

Assessment of right ventricular function in patients with pulmonary arterial hypertension-congenital heart disease and repaired and unrepaired defects: Correlation among speckle tracking, conventional echocardiography, and clinical parameters

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ABSTRACT

Objective: The purpose of this study is to compare the analysis of right ventricular (RV) free wall strain via 2D speckle tracking echocardiography with conventional echocardiography and clinical parameters in patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) receiving specific treatment. This study also aims to describe the differences between patients with repaired and unrepaired defects.

Methods: This prospective study included 44 adult patients with PAH-CHD who were receiving PAH-specific treatment in a single center. This study excluded patients with complex congenital heart disease. The authors studied the conventional echocardiographic parameters, such as RV fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), right atrial (RA) area, Tricuspid S', and hemodynamic parameters, such as functional class, 6-minute walking distance (6MWD), and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

Results: The mean age of participants was 33.8±11.6 years, and 65.9% of participants were female. The mean RV free wall strain was -14.8±4.7%. Majority of the patients belonged to WHO functional class 2 (61.4%) with a mean NT-proBNP level of 619.2±778.4 and mean 6MWD of 400.2±86.9 meters. During the follow-up of 30.8±9.0 months, 6 patients (13.6%) developed clinical right heart failure, whereas 9 (20.5%) of them died. There was a positive and significant correlation between RV free wall strain and WHO functional class ($r=0.320$, $p=0.03$), whereas there was a negative correlation between RV free wall strain and FAC ($r=-0.392$, $p=0.01$), TAPSE ($r=-0.577$, $p=0.0001$), and Tricuspid S' ($r=-0.489$, $p=0.001$). There was no significant correlation of RV free wall strain with either RA area or 6MWD. Patients with repaired congenital heart defects had worse RV functional parameters and RV free wall strain than patients with unrepaired defects.

Conclusion: The assessment of RV free wall strain via 2D speckle tracking echocardiography is a feasible method and correlates well with conventional echocardiography and clinical parameters in patients with PAH-CHD receiving specific treatment. (*Anatol J Cardiol* 2020; 23: 277-87)

Keywords: congenital heart disease, pulmonary hypertension, right ventricle, strain imaging

Introduction

Congenital heart disease (CHD) occurs in almost 1% of all newborns worldwide. This special group of patients with CHD represents a heterogeneous population whose life expectancy has witnessed a dramatic improvement following the advances in diagnosis and surgical techniques. Nowadays, the majority of patients with CHD reach adulthood with a better quality of life (1). However, in adulthood, ongoing and lifelong cardiac issues, such as residual and progressive hemodynamic lesions, arrhythmias,

and sudden cardiac death (SCD), as well as the development of chronic heart failure and pulmonary arterial hypertension (PAH), affect many of these patients. The prevalence of PAH associated with CHD (PAH-CHD) is yet to be determined; however, the rates of 5–10% and 4.2% were reported in a European survey (2) and a national CHD registry (3), respectively. There is a marked reduction in the life expectancy and the quality of life in patients with PAH-CHD (4).

Several clinical scenarios are expected for patients with PAH-CHD. In recent guidelines, four clinical classifications has

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been defined (5): Eisenmenger syndrome (ES), PAH associated with systemic-to-pulmonary shunts, PAH associated with small defects, and PAH after the correction of cardiac defect.

In clinical practice, PAH-specific therapy either as monotherapy or combination is initiated on patients with PAH. The treatment plan is shaped depending on clinical worsening events such as an arrhythmic episode, signs and symptoms of right heart failure (RHF) or worsening functional capacity. It is commonly known fact that the survival and symptoms are closely related to right ventricular (RV) function and adaptation (6). Therefore, an early detection of RV dysfunction is of high clinical importance because it will guide the treatment plan and affect the survival rate in this special population.

There is a paucity of studies on the prognosis and factors that affect survival in patients with PAH-CHD. Additionally, there are only a few studies that evaluated the prognostic values of baseline characteristics, such as RV dysfunction (6, 7), increased N-terminal pro-brain natriuretic peptide (NT-proBNP) level (8), and 6-minute walking distance (6MWD) (9), associated with poor outcome in CHD-PAH. A few studies have evaluated the values of 2-dimensional (2D) speckle tracking echocardiography in PAH-CHD; however, these studies were inadequate in determining its role. Moreover, studies depending on the etiologies, such as pre-tricuspid shunt and post-tricuspid shunt, have been performed over the years (7, 10), whereas there are limited studies on patients with repaired and unrepaired defects (11, 12).

