Evaluation of Right Ventricular Systolic Function by Echocardiography in Pulmonary Hypertension Associated With Congenital Heart Disease: a Cross Sectional Study

Shahla Roodpeyma [1,*]; Sima Rafieyian [1]; Seyed Hassan Sharifi [1]

[1]Department of Pediatric Cardiology, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

Corresponding author: Shahla Roodpeyma, Department of Pediatric Cardiology, Shahid Beheshti University of Medical Sciences, P. O. Box: 1998734383, Tehran, IR Iran. Tel: +98-2122074087-98, Fax: +98-2122074101, E-mail: roodpeyma_shahla@yahoo.com

Background: Pulmonary arterial hypertension (PAH) is a serious complication of unrepaired congenital left-to-right shunts. The final consequence is right ventricular (RV) systolic dysfunction and reversal of shunt.

Objectives: The aim of this study was to evaluate the clinical course and paraclinical findings in a group of patients with PAH associated with congenital heart disease (PAH-CHD). We also compared the results obtained by echocardiographic technique used for assessment of RV systolic function (Tricuspid annular plane systolic excursion TAPSE) with parameters obtained by diagnostic cardiac catheterization.

Patients and Methods: During a one-year period (2011-2012), all patients with confirmed diagnosis of PAH-CHD in pediatric cardiology ward of a teaching hospital enrolled in the study. They underwent through echocardiographic assessment and cardiac catheterization.

Results: Forty-one patients (22 males, 19 females) with mean age of 5.5 ± 5.5 years (4 months to 18 years) entered in the study. Ventricular septal defect (VSD) was the most common (65.8%) underlying CHD. Patients ≤ 10 years old comprised 71, 8% of subjects. The higher level of Tricuspid regurgitation (TR) was correlated with higher mean pressure of pulmonary artery (PAP), and greater resistance ratio (Rp/Rs) ($P = 0.001$, and $P = 0.044$ respectively). Indexed TAPSE (TAPSE/body surface area) had a significant reverse correlation with mean PAP ($P = 0.015$), and Rp/RS ($P = 0.002$). There was a significant reverse correlation between indexed TAPSE and TR ($P = 0.032$).

Conclusions: TAPSE is an easy echocardiographic measurement and reflected RV systolic function. Indexed TAPSE has good correlation with hemodynamic data obtained by cardiac catheterization. TAPSE index is recommended for evaluation of RV systolic function in pediatric patients with PAH-CHD.

Keywords: Congenital Heart Defect; Echocardiography; Pulmonary Hypertension; Right Ventricle; Tricuspid Valve

1. Background

Pulmonary artery hypertension (PAH) is a kind of pre capillary pulmonary hypertension (PH) (1). The two most common types of PAH, i.e. PAH associated with left-to-right shunts (up to 50%), and idiopathic PAH (up to 40%) accounts for 90% of PAH cases in pediatric age group. Female gender is predominant in both types. In the majority of cases, the underlying heart anomaly is a kind of septal defect. Ventricular septal defect (VSD) is the most common type of CHD associated with PAH (2). Right-to-left or bidirectional shunt gives rise to cyanosis or Eisenmenger syndrome. Fifty percent of all patients with large unrepaired VSD, approximately 10% of patients with large unrepaired atrial septal defect (ASD), and almost all patients with truncus arteriosus are at risk for developing Eisenmenger syndrome (3). In developing countries, there is a high frequency of PAH in children. This may be due to lack of opportunity for closing the defects in this age group (4). Right heart failure and tricuspid regurgitation may be the presenting symptoms in these children. Right heart catheterization is necessary to confirm the diagnosis of PH, and to distinguish hemodynamic mechanisms. PH has been defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest as assessed by right heart catheterization. The pulmonary artery wedge pressure is normal unless there are left heart diseases, such as mitral stenosis, mitral regurgitation, or left ventricular dysfunction causing venous hypertension (1).

Right ventricle (RV) function is an important determinant for assessment of prognosis in PH; however noninvasive evaluation of RV function is often limited due to complex geometry of this chamber. Rushmer et al. for the first time noticed that left ventricular contraction takes place in both transverse and longitudinal planes, but RV contraction requires longitudinal shortening of its muscle fibers (5). Systolic displacement of the tricuspid annulus towards the RV apex along the longitudinal axis referred as tricuspid annular plane systolic excursion (TAPSE) closely correlates with RV ejection fraction. Forfia et al. found that TAPSE is a valuable predictor of survival in adult patients with PAH, and concluded that TAPSE mea-

surement should be incorporated in echocardiographic assessment of PAH patients (6). In adult patients, TAPSE > 15 mm is indicative of satisfactory or stable condition and TAPSE ≤ 15 mm shows unstable or deteriorating condition (7). Studies specifically conducted in children are limited in number and scope. A research by Lammers et al. on 41 children with PH showed that pulmonary acceleration time and TAPSE have good correlation with tissue Doppler imaging of systolic velocities (8). Cardiac magnetic resonance imaging requires general anesthesia or heavy sedation in young children, thus its application is limited in this age group. TAPSE measurement does not relate to RV geometry and thus it is useful and practical. It can be measured by transthoracic echocardiography.

