.9</td>
<td>0.05</td>
<td>0.2</td>
</tr>
</tbody>
</table>

p: significance between group A and group B before closure; p*: significance between group A and group B after closure. ASI: arterial stiffness index; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; BNP: brain natriuretic peptide; PAP: pulmonary artery pressure.
The BNP level was significantly higher in children in group B than in group A ($p < 0.05$) prior to PDA closure (Table 2). However, the BNP level was significantly enhanced in both groups after PDA closure ($p < 0.05$) and approached non-significance compared with that in the control group ($p = 0.09$ and 0.5, respectively) (Tables 3, 4).

Prior to PDA closure, the PAP was significantly higher in both groups ($p < 0.05$) and approached non-significance compared with the control group at the six-month follow-up assessment. The mean PAP in group A after the intervention was $23.9 \pm 4.9$, and in group B it was $21.9 \pm 4.7$ (Tables 3, 4).

The ASI was positively correlated with the left ventricular end-diastolic diameter (LVEDD) ($r = 0.58$, $p < 0.05$) (Fig. 1), BNP level ($r = 0.303$, $p < 0.05$) (Fig. 2) and PAP ($r = 0.68$, $p < 0.05$). It was negatively correlated with LVEF ($r = 0.66$, $p < 0.05$) (Fig. 3).

### Discussion

PDA causes volume overload of the left side of the heart, which can lead to pulmonary hypertension. The planning of treatment for congenital heart deformities depends on the haemodynamic and anatomical circumstances when considering myocardial cell adjustment and chamber remodelling.

It is critical to have various techniques for observing patients with PDA. In our study we attempted to assess the impact of postponement of PDA closure on aortic stiffness and its

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before closure</th>
<th>After closure</th>
<th>Control group</th>
<th>p-value</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASI, mean ± SD</td>
<td>6.7 ± 2.8</td>
<td>3.8 ± 1.4</td>
<td>1.6 ± 0.74</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF (%) mean ± SD</td>
<td>59.4 ± 5.3</td>
<td>66 ± 4.2</td>
<td>66.7 ± 3.4</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>0.6</td>
</tr>
<tr>
<td>LVEDD (mm) mean ± SD</td>
<td>3.4 ± 0.8</td>
<td>3 ± 0.28</td>
<td>2.8 ± 0.55</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESD (mm) mean ± SD</td>
<td>2.2 ± 0.37</td>
<td>2.0 ± 0.32</td>
<td>1.9 ± 0.54</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E/Ea, mean ± SD</td>
<td>11.2 ± 1.9</td>
<td>6.9 ± 0.8</td>
<td>6.5 ± 1.06</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BNP, mean ± SD</td>
<td>59.6 ± 16.1</td>
<td>19.9 ± 5.5</td>
<td>19.8 ± 5.1</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>0.9</td>
</tr>
<tr>
<td>PAP, mean ± SD</td>
<td>43.5 ± 7.3</td>
<td>23.4 ± 4.7</td>
<td>23.2 ± 5.1</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>0.8</td>
</tr>
</tbody>
</table>

$p$: significance between patients before and after closure; $p^*$: significance between patients before closure and controls; $p^*$: significance between patients after closure and controls; ASI: arterial stiffness index; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter; E/Ea: ratio of early mitral flow velocity to early mitral annular velocity; BNP: brain natriuretic peptide; PAP: pulmonary artery pressure.
connection with heart function prior to and after transcatheter closure of PDA as a tool for observing patients with PDA.

Our study demonstrated that patients in group A had a significantly higher ASI than those in the control group before closure \( (p < 0.05) \). After closure, the ASI diminished significantly, however it was significantly higher in group A than in the control group at the six-month follow-up assessment \( (p < 0.05) \) (Table 3). Patients with PDA in subgroup B had a significantly higher ASI than the control group before closure \( (p < 0.05) \). After closure, the ASI diminished significantly; however it was significantly higher in group B than in the control group at the six-month follow-up assessment \( (p < 0.05) \) (Table 4).