The purpose of this study is to determine whether the detection of RV free wall strain by 2D speckle tracking echocardiography correlates with the conventional echocardiography parameters of RV systolic function, such as tricuspid annular plane systolic excursion (TAPSE), Tricuspid annular S', RV fractional area change (FAC), along with clinical parameters, such as 6MWD, NT-proBNP, and WHO functional class in the treatment of patients with prevalent PAH-CHD. Additionally, this study aims to describe the differences between patients with repaired and unrepaired defects.

Methods

This prospective study included 44 consecutive adults (age ≥ 18 years) with PAH-CHD, including patients with Down syndrome who were followed at a pulmonary hypertension outpatient clinic in a single center between December 2013 and July 2017. Additionally, this study included patients with both open and closed systemic-to-pulmonary shunts, patients with PAH diagnosed with right heart catheterization (RHC), patients fulfilling the diagnostic criteria for PAH-CHD (5), and patients who were receiving the stable doses of PAH-specific therapy for at least 3 months. This study excluded patients with complex CHD and patients with poor acoustic echocardiographic windows and inadequate images for strain measurements. The Institutional Ethics Committee (13-11/8) approved the conduct of this study. More-

over, all participants granted their written informed consent for participation in this study.

Our institution sees regular visits from patients at the PAH outpatient clinic for a regular follow-up, 6MWD, echocardiographic evaluation, and laboratory measurements and results. Each patient has their own files that contain clinical findings, RHC, echocardiographic evaluation, laboratory findings at diagnosis, and a follow-up period.

Demographic and clinical data (age, gender, diagnosis, WHO functional class, and specific advanced therapy), NT-proBNP plasma concentrations, and 6MWD results were collected at the time of inclusion (at the time of echocardiography). NT-proBNP levels were determined by electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Almere, The Netherlands) was used to determine the NT-proBNP levels. The 6MWD was performed by adhering to the guidelines of the American Thoracic Society with continuous pulse oximetry monitoring (13).

A single physician, in person, undertook the regular follow-ups of the patients at three-month intervals and recorded the adverse events (if there was an occurrence). Clinical RHF was defined as peripheral edema and/or ascites, dyspnea with a decrease in exercise capacity, and the regression of symptoms and signs with diuretic therapy. Arrhythmias were defined as any episode of documented atrial- or ventricular- brady- or tachy- arrhythmia that required electrocardioversion, implantation of pacemaker, or a change of medication. Syncope was defined as a transient loss of consciousness, with a short onset and spontaneous recovery. The occurrence of death due to worsening of disease or SCD was included as mortality data. Patients were censored at death or the end of data collection, whichever came first.

Echocardiographic study

All the patients underwent transthoracic echocardiography in the left decubitus or supine position by using commercially available echocardiography systems with a 1.7–3.4 MHz transducer (Vivid 7; GE Vingmed Ultrasound, Horten, Norway) including 2D, color-flow, spectral Doppler as well as tissue Doppler imaging. All of the data were acquired in the parasternal, apical, and subcostal views. The depth, image sector, and frame rate (50–70 fps) of images were adjusted to obtain the accurate 2D speckle tracking analysis of myocardial deformation. Three consecutive beats were stored in the cine-loop format, and the images were analyzed offline by using dedicated software (EchoPAC GE Healthcare, Milwaukee, USA). RV dimensions and functions were evaluated as per the current guidelines (14). An M-mode cursor was oriented to the junction of the tricuspid valve plane and the RV free wall to measure TAPSE. RV end-diastolic and end-systolic areas were calculated from the RV-focused view, which included the RV apex. RV FAC was calculated as $(RV \text{ end-diastolic area} - RV \text{ end-systolic area}) / (RV \text{ end-diastolic area}) \times 100\%$. The sum of RV isovolume contraction and relaxation time was obtained by subtracting the RV ejection time from the interval between the cessation and

onset of the tricuspid inflow velocities that were determined by the means of pulsed-wave Doppler. RV myocardial performance index (MPI) was obtained by dividing the sum of both isovolume times by the ejection time. Tricuspid annular S' and tissue Doppler imaging records were obtained from the RV-focused view. Right atrial (RA) area was traced in the apical four-chamber view at the end of ventricular systole. The RA pressure was estimated by measuring the diameter and the inspiratory collapse of the vena cava inferior (VCI). If the VCI diameter was ≤ 2.1 cm, then the RA pressure was estimated at 5 mm Hg. Moreover, if the VCI pressure collapsed more than 50% with a sniff, then the RA pressure was estimated at 15 mm Hg. Additionally, if the VCI diameter was more than 2.1 cm and collapsed in less than 50% with a sniff, then the RA pressure was estimated at 10 mm Hg. The collapsed VCI diameter did not fit this paradigm. By adding the RV pressure to the RA pressure, the systolic pulmonary artery (PA) pressure was estimated. Pulmonary stenosis was ruled out in all the patients.

