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Right Ventricular Isovolumic Acceleration in Children with Patent Ductus Arteriosus: Short and Mid-term Follow-up after Percutaneous Device Closure

Abstract

Objective: We aimed to assess the association of right ventricular acceleration during isovolumic contraction (RVIVA) to functional recovery after device closure of patent ductus arteriosus (PDA).

Methods: 84(7.5+6.8 year; 49 female) patients who underwent device closure of PDA were evaluated with conventional and tissue Doppler echocardiography pre closure, at 24 hours and at 6 months post closure to assess RVIVA, myocardial performance index (MPI). Brain natreuretic peptide (BNP) was assessed pre closure and 6 months post closure

Results: RVIVA was significantly decreased in children with PDA, while other conventional Echo Doppler parameters were comparable to controls. Following closure of PDA, RVIVA was significantly increased (P<0.001). These changes were correlated with significant decrease in LVMPI, BNP and sPAP (P <0 .001, for all). At 6 month of follow-up the BNP markedly decreased with significant improvement of LVMPI in 78 (92.9) patients. With multivariate analysis, RV IVA were the strongest predictors of functional recovery (r= 0.582, P<0.001 and r=--0.518; P<0.001). ROC sowed that RVIVA > 2.4 m/s was the best cutoff value in predicting functional recovery after percutaneous closure of PDA.

Conclusion: Measurement of RVIVA in patients with PDA specially those presented late are important to differentiate high- and low-risk groups in terms of prognosis.. RVIVA might be considered a useful indicator for functional recovery after device closure of PDA

Keywords: Isovolumetric acceleration; Pulmonary stiffness; Patent ductus arteriosus

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Introduction

In patients with patent ducts arteriosus, cardiovascular system is generally exposed to much overload and subsequently several complications as congestive heart failure, pulmonary hypertension and infective endocarditis. These complications depend on the size of the defect and the timing of intervention [1]. It is important to close PDA to prevent occurrence of these complications [2]. Today percutaneous transcatheter closure method is the first choice for PDA closure, mostly utilizing Amplatzer Duct Occluder. Right ventricular echocardiographic indices before and after PDA closure are scarcely studied. Right ventricular systolic function can be determined with assessment of tricuspid annular motion utilizing pulsed-wave Doppler tissue imaging [3-5]. Why…. Pauliks et al. [3] and Turhan et al. [4] reported that IVA assessment seems to be a more reliable and sensitive for predicting cardiac function than tissue Doppler imaging (TDI)-derived peak systolic velocity. Tissue Doppler echocardiography (TDE) derived myocardial performance index (MPI) is a widely accepted parameter for quantitative assessment of myocardial function [5], and it is more sensitive for global myocardial function than separately assessing systolic and diastolic function [6].

We hypothesized right ventricular dysfunction may occur as well in patients with PDA and early identification of these changes may improve evaluation of cardiac function and timing of interventions. The purpose of this study was to evaluate the right ventricular isovolumic acceleration in children with patent ductus arteriosus and its relation to functional recovery after transcatheter closure of the PDA

Patients and Methods

84 consecutive patients, with hemodynamically significant PDA, were included in a prospective study. Inclusion criteria for percutaneous closure of PDA were children with PDA, who the murmur was significantly auscultated, had bounding pulse, and their body weight ≥ 6 kg, and the duct size less than 12 mm. Exclusion criteria: PDA not suitable for percutaneous closure, irreversible pulmonary vascular disease (pulmonary vascular resistance index i.e. PVRI > 7 WU.m2), and other associated

significant congenital heart disease. Informed consent was obtained from the patients' or their parents. The study was approved from the faculty ethical committee. Forty two healthy subjects with age and sex matched were recruited as control group.