The explanation of these findings is that since the PDA is typically connected with a hyperdynamic status and there is a vascular shunt between the aorta and pulmonary artery, congenital aortic changes occur (aortic stiffness). Additionally, shunt injuries may be related to a provocative inflammatory process, and endothelial malfunction may hasten the ageing of vessels, particularly the aorta. Haemodynamic and oxygen saturation changes (nocturnal hypoxaemia) may be the fundamental components of aortic stiffness in shunt injuries because of increased PAP, notwithstanding the inflammation and endothelial disruption.

Our study additionally discovered that patients in group B had a higher ASI than those in group A preceding closure \( (p < 0.05) \). After closure, the ASI diminished significantly \( (p < 0.05) \); however the ASI was higher in group B than in group A at the six-month follow-up assessment \( (p < 0.05) \) (Table 2). There was no notable difference between patients in group A and B with regard to the PDA size \( (p = 0.1) \). This was in accordance with previously published information, which demonstrated that ageing is related to expanding aortic stiffness as evaluated by both aortic pulse wave velocity and local aortic dispensability. In group A, our study indicated that patients with PDA had significantly lower LVEF than the control group before closure \( (p < 0.05) \). After closure, the LVEF was significantly enhanced \( (p < 0.05) \), and there was no notable distinction between the patient groups and the control group \( (p = 0.6) \) at the six-month follow-up assessment \( (p < 0.06) \) (Table 3).

In group B, patients with PDA had a significantly lower LVEF than the control group before closure \( (p < 0.05) \). After closure, the LVEF was significantly enhanced and there was a significant difference between the patient groups and the control group at the six-month follow-up assessment \( (p < 0.05) \) (Table 4). There was a significant distinction between the patient groups and the control group with regard to the LVEDD and LVESD before closure \( (p < 0.05) \). After closure, the LVEDD decreased \( (p < 0.05) \); however, it was somewhat higher in the patient groups than in the control group at the six-month follow-up assessment \( (p < 0.05) \) (Table 4). The explanation of these findings is that the change in heart function in both groups after PDA closure was clarified by interruption of the left-to-right shunt, which limited the left ventricular volume overload.

Our discoveries are in agreement with previous studies that demonstrated that subjects with PDA had higher LV end-systolic volume index and LV end-diastolic volume index, a decreased LVEF, and a higher BNP level compared with those in the control group. These progressions are reported and settled over a six-month follow-up period after percutaneous PDA closure.11

Our findings with regard to diastolic physiological changes demonstrated that there was a diastolic physiological weakness in patients with PDA. Park16 discovered a weakened pattern in the early change of diastolic capacity after the development of a restrictive pattern. In this study, we revealed that patients with PDA had a significantly higher E/Ea ratio (ratio of early mitral flow velocity to early mitral annular velocity) than the control group before closure \( (p < 0.05) \). After closure, the E/Ea ratio was enhanced \( (p < 0.05) \) and higher than that in the control group at the six-month follow-up assessment \( (p < 0.05) \) (Tables 3, 4).

BNP is discharged by the ventricular myocytces in light of the LV volume overload, which is associated with a large left-to-right shunt.15 The BNP hormone could be developed as a marker for heart failure and treatment assessment.15

In this study, we discovered that BNP level was significantly higher in children with PDA in both groups prior to closure than in control subjects \( (p < 0.05) \), while levels diminished significantly six months after closure \( (p < 0.05) \), approaching non-significance compared with that in the control group \( (p > 0.05) \) (Tables 3, 4). We discovered that the BNP level was significantly higher in patients in group B than in those in group A preceding closure \( (p < 0.05) \). After closure, there was no substantial distinction between groups with regard to BNP levels \( (p = 0.3) \) (Table 2).

Eerola et al.11 found that the BNP level diminished significantly from 141 (31–974) ng/l to 79 (21–480) ng/l in six months after PDA closure. They likewise found that the BNP level of children with PDA was significantly different compared to that in healthy children.11 Therefore the BNP level could be utilised as a marker of heart dilatation.

