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Original Article

Right Atrial Mechanics in Children with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

Konjenital Kalp Hastalığına Sekonder Arteryel Pulmoner Hipertansiyon Olan Çocuklarda Sağ Atrium Dinamiklerinin Değerlendirilmesi

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ABSTRACT

Objective: This study aims to evaluate right atrial functions in children with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) by deformation indices assessed by two dimensional-speckle tracking echocardiography.

Method: A total of 40 patients, including 15 patients with World Health Organization Functional class II-III CHD-PAH and 25 age-matched healthy controls were enrolled in the study. Deformation indices were measured by electrocardiogram-gated right atrial longitudinal strain recordings.

Results: Peak atrial strain/reservoir phase (24.19±15.81 vs. 40.62±12.35%,) (p=0.01), conduit phase (15±00.13.6% vs. 26.4±10.7%) (p=0.006) and pump phase (10.06±9.07% vs. 14.21± 5.05%) (p=0.07) were comparatively evaluated in the patient and control groups, respectively Regional peak atrial strain measurements performed for basal anterolateral (p=0.06), mid anterolateral (p=0.12), apical anterolateral (p=0.61), apical inferoseptal (p=0.28) and mid inferoseptal (p=0.001), basal inferoseptal (p=0.02) segments were also compared between the patient and control groups.

Conclusion: Right atrial deformation indices were significantly impaired in patients with CHD-PAH. Deterioration in the right atrial reservoir and conduit functions are associated with right ventricular diastolic dysfunction. Both global and regional changes can be observed in the measurement of right atrial strain secondary to the existing heart defects and operative conditions of the patients.

Keywords: Pulmonary hypertension, right atrial strain, speckle tracking echocardiography

ÖZ

Amaç: Bu çalışmada konjenital kalp hastalığı (CHD) ile ilişkili pulmoner arteriyel hipertansiyonu (PAH) olan çocuklarda iki boyutlu-speckle strain ekokardiyografi ile sağ atriyum deformasyon indekslerinin değerlendirilmesi amaçlanmıştır.

Yöntem: New York Kalp Derneği fonksiyonel sınıfı II-III olan, CHD ile ilişkili pulmoner hipertansiyonlu 15 hasta ve yaşları eşleştirilmiş 25 sağlıklı kontrol olmak üzere toplam 40 hasta çalışmaya dahil edildi. Deformasyon indeksleri, elektrokardiyografi senkronize sağ atriyal strain yöntemiyle ölçülmüştür.

Bulgular: Pik atriyal strain/rezervuar fazı (hasta ve kontrol grupları, sırasıyla 24,19±15,81 vs. 40,62±12,35) (p=0,01), konduit fazı (hasta ve kontrol grupları, 15,00±13,6 vs 26,4±10,7; sırasıyla) (p=0,006) ve pompa fazı (hasta ve kontrol grupları sırasıyla 10,06±9,07 ve 14,21±5,05) (p=0,07) hasta ve kontrol grupları karşılaştırmalı olarak değerlendirildi. Altı farklı alanda bölgesel pik atriyal strain ölçümleri; bazal anterior lateral (p=0.06), medial anterior lateral (p=0.12), apikal anterior lateral (p=0.61), apikal inferior septal (p=0.28) ve medial inferior septal (p=0.001), bazal inferior septal (p=0.02) hasta ve kontrol grupları karşılaştırmalı olarak değerlendirildi.

Sonuç: Sağ atriyal deformasyon indeksleri CHD ile ilişkili pulmoner hipertansiyonlu hastalarda anlamlı olarak düşük saptandı. Sağ atriyal rezervuar ve konduit fonksiyonlarındaki bu bozulma sağ ventrikül diyastolik disfonksiyonu ile ilişkilidir. Sağ atriyum strain ölçümünde, hastaların mevcut kalp defektlerine ve ameliyat koşullarına bağlı olarak hem global hem de bölgesel değişiklikler gözlemlenebilmektedir.