Echocardiographic studies

Echocardiography was performed in all patients in the left lateral decubitus position with standard views using a Vivid 5 machine (GE Vingmed, Horten, Norway). Left atrial systolic dimension and LV internal dimensions and wall thicknesses were measured from two dimensional guided M-mode tracings obtained at the mid chordal level in the parasternal long-axis view according to the criteria of the American Society of Echocardiography [7-9]. Mitral inflow velocities were obtained by pulsed-wave Doppler in the apical 4-chamber view with the sample volume placed at the tips of the mitral valve leaflets. The peak early (E) and late (A) diastolic mitral inflow velocities, deceleration time, E/A ratio, and isovolumic relaxation time were measured and averaged over three cardiac cycles. Color tissue Doppler imaging was performed from the apical 4-chamber view using a 2.5-MHz transducer and frame rates of >80/sec and the images were digitized. Derivation and analysis of TDI-derived velocity profiles were performed offline using commercial computer software (Echopac, GE Vingmed). Myocardial velocity profiles of the basal septal and lateral mitral annulus were obtained by placing a 6-mm sample volume at the junction of the mitral annulus with the septum and lateral myocardial wall. Myocardial velocities of the lateral tricuspid annulus were obtained similarly by placing the sample volume at the junction of the tricuspid valve annulus and right ventricular free wall. The ratio of peak early diastolic mitral inflow velocity by pulsed wave Doppler to peak early diastolic mitral annular velocity by TDI was calculated as a measure of LV filling pressure. The MPI of LV obtained by TDE, defined as the sum of the isovulumetric relaxation time and isovolumetric contraction time divided by ejection time. Doppler measurements were made at a recording rate of 100 mm/s. Myocardial isovolumic acceleration was measured by dividing the peak velocity bythe time interval from the onset of the wave (zero-crossing) during isovolumic contraction to the peak velocity of this wave as previously described [10].

Cardiac catheterization

A hemodynamic study was performed first: Right and left heart cardiac catheterization was performed. Mean pulmonary artery pressure was obtained by the data of right heart catheterization. Data from right and left heart catheterization were obtained and with the use of Fick" principle, the systemic flow (Qs), pulmonary flow (Qp) and pulmonary vascular resistance (PVR) were calculated. The PVR was calculated using the formula: PVR = (MPAP - PCWP)/Qp. After sizing, PDA percutaneous closures of PDA were performed with all children under general anesthesia, by standard technique utilizing a loading catheter, a Mullin delivery sheath and a delivery cable. Amplatzer type (Cocoon) ductal occluder device (Vascular Innovations Co. Ltd., Bankok, Thailand) was used in all subjects. After device deployment, echocardiographic assessment was done for the device position, and 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.

Brain natreuretic peptide measurement

The blood samples were collected by veni-puncture into EDTA tubes kept at room temperature and analyzed within 4 hours of sampling usingthe Triage BNP assay (Biosite diagnostics. The BNP assay was as andwich immuno- assay that consisted of a disposable device to which 250mL of EDTA-anticoagulated whole blood or plasma was added. The Triage meter 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 lab reference for BNP was 42 pg/ml [11].

Follow-up

Patients underwent serial follow-up examinations at 24 hours, 3, 6, and 12 months, and then yearly after the procedure. Follow-up studies included clinical examination, ECG, and transthoracic echocardiogram. BNP was assessed during follow-up only at 6 months.

Statistics

The SPSS software (Statistical Package for the Social Sciences, Version 21.0, SSPS Inc., Chicago, IL, USA) was used to analyze the obtained data of the study. Continuous variables were expressed as mean ± S.D. and categorical variables were expressed as percentages. The Pearson correlation analysis was used to estimate the correlations between LV functional recovery assessed by (MPI and BNP) and PAS, RVIVA. A linear regression-stepwise analysis model was performed to test the effects of PAS, and RVIA on left ventricular functional recovery assessed by (MPI and BNP). ROC curve analysis was used to determine the best cutoff values of RVIVA and PAS in predicting functional recovery after device closure of PDA

Results

The study included 84 patients. The mean age was 7.5 + 6.8 year (49 female and 35 male) and 42 matched healthy subjects were studies as a control group. Table 1 shows the basic characteristics characteristics of the study population. Left atrial volume index, E/E' ratio, LV-MPI, sPAP and BNP levels were significantly higher in patients with PDA compared to controls. On the other hand LVIVA, RVIVA were significantly lower in children with PDA. The catheterization data of children with PDA are represented in Table 2.