2D speckle tracking strain echocardiography of RV free wall longitudinal deformation was performed by using a routine greyscale-modified apical four-chamber view that was focused on the RV free wall by using commercially available equipment (EchoPAC GE Healthcare, Milwaukee, USA). The endocardial border of the RV free wall was manually traced at end-systole and automatically adjusted to include the entire myocardium. The region of interest was manually adjusted to the thickness of the myocardium. The RV longitudinal strain was measured in the basal, midventricular, and apical segments of the RV free wall and calculated as the average of the three segments. Longitudinal strain is defined as the percentage of myocardial shortening relative to the original length, and is presented as a negative value; however, a more negative value of strain reflects more preserved shortening (15).

Statistical analysis

SPSS for Windows (Version 18.0, SPSS, Chicago, IL, USA) was employed to conduct all statistical analyses of this study. Data are presented as the percentage and mean \pm SD values for discrete and continuous variables, respectively. A p-value of greater than 0.05 (two-sided) was regarded as statistically significant. The comparisons between groups were made by t-test or by Mann-Whitney U test based on the distribution pattern of the variables. Discrete variables were compared by Fisher-exact test or by Chi-square analysis, as appropriate. Spearman correlation analyses were performed to identify the factors associated with the development of cardiovascular events and mortality.

Results

General characteristics of the study population

This study included 44 patients with PAH-CHD, in which 4 of them had Down syndrome. The average age of participants at inclusion was 33.8 \pm 11.6 years. In total, 65.9% of the participants

were female, and the number of participants with repaired and unrepaired defects was 10 and 34, respectively. Table 1 summarizes all the baseline characteristics of the studied population. The clinical classification of patients was as followed: 22 had ES, 10 had PAH associated with systemic-to-pulmonary shunts, 2 had small defects, and 10 had corrected defects (Table 2).

All patients (100%) were undergoing PAH-specific therapy, in which 34 were receiving monotherapy (88.2% bosentan, 11.8%

Table 1. Characteristics of patients (n=44)

Gender (Female%)	29 (65.9)
Age, years	33.8 \pm 11.6
Repaired congenital defect	10
ASD	3
Isolated PDA	3
VSD \pm PDA	3
AVSD	1
Unrepaired congenital defect	34
Isolated PDA	6
ASD	7
AVSD	5
VSD \pm PDA	16
WHO-FC, n (%)	
I	14 (31.8)
II	27 (61.4)
III	3 (6.8)
6-min walk distance, m	400.2 \pm 86.9
NT-proBNP, pg/mL	619.2 \pm 778.4
Specific treatment, n (%)	44 (100)
Monotherapy	34 (77.3)
Combination of drugs	10 (22.7)
Development of clinical RHF, n (%)	6 (13.6)
Cardiovascular event, n (%)	16 (36.4)
Death, n (%)	9 (20.5)
Cardiovascular events, death included, n (%)	18 (40.9)

Data are expressed as mean \pm standard deviation. ASD - atrial septal defect; AVSD - atrioventricular septal defect; NT-proBNP - NT pro-brain natriuretic peptide; VSD - ventricular septal defect; PDA - patent ductus arteriosus; RHF - right heart failure

Table 2. Clinical classification of PAH-CHD (5)

Eisenmenger's syndrome	22 (50%)
PAH associated with prevalent systemic-to-pulmonary shunts	10 (22.7%)
PAH with small/coincidental defects	2 (4.5%)
PAH after defect correction	10 (22.7%)

CHD - congenital heart disease; PAH - pulmonary arterial hypertension

others), 8 were receiving combination therapy with two medications (an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor), and 2 patients were receiving triple medications (an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor, and an inhaled or intravenous prostacyclin analog) at the time of enrolment. The majority of the patients belonged to WHO functional class II (61.4%), with a mean NT-proBNP level of 619.2 ± 778.4 pg/mL and mean 6MWD of 400.2 ± 86.9 meters. In total, 52.2% of patients had cyanosis at rest.