Anahtar kelimeler: Pulmoner hipertansiyon, sağ atriyal strain, speckle tracking ekokardiyografi

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INTRODUCTION

Pulmonary hypertension is a progressive disease that results in hypertrophy, dilatation, and failure of the right ventricle (RV) due to increased pulmonary vascular resistance (PVR). Right atrium (RA) is also affected secondary to pulmonary hypertension. An increase in RA pressure and dilatation is reported to be a prognostic predictor for adverse outcomes[1-3]. However, data regarding right atrial reservoir, conduit, and pump functions are unsatisfactory. Two dimensional-speckle tracking echocardiography (2D-STE) is a reliable technique that allows the assessment of global and regional myocardial function as a noninvasive and quantitative approach[4,5]. After its availability, evaluation of intended cardiac cavity deformation became possible during whole cardiac cycle at one heartbeat. The method was originally used to assess left ventricular deformation, then right ventricular, left atrial, and more recently right atrial deformation[6-8]. Its usage in adult population with pulmonary hypertension, indicated that right atrial longitudinal strain decreased substantially compared to the control group and displayed an inverse correlation with RA pressure[9-11]. It has been implied in a quite limited number of studies conducted in pediatric pulmonary hypertension cases that RA functions reduced distinctly compared to the control group, suggesting that deformation indices could have a prognostic potential to predict the adverse clinical results[12].

The aim of this study was to evaluate the global and regional RA functions in patients with congenital heart disease (CHD) - pulmonary arterial hypertension (PAH) using 2D-STE. The measurements were compared with those of the control group.

MATERIALS and METHODS

Study Population

Fifteen children diagnosed with CHD-PAH were included in this study. Children in the study group have been receiving specific anti-PAH therapy (bosentan, sildenafil, iloprost, masitentan, tadalafil) and had World Health Organization functional class II or III PAH. Patients with primary pulmonary hypertension, large atrial septal defects, and left ventricular dysfunction or pulmonary vein obstruction and children that did not undergo right heart catheterization were not included in the study. Gender- and age-matched 25 healthy children were enrolled as a control group in the study. The control group included children referred to the pediatric cardiology clinic due to chest pain, tachycardia, cardiac murmur, but with cardiological examination (echocardiography and electrocardiography) results within normal range. Data related to echocardiographic parameters, results of the 6-minute walk test (6-MWT), serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, the measurements of PVR, mean pulmonary artery pressure levels performed during cardiac catheterization were retrieved from electronic patient folders of the hospital. Informed consent was obtained from all patients and/or their parents. This prospective study and its protocol were approved by the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol no: 534, date: 11.03.2021).

Echocardiography

Echocardiographic examinations were performed using a Philips Epiq7 ultrasound machine (Philips Medical Systems, Andover, MA, USA).

Two-dimensional Speckle Tracking Analysis

Apical four-chamber views were acquired and uploaded for further analysis. The frame rate of the acquired images was generally within 40-80 Hz range. Speckle-tracking software was used to measure peak RA strain which was traced manually along the RA endocardial border. To refrain from the confounding effect of tricuspid annular motion, tracing was performed 1 mm above the atrioventricular junction. Three functional components of the RA were assessed: reservoir function (storage of blood from the systemic venous circuit during ventricular systole when the tricuspid valve is closed), conduit function (passive blood emptying into the RV when the tricuspid valve is open), pump function (contraction of the atria in late diastole to complete ventricular filling). According to the software used in this study, the RA reservoir, conduit, and pump strains were calculated with the initial reference frame set at the beginnig of the QRS-wave of the surface electrocardiogram[13]. After right atrial endocardial borders were drawn manually, RA wall was automatically split into six segments by the software program as: basal anterolateral (BAL), mid anterolateral (MAL), apical anterolateral (AAL), apical inferoseptal (AIS), mid inferoseptal (MIS), and basal inferoseptal (BIS). The global right atrial strain was automatically calculated as the averages of these six segments.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and nominal variables as frequencies

and/or percentages. In the comparisons of variables with normal distribution between patient and control groups t-test, and for variables with non-normal distribution Mann-Whitney U test were used.

Chi-square test was used for the comparison of categorical variables. The p-value <0.05. was accepted to be statistically significant. Inter- and intra-observer variabilities were evaluated in randomly selected 15 patients. RA strain measurements were carried out by two observers. Differences between measurements of two observers showed interobserver variability. RA measurements were repeated by an observer after four weeks. Differences between measurements performed by the same observer at baseline and four weeks later were defined as intraobserver variability. Intraclass correlation coefficient was used to in the analyses of inter- and intra-observer variabilities.