Table 3 shows that Left atrial volume index, E/E' ratio, LV-MPI, LVIVA, RVIVA were significantly improved at 6 months of follow-up after device closure of PDA. LV-MPI was significantly decreased at 6 months of follow-up compared to pre-closure and at 24 hours post-closure ($P<0.001$ for all). The BNP levels as well were significantly decreased at 6 months post-closure of PDA compared to both pre-closure and at 24 hours post-closure ($P<0.001$ for both).

The results showed that RVIVA tends to improve 24 hours after closure ($P<0.05$), and continued to increase to be comparable

to normal at 6 months of follow-up (P<0.002). In contrast, the other right ventricular echocardiographic parameters (S', TAPSE, FAS%,), didn't changed significantly either early or late at 6months of follow-up (P>0.05 for all).

Table 1: Demographic characteristics of patients with patent ductus arteriosus and controls.

Variables	Patients (n = 84)	Controls (n = 46)	p
Age (years)	12.5+9.8	12.9 ± 7.5	>0.05
Gender (m/f)	39/45	21/23	>0.05
SBP	143 ± 8.7	138.1 ±7.3	>0.05
DBP	56.5 ± 4.2	69.7 ± 4.6	<0.05
LVEF (%)	68.75+5.92	72.15 ± 6.11	0.38
LAVI	33.5 ± 4.4	21.46	<0.003
E/E'	9.8+1.2	5.1+0.9	<0.001
LVMPI	0.51 ± 0.06	0.37	<0.001
e PASP (mm Hg)	56.2+5.3	19.7 ± 4.25	<0.001
TAPSE (mm)	23.62 ± 5.71	26.35 ± 4.19	>0.05
RV-MPI	0.47±0.06	0.45±0.09	>0.05
S' (cm/s)	13.26 ± 3.54	12.35 ± 2.31	>0.05
RV-FAC (%)	38.21 ± 6.45	36.92 ± 9.47	>0.05
RV-MPI	0.48 ± 0.11	0.47 ± 0.17	>0.05
RVIVA m/s^2	2.15 ± 1.21	3.95 ± 0.82	<0.002
Pulmonary artery stifness kHz/s	3.95+1.05	2.13+0.36	<0.001
BNP (pg/ml)-baseline	143± 19	28 ± 7	<0.0001

Table 2: Catheterization findings of children with patent ductus arteriosus.

Variable	
Mean PAP	30.8 ± 9.1
Qp/Qs	2.9 ± 0.9
PDA minimum diameter mm	3.6 ± 1.8
Aortic end of PDA diameter (mm)	8. 2 ± 3.5
Length of PDA (mm)	7.6 ± 2.5
Devices	
· ADO	80 (95.2%)
· Coil	4 (4.8%

PAP: Pulmonary Artery Pressure; ADO: Amplatzer Duct Occluder.

Table 3: Echocardiographic characteristics of patients with PDA before, at 24 hours and 6 months after device closure.