Our patient population had dilation in their right heart (atrium and ventricle), low TAPSE, and RV FAC than the recommended normal values for RV chambers (16). The mean RV free wall strain of the whole population was $-14.8 \pm 4.7\%$. Moreover, the mean RV free wall basal strain value was slightly higher (better) than midventricular and apical segment strain values. Table 2 presents the echocardiographic variables of the group. RV free wall global strain along with midventricular and apical segment strain values were found to be negatively correlated with Tricuspid annular S' ($r = -0.501$; $p = 0.001$, $r = -0.452$; $p = 0.002$, $r = -0.561$; $p = 0.0001$, respectively). Also, RV free wall global strain along with midventricular and apical segment strain values were negatively correlated with RV FAC ($r = -0.406$; $p = 0.009$,

$r = -0.457$; $p = 0.003$, $r = -0.409$; $p = 0.011$, respectively). Furthermore, RV free wall global strain along with basal, midventricular, and apical segment strain values showed a negative correlation with TAPSE ($r = -0.563$; $p = 0.0001$, $r = -0.345$; $p = 0.024$, $r = -0.560$; $p = 0.0001$, $r = -0.465$; $p = 0.003$ respectively). However, there was a significant positive correlation between RV free wall strain and WHO functional class ($r = 0.320$, $p = 0.031$). There was no correlation among MPI, RV wall thickness, NT-proBNP, and 6MWD. Echocardiographic variables of the groups are presented in Table 3.

Differences between patients with repaired and unrepaired defects

The mean ages of patients with a repaired and unrepaired defect were 39.8 ± 16.6 years and 32.0 ± 9.3 years, respectively. There was a higher prevalence of female participants in both the groups (61.8% in unrepaired and 80% in repaired group, $p = 0.452$). The mean NT-proBNP levels of patients with a repaired CHD was 559 ± 622.1 pg/mL, whereas the mean NT-proBNP levels of patients with an unrepaired defect ($p = 0.522$) was 635.7 ± 825.1 . The mean 6MWD of patients with a repaired CHD was 382 ± 73.7 meters, whereas and the mean 6MWD of patients with an un-

Table 3. Echocardiographic characteristics and differences

	Total population (n=44)	Repaired defect (n=10)	Unrepaired defect (n=34)	P
RV basal diameter, mm	4.2±0.9	4.3±1.1	4.1±0.8	0.760
RV midventricular diameter, mm	3.6±1.1	3.6±1.2	3.5±1.1	0.658
RV longitudinal diameter, mm	7.2±1.2	7.5±0.9	7.0±1.2	0.479
RVOT proximal diameter, mm	3.1±0.5	3.3±0.5	3.0±0.5	0.658
RVOT distal diameter, mm	2.8±0.5	2.8±0.5	2.8±0.6	0.724
RV wall thickness, mm	8±2.1	8±2	7±2	0.843
RA end-systolic area, cm ²				
Median (IQR)	20.0 (8.0)	28.0 (24)	20.0 (7.0)	0.567
TAPSE, mm	17.7±3.9	16.0±4.1	18.2±3.8	0.843
SPAP, mm Hg				
Median (IQR)	82.0 (43.0)	72.5 (51)	85.0 (41.0)	0.731
RV FAC, %	29.1±6.4	28.6±5.4	29.3±6.7	0.407
Tricuspid annular S', cm/s				
Median (IQR)	11.0 (5.0)	9.5 (7.0)	11.0 (4.0)	0.470
RV MPI	0.56±0.1	0.73±0.2	0.52±0.1	0.775
RV free wall systolic strain				
Basal, % Median (IQR)	-14.0 (10.0)	-12.0 (14)	-15.0 (9.0)	0.643
Midventricular, % Median (IQR)	-16.0 (6.0)	-12.5 (8.0)	-17.0 (4.0)	0.411
Apical, % Median (IQR)	-16.0 (11.0)	-9.0 (10)	-17.0 (7.0)	0.565
Global, % Median (IQR)	-15.3 (5.0)	-12.1 (7.7)	-15.6 (4.3)	0.564

Data are expressed as mean±standard deviation. FAC - fractional area change; IQR - interquartile range; MPI - myocardial performance index; RA - right atrium; RV - right ventricle; RVOT - right ventricle outflow track; SPAP - systolic pulmonary artery pressure; TAPSE - tricuspid annular plane systolic excursion

repaired defect was 405.5 ± 90.8 meters ($p = 0.688$). Most of the patients belong to WHO functional class II (61.8% and 60% in unrepaired and repaired groups, respectively) in both groups and were mostly on monotherapy (79.4% and 70% in unrepaired and repaired groups, respectively). Patients belonging to WHO functional class III were more frequent in the repaired group (20%) as compared to 2.9% in the unrepaired group; however, the difference was not statistically significant.