2. Objectives

The purpose of the present study was to evaluate the clinical and paraclinical data, and assess right ventricular function in a group of patients with PH associated CHD by echocardiographic measurement of tricuspid regurgitation and TAPSE. We also wanted to evaluate the association between these echocardiographic parameters and hemodynamic data such as mean pressure of pulmonary artery, and the ratio of pulmonary vascular resistance to systemic vascular resistance obtained by catheterization technique.

3. Patients and Methods

During a one-year period from January 2011 to December 2012, a cross sectional study was conducted in pediatric cardiology ward of Shahid Modarres hospital in Tehran. All patients with confirmed diagnosis of PAH due to CHD were included in the study. Two patients with idiopathic PH were excluded. Each patient entered only one time in the study. The following data were collected for each patient: gender, age, height, and weight, body surface area, functional class, underlying CHD, electrocardiographic parameters, chest X-ray findings, echocardiographic, and cardiac catheterization measurements. PAH was defined as mean pressure of pulmonary artery ≥ 25 mmHg by right heart catheterization. Eisenmenger syndrome was defined as supra systemic pulmonary artery pressure with right to left shunt and cyanosis. All patients underwent a complete transthoracic echocardiographic study including, M-mode, 2-D, color Doppler flow, and TAPSE measurement using a Vivid 7 system. Echocardiography was performed by a single experienced pediatric cardiologist. The underlying CHD was detected, and the velocity of tricuspid regurgitation jet in meter per second (m/s) converted to pressure in millimeter mercury (mmHg) by using the simplified Bernoulli equitation ($P = 4V^2$) without adjustment for right atrial pressure. All the patients had measureable TR jets. TAPSE was measured by 2-dimensional echocardiography-guided M-mode recording from the apical 4-chamber view, with the cursor placed at the free wall of the tricuspid annulus. Care was taken to align the sample volume as vertically as possible with respect to

the cardiac apex. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent, to the lowest point of descent during ventricular systole. Simultaneous ECG tracings obtained during M-mode recording were used to measure R-R intervals. TAPSE index (indexed TAPSE) was defined as TAPSE/body surface area (mm/m^2). Measurements were repeated on 3 occasions; and average was obtained.

Cardiac catheterization with standard method was performed. Oral chloral hydrate was prescribed for each patient 30 minutes before procedure. Mild anesthesia was necessary to catheterize infants. These patients were adequately ventilated during the entire procedure, with Pco_2 maintained at normal level or slightly decreased and peripheral oxygen saturation close to the pre-catheterization level. Vaso reactivity test by administration of 100% oxygen was performed in cases with systemic pulmonary hypertension and a reduction of 20% in PAP considered positive response. The oxygen saturations and pressures of superior vena cava, right atrium, right ventricle, pulmonary artery, left ventricle, and aorta were measured. Pulmonary artery wedge pressure was measured. Pulmonary and systemic vascular resistance, pulmonary and systemic blood flow were calculated. Pulmonary vascular resistance was calculated by the following equation; mean-PAP mean left atrial pressure (pulmonary capillary wedge pressure)/pulmonary blood flow. Systemic vascular resistance was calculated by the following equation; mean aortic pressure-mean right atrial pressure/systemic blood flow. Pulmonary to systemic blood flow-ratio was calculated using measured oxygen consumption and the following equation: saturation of aorta minus saturation of right atrium/saturation of pulmonary vein or left atrium minus saturation of pulmonary artery. Functional class of patients was defined according to World Health Organization (WHO) classification of pulmonary hypertension which is modified after the New York Heart Association (NYHA) functional class 1. Angiocardiography confirmed the diagnosis. The Medical Ethic Committee of the hospital approved the study and all parents gave their informed consents.SPSS software (version 16) was used for statistical analysis. Continuous data were presented as mean with standard deviation. Discrete data were given as counts or as percentage. Pearson correlation coefficient test was used for evaluation of correlation between hemodynamic data. No multivariable analysis was performed due to the low number of patients. P value less than 0.05% was considered significant.