RESULTS

Demographic, clinical, and hemodynamic data are listed in Table 1. A total of 40 people were enrolled in the study, including 15 pulmonary hypertension patients with a mean age of 8.4± 6.7 years (5 female, 10 male), and 25 healthy control subjects (6 females, 19 males, average age 8.4± 4.12 years). The age and sex of the controls subjects were not significantly different from the PAH group. Thirteen of 15 patients with pulmonary hypertension had New York Heart Association (NHYA) class II, and two patients had NHYA class III PAH. Ten patients were receiving monotherapy, 5 were receiving

Table 1. Demographic, functional capacity, and right heart catheterization parameters

Demographic, functional capacity, and right heart catheterization parameters		
	Patient (n=15)	**Control (n=25)**
Age (years), [median, ([1]IQR*)]	8.4±6.77	8.4±4.12
Gender (female/male)	5F/10M	6F/19M
WHO classification	Class II: 13 Class III: 2	
Diagnoses		
[2]VSD s/p repair	4	
Unrepaired VSD	5	
Coarctation s/p repair and pulmonary banding and VSD	1	
[3]PDA (transcatheter closure) and VSD	1	
Unrepaired truncus arteriosus	1	
[4]AP Window s/p repair	1	
[5]Unrepaired DORV	1	
Tricuspid atresia	1	
Medical treatments		
Bosentan	4	
Macitentan	1	
Ilioprost	5	
Tadalafil	1	
Monotherapy	10	
Combined therapy	5	
[6]NT-pro BNP (pg/mL), [median, (IQR*)]	725 (123-12800)	
[7]6-MWT (m), [median, (IQR*)]	360 (90-520)	
[8]mPAP (mmHg), [median, (IQR*)]	63 (26-104)	
[9]PVR (Wood Units.m^2) [median, (IQR*)]	5 (2.3-45)	
PVR/SVR [median, (IQR*)]	0.4 (0.3-1.4)	

[1]IQR: Interquartile range, [1]VSD: Ventricular septal defect, [2]VSD s/p repair, VSD closed primarily with sutures or a patch, [3]PDA: Patent ductus arteriosus, [4]AP window: Aortopulmonary window, [5]DORV: double outlet right ventricle, [6]NT-pro BNP, N-terminus pro-B-type natriuretic peptide, [7]6-MWT: Six minute walk test, [8]mPAP: Mean pulmonary arterial pressure, [8]PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance

combined treatment. Five of these patients had undergone surgical interventions including VSD repair (n=3), ASD and VSD repair (n=1), aortic coarctation repair and pulmonary banding (n=1). In one case, the PDA was closed with a device using the transcatheter technique. Four patients had small-medium secundum ASD.

Peak strain values in CHD-PAH patients, right atrial reservoir function was significantly lower than the control group (24.19±15.81 vs. 40.62±12.35 respectively; p=0.001). Also right atrial passive conduit function was substantially impaired in CHD-PAH patients compared to controls (15.00±13.6 vs. 26.4±10.7, p=0.006). Although right atrial active pump function was -though not statistically significant-decreased in CHD-PAH patients relative to control subjects (10.06±9.07 vs. 14.21±5.05, p=0.07).

Regional peak atrial strain measurement values obtained from 6 different segments were lower in the study group when compared to the control group: BAL (p=0.06), MAL (p=0.12), AAL (p=0.61), AIS (p=0.28) and MIS; (p=0.001), BIS (p=0.02) (Table 2).

The intra-observer ICC coefficients for BAL (0.93), MAL (0.94), AAL (0.91), AIS (0.90), MIS (0.96), BIS (0.94) , and RA GLS (0.93) were as indicated in parentheses. The inter-observer ICCs for variability was 0.92, 0.90, 0.91, 0.93, 0.94, 0.93, 0.92 for BAL, MAL, AAL, AIS, MIS, BIS, RA GLS, respectively.

DISCUSSION

Right atrial deformation indices are promising tools to evaluate functional alterations in the mechanics of right heart in children with CHD-PAH. Previous pediatric studies had shown abnormal strain results in univentricular children[14] and patients with repaired tetralogy of Fallot[15]. Studies performed in pediatric and adult patients showed a diminished right atrial longitudinal strain in patients with PAH[10,12]. Querejeta Roca et al.[9] showed that reservoir and conduit functions of RA are reduced regardless of RA size and pressure and revealed the presence of a correlation between poor RA longitudinal strain and RV dysfunction. In our study, right atrial reservoir and conduit functions were markedly diminished in children with PAH compared with controls. Bhave et al.[15] showed that speckle strain-derived RA reservoir function may predict clinical outcome and invasive hemodynamic parameters in patients with group I PAH[16]. In another study, reservoir and conduit functions of the RA were significantly decreased although pump function was protected until the late phases of the PAH. In our study, pump phase values of PAH patients were lower than the control group without any substantial intergroup difference. In these studies mentioned above, we stated that right atrial strain values were found to be lower in the PAH group than in the control group, which is similar to our study. Nevertheless, upon comparing the studies, variations in strain values were observed both in the PAH group and the control group. This discrepancy may stem from variations in the functional capacities of the patients and differences in the methodology and software employed for the evaluation of cardiac strain. In addition, in our study, in the PAH group three patients had undergone VSD surgery, one had experienced both VSD and ASD surgery, and four patients had small - moderate