Patients with repaired CHD had shown increased RV wall thickness with slightly larger right chambers and decreased TAPSE and RV FAC than patients with unrepaired defects; however, there were no statistically significant differences between the patients. Speckle tracking analysis showed differences between patients with repaired and unrepaired defects: global RV free wall, apical, midventricular, and basal segment strain values were much lower (worse) in patients with repaired defects ($p = 0.564$, $p = 0.565$, $p = 0.411$, $p = 0.643$, respectively) than the patients with unrepaired defects. Table 3 presents the echocardiographic characteristics and differences.

Cardiac events during follow-up

The mean duration of follow-up was 30.8 ± 9.0 months, and 6 patients had developed clinical evidence of edema and/or ascites, which was suggestive of clinical RHF, and 9 (20.5%) patients had died. At least one cardiovascular event was observed in 16 patients (36.4%). The reason of death was SCD in three patients, respiratory failure in one, and RHF in two of the patients. However, three patients died due to unknown reasons.

Clinical RHF was significantly higher in patients with repaired defects than patients with unrepaired defects (4 and 2, respectively, $p = 0.018$). There was no statistically significant difference between death (3 and 6, respectively, $p = 0.402$) and all other cardiovascular events (death included) (6 and 12, respectively, $p = 0.273$) during the follow-up between patients with repaired and unrepaired PAH-CHD.

Discussion

This study investigated the clinical and echocardiographic parameters in patients with PAH-CHD who were receiving the stable doses of specific treatments. The RV free wall global strain evaluated with conventional echocardiographic parameters showed a negative association with Tricuspid annular S', RV FAC, and TAPSE. Moreover, the study examined the differences between patients with repaired and unrepaired CHD and observed that patients with repaired defects had lower RV free wall strain values.

Table 4 summarizes all the available studies that reported echocardiographic findings in patients with PAH-CHD. To the best of our knowledge, there are 11 studies reporting echocardiographic findings of patients with PAH-CHD and only 7 of them (including the present study) reported RV free wall strain. Our

study population showed RV free wall longitudinal strain value of $-14.8 \pm 4.7\%$, which is similar to the study of Mocerri et al. (7) ($-15.0 \pm 4.7\%$). However, different than ours, their study group consisted mainly of patients belonging to NYHA class III and IV (54.1%), with shorter 6MWD, and with only 78.4% of patients receiving specific treatment. RV free wall longitudinal strain was reported as $-16.3 \pm 7.3\%$ in an ES group, and no significant difference was observed from other PAH etiologies (17). On the contrary, a different study showed that RV free wall longitudinal strain mirrored a better RV function in patients with ES than patients with idiopathic PAH and chronic thromboembolic pulmonary hypertension (18). Yet again, the global RV wall strain was reported as $-15.6 \pm 4.7\%$ in 25 patients with ES, and the more depressed long-axis function differed from other PAH etiologies (19). Mocerri et al. (6) studied the predictors of mortality in a group of patients with ES, in which 40.9% were receiving specific treatment and had shown that conventional 2D echocardiography parameters could be used to predict the clinical outcomes; however, no strain echocardiography was performed. Toro et al. (20) studied the patients with ES and cardiac shunts, in which 40.9% were receiving specific treatment with a global RV strain of $-18 \pm 9\%$. Moreover, they reported that RV impairment is reflected in the left ventricle mechanics. Another study involved 11 patients with ES who were newly started on PAH-specific treatment. The baseline RV free wall strain was reported as $-15.7 \pm 1.6\%$, and at the end of 48-week follow-up, a considerable improvement was observed in RV functions (21). Similar to our study, Schuurin et al. (22) studied 91 patients with PAH-CHD receiving specific treatment and have reported that baseline TAPSE and NT-proBNP were the determinants of mortality; however, echocardiographic evaluation of strain was not performed in contrast to our study.