Variable	Before Closure	At 24 Hour	At 6 Months	P1	P2
LAVI (mL/m^2)	34.5 ± 4.4	33.9+3.9	26.5 ± 4.1	>0.05	<0.05
LVEF%	69.7+5.9	67.5+4.9	71.2+4.5	>0.05	>0.05
E/A	1.3+0.3	1.3+0.2	1.22+0.3	>0.05	>0.05
E/E'	9.8+1.2	7.5+1.3	6.4+1.3	<0.05	<0.05
LV-MPI	0.51 ± 0.06	0.52 ± 0.09	0.39+0.07	>0.05	<0.001
TAPSE (mm)	23.6 ± 5.7	24.9+5.5	23.9 ± 4.3	>0.05	>0.05
S' (cm/s)	14.4 ± 2.6	14.8+3.1	15.8 ± 2.4	>0.05	>0.05
RV- FAC (%)	53.8 ± 3.9	53.6+2.5	55.2 ± 4.1	>0.05	>0.05
e PASP (mmHg)	56.2+5.3	38.6+5.1	27.5+4.2	0.005	<0.001
Qp/Qs	2.2 ± 0.4	1.7±0.4	1.3. ± 0.5	<0.01	<0.003
PAS kHz/s	3.95+1.2	3.64±0.9	2.43+0.42	>0.05	<0.001
RVIVA (m/s^2)	2.53 ± 0.61	2.99±0.85	3.96±1.12	<0.003	<0.001

LVEF: Left Ventricular Ejection Fraction; E/E': Ratio of Early Mitral Flow Velocity to Early Mitral Annular Velocity, ePASP: Estimated Pulmonary Artery Systolic Pressure; FAS: Fractional Area Shortening; TAPSE: Tricuspid Annulus Systolic Excursion, PAS: Pulmonary Artery Stiffnes, RVIVA: Right Ventricular Isovolumetric Acceleration

At the 6-month follow-up, 78 patients showed complete functional recovery (LV-MPI and BNP levels came back to values comparable to control subjects). However, 6 patients did not show complete functional recovery. (MPI>0.49 ± 0.08 versus 0.35+0.06 and BNP103+15 versus 53+9' P<0.001). The pre-closure RVIVA was significantly lower and E/E' were significantly higher in patients without complete recovery compared to those with complete recovery (Table 4).

Table 4: Preclosure variables of patients with versus without complete functional recovery after device closure of patent ductus arteriiosus.

Preclosure Variable	Patients without Complete Recovery (n= 6)	Patients with Complete Recovery (n= 78)	P value
BNP	103+15	53+9	<0.001
LV-MPI	0.49 ± 0.08	0.35+0.06	<0.05
E/E'	11.5+2.1	7.3+1.7	<0.02
TAPSE	21.8 ± 4.4	24.2 ± 4.7	>0.05
RV- FAS%	53.8 ± 3.9	55.2 ± 4.1	>0.05
sPAP mmHg	62.9±8	41.5±11	<0.001
RVIVA m/s^2	1.8±0.5	2.5±0.7	<0.001

BNP: Brain Natriuretic Peptide; PDA: Patent Ductus Arteriosus; LVEF: Left Ventricular Rjection Fraction; PAP: Pulmonary Artery Pressure; E/E': Ratio of Early Mitral Flow Velocity to Early Mitral Annular Velocity.

Univariate regression analysis demonstrating that age (r=-0.312; P<0.05), LAVI (r=-385; P<0.03), E/E' ratio (r=-317; P<0.05), baseline sPAP (r=- 0.323; P<0.05), RVIVA (r=0.724; P<0.001) were significantly correlated with functional recovery after device closure of PDA. On the other hand multivariate regression analysis shows that RVIVA and PAS were the strongest independent predictors of functional recovery at 6 months of follow-up of PDA closure (r=0.582; <0.001 and r= -0.518; <0.001) (Table 5).

Table 5: linear regression analysis for left ventricular functional recovery at 6 months post-closure (significant reduction in both LV performance index and BNP (Pg/ml) levels).

Pre-closure Variables	Univariate		Multivariate	
	r	P value	r	P value
Age (years)	-0.312	<0.05	-0.164	--
LAVI	-0.385	<0.03	-0.252	<0.05
E/E'	-0.317	<0.05	-0.185	--
Baseline-sPAP (mmHg)	-0.323	<0.05	-0.21	--
RV-IVA	0.724	<0.001	0.582	<0.001

LAVI: Left Atrial Volume Index; E/E': Ratio of Early Mitral Flow Velocity to Early Mitral Annular Velocity; PAP: Pulmonary Artery Pressure.