4. Results

The study population consisted of 41 patients (22 males, 19 females). The mean age of patients was 5.5 ± 5.5 years with a range of 4 months to 18 years. The age group of less than one-year old accounted for 8 (17.4%), 1 to 5 years old 13 (28.3%), and 5 to 10 years old 12 (26.1%) cases. Patients less than 10 years old comprise 71.8% of our subjects. The frequency of different types of CHD (simple, combined,

complex) was as follow: VSD (27, 65.8%), patent ductus arteriosus PDA (14, 34.1%), atrial septal defect ASD (8, 19.5%), atrioventricular septal defect AVSD (5, 12.2%), and complex cyanotic heart lesion with increased pulmonary blood flow such as D-transposition of great arteries (D-TGA) + large VSD, L-TGA, Tricuspid atresia + L-TGA, and double outlet right ventricle (DORV) + large VSD each (1, 2,4%) case.

The findings of chest x-ray showed increased C/T ratio in 27/41 patients, increased pulmonary vascular marking in 30/41, and prominent PA segment in 35/41 patients. Electrocardiographic evaluation revealed normal sinus rhythm in all, RAD in 30, RVH in 22, and BVH with dominancy of right ventricle in 15 cases. At enrolment, 26 patients were in functional class 1 and 12 in functional class II. During the course of study, sixteen patients underwent cardiac surgery and two of them died due to presumed post-operative pulmonary hypertension crisis within 24 hour after surgery. There were seven patients with Down syndrome. Pulmonary artery pressure in all cases was more than 50 mmHg, in 8 cases was equal or near to systemic pressure, and in 2 patients it was supra systemic. Two of eight cases with near systemic pressure showed positive response to vaso reactivity test. Patients with negative response and those with supra systemic pressures were scheduled for medical therapy and regular follow-up. Table 1 summarizes the demographic and hemodynamic data of patients.

Table 2 shows the correlation between hemodynamic variables. As it is shown in this table, there was a significant correlation between higher level of TR jet and both increased mean PAP; and increased Rp / Rs ratio (P = 0.001, and P = 0.044 respectively). We did not find a significant correlation between TAPSE values and mean PAP or resistance ratio, but there was a significant reverse correlation between TAPSE index and both mean PAP, and Rp/Rs. Higher level of mean PAP, and Rp/Rs were correlated with lower TAPSE index (P = 0.015, and P = 0.002 respectively). Increased TR was significantly correlated with decreased TAPSE index (P = 0.032).

Table 1. Demographic and Hemodynamic Data of Patients [a]

Variable	Range	Value [b]
Age, y	0.3-18	5.5 ± 5.5
Weight, kg	4.9-61	17.5 ± 14.2
Height, m	0.61-1.65	0.97 ± 0.31
Body surface area, m^2	0.27-1.53	0.58 ± 0.32
Mean aortic blood pressure, mmHg	47-93	67.4 ± 10.9
Mean pulmonary blood pressure, mmHg	27-90	53.7 ± 18.9
Pulmonary vascular resistance/systemic vascular resistance	0.1-1	0.2 ± 0.5
Pulmonary blood flow/systemic blood flow	2-3	2.2 ± 1.4
Tricuspid regurgitation jet, mmHg	30-80	56 ± 26
TAPSE, mm	9-20	15.9 ± 2.9
TAPSE index, mm/m^2	14-46	21.8 ± 5.3

[a] Abbreviation: TAPSE, tricuspid annular plane systolic excursion.
[b] Data are presented as mean ± SD.

Table 2. Correlation Between Hemodynamic Data [a]

Variable	r (Correlation)	P Value
Mean PA pressure mmHg *vs.* Mean TR, mmHg	0.487	0.001
Mean Rp/Rs *vs.* Mean TR, mmHg	0.320	0.044
Mean PA pressure, mmHg *vs.* Mean TAPSE, mm	-0.216	0.175
Mean Rp/Rs *vs.* Mean TAPSE, mm	-0.231	0.151
Mean PA pressure, mmHg *vs.* Mean TAPSE index, mm/m^2	-0.463	0.015
Mean Rp/Rs *vs.* Mean TAPSE index, mm/m^2	-0.427	0.002
Mean TR, mmHg *vs.* Mean TAPSE index, mm/m^2	-0.390	0.032

[a] Abbreviations: PA, pulmonary artery; TR, tricuspid regurgitation; Rp, pulmonary artery resistance, Rs, systemic resistance; TAPSE, tricuspid annular plane systolic excursion.