Half of our study group consisted of ES, and we did not perform statistical analyses between the groups regarding clinical, functional, and echocardiographic characteristics due to a small sample size. ES includes all systemic-to-pulmonary shunts due to large defects. The patients with PAH associated with systemic-to-pulmonary shunts have moderate-to-large defects, whereas patients with PAH had small defects and had a very similar clinical picture to idiopathic PAH. In patients with PAH after the correction (percutaneous or surgical) of cardiac defect, PAH is either still present immediately after the interventions or has recurred several months or years after the procedure in the absence of considerable post-operative residual congenital lesions or defects. Manes et al. (23) compared the subgroups of 192 patients with PAH-CHD. Their results suggested that patients with corrected defects needed combination therapy more than the other groups and had a far worse outcome than any other type of PAH-CHD. They have shown that patients with ES had a similar survival rate as the patients with PAH associated with systemic-to-pulmonary shunts. Additionally, patients with ES had significantly better survival rate than patients with small defects or corrected defects (23).

Table 4. The comparison of this study with the published data on congenital heart disease associated with pulmonary arterial hypertension and echocardiography

Study	Year/ Study method	Country	Patient population and number	Age	Follow-up	PAH-specific treatment	Assessment tool	RV strain	Outcomes
Kemal et al.	2013–2017 Prospective single center	Turkey	"44 PAH-CHD"	34±12	30.8±9.0 months. Cardiac events death	100% (under monotherapy or combined)	Conventional+Strain echo -RV free wall longitudinal strain Functional Biochemical	-14.8±4.7% (RV free wall)	The assessment of RV free wall strain is a feasible method via speckle tracking electrocardiography and correlates well with conventional echocardiographic and clinical parameters in patients with PAH-CHD receiving specific treatment.
Moceri et al. (7)	2012–2015 Prospective 2 centers	France	37 ES and 30 control (pre- vs. post- tricuspid shunt)	42±17	None	78.4%	Conventional +Speckle tracking echo -Global LV longitudinal, circumferential strain -RV free-wall longitudinal, transverse strain	-15.0±4.7% (RV free wall)	Patients with ES had impaired longitudinal RV and LV strain, but present a relatively important apical deformation. RV and LV remodeling, as assessed by speckle tracking imaging, differ between patients with pre- and post-tricuspid shunts.
Giusca et al. (18)	Multicenter	Romania Belgium	12 IPAH 11 CTEPH 11 ES 13 control	42±13 IPAH, 51±12 CTEPH, 41±15 ES, 38±15 Control	None	-	Conventional+ Speckle tracking echo -RV free wall strain Right Heart Catheterization	-20.6±3.5% (RV free wall- ES group)	Patients with ES have a more hypertrophied RV free wall and better RV performance as assessed by RVFAC and RV free wall strain than patients with other types of PH.
Moceri et al. (6)	2005–2011 Prospective Single center	UK	181 ES (post- tricuspid, vs. pre-tricuspid shunt)	39±13	16.4 months Mortality	40.9%	Conventional 2D echo	-	Echo parameters of RV function and RA area predict mortality in ES. Also, the echo score including 1 point for each of the following: TAPSE<15 mm, ratio of RV effective systolic to diastolic

Table 4. Cont

Study	Year/ Study method	Country	Patient population and number	Age	Follow-up	PAH-specific treatment	Assessment tool	RV strain	Outcomes
Toro et al. (20)	2009–2012 Prospective Single center and 28 Control	Spain	28 ES+cardiac shunts	37±15	None	40.9% (Bosentan, Sildenafil, Iloprost or Bosentan+Sildenafil)	Conventional 2D+ Speckle tracking echo-Global Left ventricle and RV strain Functional Biochemical	-18±9% (global RV strain)	duration>1.5, RA area>25 cm ² , ratio of RA to LA area>1.5, was highly predictive of clinical outcome. The ventricular interdependence in the patients with ES physiology has an adverse effect on both ventricles. The typical RV impairment in this population is reflected in the LV mechanics.
Chon et al. (21)	2010–2012 Prospective single arm Multicenter	South Korea	11 ES	44±12	48 weeks. Effect of long-term iloprost treatment on RV function	100% (iloprost initiated at inclusion)	Conventional+ Speckle tracking echo -RV longitudinal strain	(RV free wall) -15.7±1.6% (global before treatment) -18.1±1.5% (global after treatment)	RV function in patients with ES evaluated by RV MPI, TAPSE, and RV longitudinal strain was significantly improved after 48 weeks of inhaled iloprost therapy.
Schuuring et al. (22)	2005–2013 Prospective	The Netherlands	91 PAH-CHD	42±14	4.7 years. Mortality Clinical events	100% (Bosentan initiated at inclusion)	Conventional 2D echo NT-pro-BNP	-	Baseline NT-pro-BNP serum level ≥ 500 ng/L and TAPSE <15 mm were the significant determinants of mortality.
Hascoet et al. (31)	Retrospective cohort Multicenter	France	340 ES	27 [12–40]	5.5 years. Mortality Cardiac events	81.2% (under monotherapy or combined)	Clinical parameters 6MWD	-	In patients with ES, specific treatment appears to be associated with a lower risk of transplantation and mortality. ES caused by pre-tricuspid shunting has distinctive characteristics, with a worse outcome despite the delayed onset of the disease.
Schuijt et al. (28)	2005–2016 Prospective observational	France	92 PAH-CHD	43±15	4–9 years. Mortality	Percentage not specified	Conventional 2D echo Functional Biochemical	-	Serial changes in WHO functional class, peak SaO ₂ , 6MWD, NT-proBNP and TAPSE predict