In our patients with PDA, a significant connection was found between serum levels of BNP and the aortic stiffness index. This was consistent with the results of a previous review18 that discovered the relationship between BNP level and ASI.

Plasma levels of BNP have been shown to relate to systolic pressure in the right ventricle (RV) in children with volume overload of the RV.19 Plasma levels of BNP have been associated with right atrial and ventricular pressures in a child populace comprising various loading conditions and a wide age range.16

The results after closure of an expansive PDA are dependent on the age at the time of repair and the presence of pre-operative
pulmonary vascular disease.\textsuperscript{17} Age is a critical indicator of pulmonary vascular disease. The consensus is that children under one year of age will probably not have irreversible PAH, and most concur that irreversibility begins at age one to two years. This speculation has a few impediments as the pathogenesis of irreversible PAH and its movement is multifactorial and inconsistent.

Blount et al.\textsuperscript{14} demonstrated that a PDA may have a greater impact on the pulmonary flow than on a ventricular septal imperfection and that irreversible pulmonary vascular changes may occur at under two years of age. This is most likely the after-effect of the high-pressure pulsatile stream transmitted from the aorta to the pulmonary artery throughout the cardiovascular cycle in patients with PDA.

In our study, we found that PAP was significantly higher in children with PDA prior to closure ($p < 0.05$) in both groups. After closure, the PAP was diminished in both groups ($p < 0.05$) and approaching non-significance compared with the control group ($p > 0.05$) (Tables 3, 4). Additionally, we discovered a significant positive relationship between ASI and PAP ($r = 0.6, p < 0.05$) (Fig. 2).

We also found in this study that the PAP was significantly higher in patients in group B than in those in group A preceding closure ($p < 0.05$). After closure, there was no significant difference between groups with regard to PAP ($p = 0.2$) (Table 2).

Note that a small number of patients with PDA and PAH and marginal haemodynamic instability can deteriorate after PDA closure because of non-regression of pulmonary hypertension, progressive PVD and right heart failure. Therefore their normal history becomes similar to that of primary or idiopathic PAH. These patients have a better normal history if the PDA is left untreated.

A safe examination to distinguish who may benefit from PDA closure with long-term regression of PAH and who may be plagued by progressive pulmonary vascular disease and right heart failure is presently not available. Future research on the type and degree of morphological changes in the pulmonary vessels, individual inconsistency, and hereditary and epigenetic variables may provide some insight into this disturbing problem. Until such time, in clinical practice, infrequently there may be a patient who will not benefit from closure of an expansive PDA and may have an adverse outcome if PDA closure is attempted; however there may be many others who have favourable outcomes.

Aortic stiffening prompts faster pulse wave velocity, and therefore a prior heartbeat wave reflection may occur, bringing about an expansion in focal systolic blood pressure (SBP) and a diminishing diastolic blood pressure (DBP) with an increment in pulse pressure. An expanded SBP may build the LV afterload, with an expansion in myocardial oxygen demand, LV hypertrophy, fibrosis, and inevitably, a reduction in the LVEF.\textsuperscript{19} In our study, we found a significant negative correlation between the ASI and LVEF prior to PDA closure ($r = 0.66, p < 0.05$) (Fig. 4) and a significant positive relationship between ASI and LVEDD prior to closure ($r = 0.58, p < 0.05$) (Fig. 3).

**Conclusion**

Aortic stiffness is increased in patients with PDA, even in cases of small-sized PDAs and is related to weakness in heart function, especially if PDA closure is deferred to after the age of one year. After device closure, the ASI diminished significantly and was associated with a notable change in heart capacity and functional class months after device closure. The ASI may be helpful in assessing the course of patients with PDA prior to and after intervention. We recommend early closure of PDA, even in cases of small-sized PDAs, and use of the ASI as a tool for following patients with PDA before and after closure.

**References**