Table 2. Right atrial longitudinal and regional strain parameters

Parameters	Patient	Control	p-value
Right atrial longitudinal strain, %			
Reservoir phase, %	24.19±15.81	40.62±12.35	0.001
Conduit phase, %	15±13.60	26.4±10.70	0.006
Pump phase, %	10.06±9.07	14.21±5.05	0.07
Right atrial regional peak atrial strain			
BAL, %	47.16±3.05	77.69±33.16	0.06
MAL, %	34.13±20.08	43.84±16.71	0.12
AAL, %	16.02±22.01	18.64±10.45	0.61
AIS, %	19.97±20.50	26.74±18.03	0.28
MIS, %	25.92±13.75	47.05±19.00	0.001
BIS, %	22.60±15.34	38.99±23.09	0.02

BAL: Basal anterolateral, MAL: Mid-anterolateral, AAL: Apical anterolateral, AIS: Apical inferoseptal, MIS: Mid inferoseptal, BIS: Basal inferoseptal

ASD. Previous researches had indicated that patients undergoing surgical ASD closure exhibit a lower right atrial longitudinal peak systolic strain compared to those undergoing device closure and control subjects. Factors such as the presence of an atriotomy scar, myocardial injury, and the use of a patch may negatively impact right atrial functions[17-18]. Another study also noted a decreased right atrial longitudinal strain in individuals with ASD when compared to a healthy control group[19]. We think that these patient characteristics may also contribute to the lower strain values detected in our patients.

Atrial function plays an important role in ventricular filling as a blood storing reservoir, a conduit during early ventricular filling, and an active emptying chamber that provides additional ventricular filling with its active contraction. Recent functional and prognostic data have improved our knowledge of atrial dysfunction in cardiac mechanics before the onset of overt heart failure. As has been shown in studies investigating left atrial function, right atrial reservoir function was also identified as a prognostic parameter[20]. PAH is a progressive disease which is characterized by persistent RV pressure overload and eventual RV dysfunction. Right ventricular ability to compensate stroke volume despite increased pressure determines the survival of the patients with PAH. Lambertz et al.[20] showed that the active emptying function of the RA increased in subjects with pressure overload in the RV, which improved the diastolic filling of the RV. An experimental animal study has demonstrated an association between increased right ventricular pressure and elevated atrial active and reservoir functions, suggesting the impact of a compensatory mechanism[17].

In our study, especially MIS and BIS wall measurements in the right atrial regional longitudinal strain showed significantly lower values in the PAH group than in the control group. This is the first study to evaluate regional atrial strain among studies investigating right atrial mechanics in PAH patients. A study in which regional strain of the RA was evaluated using the 3D-STE method in operated tetralogy of Fallot patients reported that basal and mid-atrial longitudinal strain measurements in the RA were significantly lower than in the control group[21], but no comment was made on the effective etiologic factors. We think that atriotomy, patch repair of ASD, tricuspid septal leaflet takedown for VSD closure may contribute to the changes in regional atrial wall deformation.

Study Limitation

Our study was a single-center trial. Due to the small number of patients, no relationship might be established between strain analysis and clinical prognostic parameters such as proBNP and 6MWT. Echocardiographic studies and pulmonary hemodynamic measurements were not performed simultaneously. Right atrial has a thinner myocardium, which may impair signal quality, especially in the RA root. There is currently no software to be used for RA-specific speckle tracking echocardiography. In this study we used speckle-tracking software developed for LV deformation, which was reportedly used for the measurement of RA deformation in previous studies. Finally, we could not provide information about the disease course and the prognosis of the study group for a long term given the cross-sectional design of the study

CONCLUSION

Our study has revealed that the right atrial functions were substantially decreased in patients with CHD-PAH. Changes in right atrial reservoir and conduit functions are associated with right ventricular diastolic dysfunction. Both global and regional changes can be seen in the measurement of right atrial strain secondary to the existing heart defects and operative conditions of the patients.

Ethics

Ethics Committee Approval: This prospective study and its protocol were approved by the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol no: 534, date: 11.03.2021).

Informed Consent: Informed consent was obtained from all patients and/or their parents.

Author Contributions:

Surgical and Medical Practices: G.V., T.M., M.M.Y., Concept: G.V., T.M., Design: G.V., T.M., Data Collection or Processing: G.V., T.M., E.G., C.Z., Analysis or Interpretation: G.V., M.M.Y., Literature Search: G.V., T.M., E.G., C.Z., Writing: G.V., T.M.

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