5. Discussion

A seven-year registry (1999 to 2005) about pediatric pulmonary hypertension was conducted in Swiss. Twenty three patients (12 males, 11 females) aged 0 to 18 years were included in the study. Etiology of PAH in the above sample was as follows; CHD with left to right shunt (12/23, 52.2%), Idiopathic PAH (8/23, 34.8%), accompanied with pulmonary diseases (3/23, 3.0%) (9). In another registry from Netherland; 5970 adult patients with CHD from 86 hospital were included, and the incidence of PAH was 4.2%. Ventricular septal defect (42%) was the most common septal defect among patients, and PAH in septal defects was around 6%. The above epidemiologic study by Duffels et al. showed that non-Eisenmenger patients with PAH (81%) were in NYHA/WHO class 1 or II; whereas, the majority of the Eisenmenger patients were in class III. They also found that female gender and increased systolic PAP were independently associated with higher functional class (10). The majorities (75%) of adult patients with PH in a report by Forfia et al. were in class 1 of WHO classification of pulmonary hypertension (6). Data of our study did not show significant difference between genders. The majority of our cases (92.6%) were in NYHA/WHO class I or II and most of them were less than 10 years old. VSD was the most common underlying defect. Eisenmenger syndrome was noted in 2 cases. There was not previous history of cardiac surgery or PAH as a result of surgical shunts in our subjects. Normal wedge pressures in our cohort reflected the precapillary etiology of pulmonary hypertension in them.

PAH due to systemic-to-pulmonary shunts is the consequence of chronic exposure of the pulmonary vasculature to increased pulmonary blood flow. Left-to-right shunt results in increased pulmonary blood flow, shear stress, and circumferential stretch. Then endothelial dysfunction and vascular remodeling occurred, and

led to increase in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR) and inverted shunt. Pre-tricuspid lesions (ASD) produce an increased flow in the pulmonary vascular bed and will show a lower and delayed occurrence of PAH than post tricuspid shunts (VSD or PDA) which produce a combined pressure and volume overload (2). Surgical correction of anomalies associated with significant left-to right shunt in early infancy prevents insult to the pulmonary vascular bed due to increased blood flow and pressure (11, 12). Post- operative PH both in the immediate period after surgical repair and during long term follow-up remains a real therapeutic dispute (4). A resistance ratio of < 0.3 is interpreted as indicative of a favorable outcome following operation (3). The resistance ratio of 2 patients with supra systemic pressure in our data was ≥ 0.4, and they were not suitable for cardiac surgery.

The characteristic ECG findings in PAH patients include: right axis deviation, right atrial enlargement and right ventricular hypertrophy. Radiographic manifestations include: right atrial and right ventricular enlargement, prominent pulmonary artery segment as well as congestion of central pulmonary arteries. As the pulmonary vasculature resistance increase and the CHD are not corrected, the heart size may decrease due to a smaller left to right shunt (12). In the present study, cardiomegaly with prominent PA segment and RV enlargement was the most common radiologic finding, and the majority of patients presented with characteristic ECG.

Our data showed a significant correlation between greater magnitude of TR and higher level of both mean PAP, and resistance ratio. The degree of tricuspid regurgitation is an important determinant of RV pump function. Among patients with preserved RV function, those with mild or no tricuspid regurgitation were at significantly lower risk of dying than those who had moderate to severe TR (7). In a population of 204 children with CHF secondary to PAH-CHD, there was a strong correlation between severities of PAH and magnitude of tricuspid and pulmonary valve insufficiency (13).

There are few data about TAPSE measurement in pediatric age group. Koestenberger et al. measured TAPSE value in 640 healthy children (age range from neonate to 18 years old). TAPSE values increased with age and BSA in a non-linear way. Normal values for TAPSE in older adolescents were very similar to adults. TAPSE values were lower in newborns and infants than in older children and adolescents, although RV systolic function was preserved. There was no significant difference in TAPSE values between male or female children (14). The findings of a research (15) which determined the normal value of TAPSE in 405 Spanish children and adolescents were similar to that described by Koestenberger et al. In another study by Koestenberger and colleagues, TAPSE value of 49 children and young adult with PAH-CHD and 156 patients with TOF were compared with age-matched normal subjects. Patients with PAH-CHD as well as patients with TOF showed positive correlation between TAPSE and RVEF, and negative correlation between TAPSE and RV indexed end-diastolic volume determined by magnetic resonance imaging (16). The results of our study showed a reverse association between TAPSE and severity of tricuspid regurgitation, and this corresponds with association between poor RV function and greater degree of TR. We did not find a significant association between TAPSE value and both parameters of mean pressure of pulmonary artery, and resistance ratio. Comparing TAPSE index with both of the above parameters, revealed a significant reverse correlation between them. These finding indicated that TAPSE index is more suitable for evaluation of RV function in pediatric patients. RV systolic function is inversely related with afterload, so it is logical that there is an inverse relationship between TAPSE and PVR, suggesting that TAPSE is afterload dependent. TAPSE is modified by increasing BSA and increasing age. Considering the developmental changes, it is logical not to use a single value throughout the pediatric period. It is better refer to TAPSE according to age and BSA to achieve correct results. Present study showed that TAPSE measurement is a reproducible echocardiographic index for assessment of RV systolic function. It is easier than measurement of RV ejection fraction. Potential limitations of this study include the small number of patients. However, this study revealed predictors of RV systolic function in a sample of pediatric patients with PAH-CHD. We did not compare TAPSE against a volumetric standard of RV function, such as magnetic resonance imaging-derived RV ejection fraction. Moreover, the current study was not designed to examine the effects of therapy on TAPSE and how such effects relate to outcome. Large scale prospective studies will be needed to more directly address the relationship between TAPSE and RV function in PAH patients.