Table 4. Cont

Study	Year/ Study method	Country	Patient population and number	Age	Follow-up	PAH-specific treatment	Assessment tool	RV strain	Outcomes
Moceri et al. (17)	2011–2015 Prospective 2 centers	UK France	43 ES 40 other PAH 37 control (post-tricuspid vs. pre-tricuspid shunt)	50±19	23 months. Mortality Hospitalization	72.3% (not specified)	Conventional+Speckle tracking echo -RV free wall longitudinal and transverse strain -LV global and circumferential strain	-16.3±7.3% (RV free wall -ES group)	mortality and were more potent than baseline parameters. There was no significant difference in RV free wall longitudinal strain between pre- and post-tricuspid shunts. Cardiac remodeling differs between adults with ES and other PAH etiologies. ES and increased RV free wall transverse strain were associated with a better survival rate.
Kalogeropoulos et al. (19)	2006–2007	Georgia	25 ES; 25 other PAH and 25 control	43±17 (ES)	None	33 patients (monotherapy)	Conventional 2D echo +Speckle tracking echo -RV global strain Functional	-15.6±4.7% (global RV strain- ES group)	The RV of patients with ES is characterized by the preserved short- axis function relative to control subjects, despite a depressed long-axis function, a finding that sets these patients apart from the population with PAH.
Moceri et al. (10)	2007–2012 Prospective Multicenter	UK France	191 ES (post- vs. pre- tricuspid shunt)	40±14	39 months. Mortality	44% (Bosentan, Sildenafil, Bosentan +Sildenafil)	Conventional 2D echo Functional Biochemical	-	Even though all patients with ES experience right-to-left shunting and, thus, benefit from the various degrees of offloading of the RV, differences in the location of the defect translate in the differences on the timing and on the extent of RV offloading, further resulting in the differences in the ability of the RV to adapt to pulmonary vascular disease.

PAH-CHD - pulmonary arterial hypertension associated with congenital heart disease; ES - Eisenmenger syndrome; LA - left atrium; LV - left ventricle; LV - left ventricle; SaO₂ - oxygen saturation; TAPSE - tricuspid annular plane systolic excursion; RA - right atrium; RV - right ventricle; 6MWD - 6-minute walking distance

The role of regional RV longitudinal function has been previously investigated in the patients with PAH. The basal RV free wall plays a predominant role in patients with PAH, whereas no difference was found in the longitudinal strain between apical and basal RV lateral walls in healthy controls (24). Our study showed a slightly better basal RV free wall strain than apical and mid segment strain values. The apical traction of the RV (apex being pulled toward to left ventricle), which is caused by an imbalance between the reduced RV and relatively normal LV functions, has been studied before and shown to be beneficial in patients with ES (17).

When compared with idiopathic PAH, the pathophysiology of PAH-CHD is more complicated due to the presence of a defect. In ES, a severe increase in pulmonary vascular resistance (PVR) results in a reversed (pulmonary-to-systemic) or bi-directional shunt. The increase in PVR is usually mild to moderate in patients with PAH associated with systemic-to-pulmonary shunts; however, the systemic-to-pulmonary shunt is still largely present. In these cases, a late reversal of shunt (pulmonary-to-systemic) may be initiated by an increase in the RA pressure due to right ventricular failure. For patients with PAH with small defects, echocardiogram is commonly used to detect/assess the ventricular septal defects (1 cm), atrial septal defects, or 2 cm of effective diameter. The relevance of the defect in the development of PAH is unclear in these cases. In patients with PAH after the correction of cardiac defect, PAH is either still present immediately after the intervention or had recurred several months or years after the procedure in the absence of significant post-operative residual congenital lesions or defects.

