Association of aortic stiffness to brain natriuretic peptide in children before and after device closure of patent ductus arteriosus

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Objectives: **We evaluated the influence of device closure for patent ductus arteriosus (PDA) on the aortic stiffness index (ASI) and brain natriuretic peptide (BNP) and their association with cardiac function.**

Patients and methods: **ASI and echocardiography assessment before and after treatment (16 ± 9 months) in 48 children with PDA (mean age 10 ± 4.5) and 52 control children (mean age 9.7 ± 4.6). BNP level was measured pre-closure for all children, and was measured six months after closure only for children with PDA.**

Results: **ASI was higher in PDA patients than in controls ($P < 0.001$). ASI correlated with age ($P < 0.05$), LVEF% ($P < 0.01$), E/E′ (<0.03), pulmonary artery pressure ($P < 0.001$), and BNP ($P < 0.001$). ASI and BNP significantly decreased after closure ($P < 0.001$). ASI and BNP were independent predictors for post-closure systolic dysfunction ($P < 0.001$and <0.005, respectively). Receiver operating curve (ROC) analysis showed that ASI $\geqslant$ 13.5, BNP level $\geqslant$75 pg/ml and basal mean pulmonary artery pressure (PAP) $\geqslant$ 23 were powerful predictors for post-closure systolic function.**

Conclusion: **ASI is significantly associated with BNP and basal PAP in children with PDA. After device closure, aortic distensibility improved significantly and was associated with significant improvement in both systolic and diastolic functions. ASI can be used for monitoring the course of patients with PDA, and may give opportunities for early intervention.**

Keywords: Aortic stiffness, Device closure, Patent ductus arteriosus

Introduction

Patent ductus arteriosus (PDA) causes volume overload of the left side of the heart [1] and predisposes the patient to pulmonary hypertension. The timing of treatment for congenital heart defects is based on the hemodynamic and anatomic situation, with consideration of myocardial cell adaptation and chamber remodeling. Therefore, it is important to have multiple methods available for follow-up. The combination of new imaging

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modalities and measurements of serum levels of natriuretic peptides may allow us to improve the evaluation of cardiac function and timing of interventions [2].

Left ventricle (LV) volume overload and compensatory remodeling alters the systolic and diastolic function of the LV as in chronic aortic and mitral regurgitation [3–5]. These changes are expected to improve after PDA closure; however, some patients develop LV systolic dysfunction. Clinical examination, X-ray chest, ECG, arterial saturation (upper and lower limbs) and echocardiography are conclusive in assessing operability in the majority of patients with PDA and pulmonary hypertension. However, the decision to intervene is difficult if the examination results are equivocal.

The purpose of this study is to evaluate the association of aortic stiffness with BNP and its relation to cardiac function before and after transcatheter closure of the PDA.

Abbreviations

PDA	Patent ductus arteriosus
BNP	brain natriuretic peptide
ASI	aortic stiffness index
TDI	Tissue Doppler imaging
EDTA	Ethylenediaminetetraacetic Acid
AoS	Aortic systolic
AOST	Aortic strain
RAO	right anterior oblique
ADO	Amplatzer duct occluder

Patients and methods

Forty-eight consecutive children, who were planned for transcatheter closure of PDA, were enrolled in this prospective observational study. All patients had clinical and/or echocardiographic evidence of hemodynamically significant PDA. Patients with silent PDA, PDA not suitable for percutaneous closure, irreversible pulmonary vascular disease (pulmonary vascular resistance index, i.e., pulmonary vascular resistance index (PVRI) >7 WU m^2), and those who had associated hemodynamically significant congenital heart disease or a significant residual shunt were excluded from the study. Study approval was obtained from the ethics committee and written informed consent was obtained from the parents of patients in all cases. Control subjects were examined once. They were asymptomatic and showed no abnormalities in clinical examination, ECG, or echocardiography.

Transthoracic 2D echocardiography and tissue Doppler imaging (TDI) was performed with the patient in the supine position using GE-Vivid 3 (General Electric, Milwaukee, WI, USA) with 2.5 and 3.5 MHz transducers on outpatient basis at baseline, one day after the procedure and at follow-up (at least three months after the procedure). LV systolic dysfunction was defined as a post-PDA closure absolute in left ventricular ejection fraction (LVEF) of <50% and/or reduction in LVEF of $\geqslant$10% from the baseline. For diastolic function analysis, the mitral inflow signal was acquired from three cardiac cycles in the apical four-chamber view; the E (early mitral inflow: rapid atrial filling) and A (late mitral inflow: late atrial filling) waves were measured, and the E/A ratio was calculated. Mitral annular diastolic velocities in early diastole (E′) and late diastole (A′) were obtained by tissue Doppler imaging and E/E′ was calculated. Anatomic attributes of the ductus were assessed for size, minimum diameter toward pulmonary end, shape, orientation of PDA as well as adequacy of the ampoule on the aortic end. PDA size was measured in the parasternal short axis and ductal view. Left atrial and aortic dimensions were also measured simultaneously.

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 using the Triage BNP assay (Biosite Diagnostics). In some cases, the sample was centrifuged and the plasma was frozen for one to two days at −70°C. Before analysis, each tube was inverted several times to ensure homogeneity. The BNP assay was a sandwich immuno-assay that consisted of a disposable device to which 250 mL of EDTA-anti-coagulated 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 [6]. The upper limit of the normal lab reference for BNP was 42 pg/ml [6].

Non-invasive evaluation of aortic stiffness

The transverse displacement of the aortic wall was measured with commercially available equipment (GE-Vivid 3; General Electric, Milwaukee, WI, USA), using 2.5 and 3.5 MHz transducers. After routine conventional echocardiographic examination, patients were placed in a left mild recumbent position and the ascending aorta was