The results of this study showed that TAPSE measurement can be useful for evaluation of PAH patients, Given the well-known limitations of standard echocardiography in the assessment of RV size and function due to complex structure and asymmetrical shape of this cardiac chamber, measurement of TAPSE index is recommended for PAH-CHD patients.

Acknowledgements

Authors' Contributions

Shahla Roodpeyma developed the study concept and design, wrote the manuscript, and is the guarantor. Sima Rafieyian provided administrative, technical and material support and provided critical revision of the manuscript for important intellectual content. Seyed Hasan Sharifi contributed in acquisition of data, analysis and interpretation of data. All the authors approved the final draft of manuscript.

References

1. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2009;**30**(20):2493–537.
2. De Wolf D. Clinical practice: pulmonary hypertension in children. *Eur J Pediatr.* 2009;**168**(5):515–22.
3. Beghetti M, Galie N. Eisenmenger syndrome a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;**53**(9):733–40.
4. Beghetti M, Tissot C. Pulmonary hypertension in congenital shunts. *Rev Esp Cardiol.* 2010;**63**(10):1179–93.
5. Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. *Circ Res.* 1953;**1**(2):162–70.
6. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med.* 2006;**174**(9):1034–41.
7. Ghio S, Klersy C, Magrini G, D'Armini AM, Scelsi L, Raineri C, et al. Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension. *Int J Cardiol.* 2010;**140**(3):272–8.
8. Lammers AE, Haworth SG, Riley G, Maslin K, Diller GP, Marek J. Value of tissue Doppler echocardiography in children with pulmonary hypertension. *J Am Soc Echocardiogr.* 2012;**25**(5):504–10.
9. Fasnacht MS, Tolsa JF, Beghetti M, Swiss Society for Pulmonary Arterial H. The Swiss registry for pulmonary arterial hypertension: the paediatric experience. *Swiss Med Wkly.* 2007;**137**(35-36):510–3.
10. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. *Int J Cardiol.* 2007;**120**(2):198–204.
11. Lopes AA, O'Leary PW. Measurement, interpretation and use of hemodynamic parameters. *Cardiol Young.* 2009;**19 Suppl 1**:8–12.
12. Suesaowalak M, Cleary JP, Chang AC. Advances in diagnosis and treatment of pulmonary arterial hypertension in neonates and children with congenital heart disease. *World J Pediatr.* 2010;**6**(1):13–31.
13. Palii I. [Characteristics of cardiac remodeling assessed by echocardiography in children with heart failure secondary to congenital heart disease and pulmonary hypertension]. *Rev Med Chir Soc Med Nat Iasi.* 2012;**116**(1):114–21.
14. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. *J Am Soc Echocardiogr.* 2009;**22**(6):715–9.
15. Nunez-Gil IJ, Rubio MD, Carton AJ, Lopez-Romero P, Deiros L, Garcia-Guereta L, et al. Determination of normalized values of the tricuspid annular plane systolic excursion (TAPSE) in 405 Spanish children and adolescents. *Rev Esp Cardiol.* 2011;**64**(8):674–80.
16. Koestenberger M, Nagel B, Avian A, Ravekes W, Sorantin E, Cvirn G, et al. Systolic right ventricular function in children and young adults with pulmonary artery hypertension secondary to congenital heart disease and tetralogy of Fallot: tricuspid annular plane systolic excursion (TAPSE) and magnetic resonance imaging data. *Congenit Heart Dis.* 2012;**7**(3):250–8.