After the surgical repair of CHDs, the shape of the RV is dramatically modified, further resulting in infundibular bulging, apical dilation, and deformation. This deformation leads to different types of RV shapes (25). We have found the differences among echocardiographic parameters: patients with unrepaired defects have less dilated right chambers display a better RV function as assessed by RV FAC and RV free wall strain. The repaired group had worse RV free wall strain values, which improved from base to apex. Also, during the follow-up, a greater number of patients with repaired defects had developed RHF. This development can be attributed to the fact that 20% of patients with repaired defects belonged to WHO functional class III, thereby reflecting poor outcomes and worse RV function. RV geometry and contraction patterns in repaired CHD differ according to the type of surgery and overload. This also results in difficulty in the interpretation of echocardiography. Due to the limited number of patients, we could not perform a correlation analysis between the conventional and strain echocardiography parameters among the repaired and unrepaired groups. But in the whole group, there was a positive correlation between RV free wall strain and WHO functional class. The RV free wall global strain showed a negative correlation with Tricuspid annular S', RV FAC, and TAPSE in our study. Prior stud-

ies have shown that RV global longitudinal peak systolic strain is decreased in repaired CHD with pulmonary regurgitation and normal RVEF (26). By contrast, Bonnemains et al. (27) found no correlation between RV longitudinal strain and RVEF in patients with repaired tetralogy of Fallot.

Mocerri et al. (10) compared the physiological differences between various types of ES and have shown that RV dilatation and systolic dysfunction was more prominent in patients with pre-tricuspid shunts. Additionally, they showed that lower RA pressures in post-tricuspid shunts suggested better RV diastolic properties. Almost half of their study group were receiving specific treatment and they only studied defect location, not repaired defects (10). They have also noted that RV function indices were better in patients with complete atrioventricular septal defects than patients with ventricular septal defects, depending on the differences in RV adaptation to the systemic levels of PA pressure between the different types of post-tricuspid shunts. This reflects the wide-ranging heterogeneity in this special patient group, thereby making it more distinctive and divergent than other PAH groups. Therefore, in everyday practice, it is inappropriate to assess the patients with CHD with a single echocardiographic parameter or a clinical finding.

Studies have shown that serial changes in clinical parameters (NT-proBNP, TAPSE, 6-MWD, Peak SaO₂) predict mortality in patients with PAH-CHD (28). The leading causes of death are heart failure, thromboembolism, infection, SCD, hemorrhage and peri-procedural in ES (29). The overall incidence of SCD is reported to be 0.4 deaths/1000 py in adults with CHD (30). In our study group, three patients had SCD. No autopsy was conducted because the patient's relatives did not provided consent. Also, the reason of death remained unknown in three patients since no information could be obtained from the families. In a large multicenter registry of patients with ES, specific treatment was associated with a lower risk of mortality and heart transplantation, although outcomes were still reported as poor (31).

The PAH guidelines make no distinction between the PAH-CHD subgroups with regard to the recommendations for follow-up or pharmacological treatment. Conventional parameters such as TAPSE and RV FAC measured with 2D echocardiography are used to evaluate the RV function, and the current guidelines recommend these parameters for estimating the RV function. The complex change of RV geometry due to the adaptation to high pressures of PA limits the echocardiographic measurements in the representation of the global RV function. RV longitudinal strain evaluates the RV function without relying on the geometrical assumptions; however, we still lack the standardized normal value data in this special group.

Study limitations

The major limitation of this study is the small sample size. Therefore, it was difficult to conduct correlation analyses between the patients with repaired and unrepaired defects. Although, there was non-availability of hemodynamic data that were synchronous

with the baseline RV speckle tracking, even though all patients had diagnostic RHC. Although TOMTEC technology is more accurate, we used speckle tracking for evaluation.

However, from a different point of view, most studies that have evaluated RV systolic strain in patients with PAH included both incident and prevalent cases of patients in a single group, whereas our study population consisted only of patients already established on the stable doses of PAH-specific therapy resulting in a more homogeneous group and reflecting real-life clinical data with a respectable follow-up time of 30.8 ± 9.0 months. Additionally, the differences about repaired and unrepaired defects have not been studied before.

Conclusion

The assessment of RV free wall strain via 2D speckle tracking echocardiography is a feasible method and correlates well with conventional echocardiographic and clinical parameters in the patients with PAH-CHD who are receiving specific treatment. Our study showed that patients with repaired congenital heart defects had worse RV functional parameters and global RV free wall strain than patients with unrepaired defects. Therefore, it is essential to acquire sound knowledge of RV physiopathology and every measured echocardiographic parameter for correct and suitable treatment.

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