Table 6 shows a significant correlation of RVIVA to LVIVA, E/E" ratio, LAVI, baseline sPAP in children with patent ductus arteriosus. With ROC analysis the results demonstrated that RVIVA with a cutoff value of >2.4 m/s (AUC=0.95) predicts functional recovery after device closure of PDA with a sensitivity of 86% and specificity of 96% (Table 6).

Table 6: ROC curve of variables for functional recovery.

	Cutoff value	AU-ROC	Sensitivity	Specificity
RV-IVA m/s^2	>2.4 m/s	0.95	86%	96%

RVIVA: Right Ventricular Isovolumetric Acceleration.

Discussion

We observed significantly lowering of IVA at the time of diagnosis of patent ductus arteriosus, that correlated with sPAP and serum levels of BNP. At 6 months postclosure of PDA, we found that RVIVA had normalized compared to the values from preclosure and at one month after closure. This normalization of RVIVA was associated with normalization of LVIVA, significant decrease in sPAP and decrease in BNP at 6 months postclosure. The RVIVA with a cut-off value of > 2.4 m/s2 was an independent predictors of functional recovery after device closure of PDA.

Subclinical right ventricular dysfunction may occur early in patients with PDA and may affect the clinical course of the disease even after closure. However, no much studies had investigated right ventricular function in patients with PDA. With significant systemic-to-pulmonary shunt, the LV volume load and right ventricular pressure load increase simultaneously. After closure of PDA, the PAP remains suspended at a high level, due to longer period of recovery of pulmonary endothelial injury, pulmonary in situ thrombosis, and LV failure [12,13]. Right ventricle is usually the victim of the different diseases affecting cardiovascular system, as it is more compliant, more thin walled and less muscular and usually forgetting in there clinical practice [14] Moreover Right ventricle dysfunction has a significant impact on the patients symptoms in addition to it's a valuable indicator of the severity and chronicity of pulmonary hypertension [15].

Echocardiographic parameters have been reported to assess the RV function, namely, TAPSE, 2D RV FAC, 2D RV EF, TDI, ratio of RV transverse diameter to left ventricular transverse diameter (RVETD/LVETD), and Sm. These parameters, however are load dependent and unreliable when RA pressure is elevated [16]. On the other hand, IVA can detect minimal changes in myocardial function, even the changes in the preload and afterload within the physiological. IVA was the most strong pre and after load independent compared to tissue Doppler derived peak systolic velocities, strain and strain rate [17].

Tugcu et al. [18] reported that spite of normal pulmonary and systemic pressure in patients with obstructive sleep apnea syndrome, IVA was the only parameter that changed significantly during right ventricular functional assessment. This may be related to subclinical RV dysfunction. We analyzed the effect of percutaneous device closure of PDA on RVIVA and other RV function parameters. There were significant rise in RV-IVA, decrease in pulmonary artery pressure. These changes were significantly associated with significant reduction in BNP and improvement of left ventricular function at 6 months of follow-up. Pauliks et al. [19] demonstrated that IVA was significantly improved after defect closure in patients with atrial septal defect.

We observed little significant difference in FAC and TAPSE in patients with PDA and controls. Moreover these parameters did not changes significantly after closure of PDA or even after 6 month of follow-up. On the other hand both RV-IVA showed a highly significant difference. Based on this information, the significant recovery in the right ventricular IVA values may help explain the improved ejection fraction and significant decrease in BNP. Moreover these observation provide that right ventricular IVA assessment seems to be a more sensitive technique to assess early changes and follow-up of right ventricular function.

Conclusion

Measurement of RVIVA in patients with PDA specially those presented late are important to differentiate high- and low-risk groups in terms of prognosis. In our study, we assessed right ventricular function in children with PDA utilizing RVIVA, RVEF, PAP, TAPSE, and MPI), and reached the conclusion that tissue Doppler RVIVA was an independent predictors for functional recovery after percutaneous closure of patent ductus arteriosus.

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