ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2018) **19**, 1026–1033
doi:10.1093/ehjci/jex205

3D echocardiographic evaluation of right ventricular function and strain: a prognostic study in paediatric pulmonary hypertension

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Received 17 May 2017; editorial decision 2 August 2017; accepted 5 August 2017; online publish-ahead-of-print 25 August 2017

Aims To evaluate right ventricular functional indices using 3D echocardiography (3DE) between normal children and paediatric pulmonary hypertension (PH) patients, and to evaluate these indices as outcome predictors in children with PH.

Methods and results Ninety-six paediatric PH patients from 2014 to 2016 were compared with 40 normal controls. All patients underwent 3DE and off-line analysis generated 3D end-diastolic volume, 3D end-systolic volume, 3D stroke volume, 3D right ventricular (RV) ejection fraction (EF), RV longitudinal strain (LS) free wall and septum, tricuspid annular plane systolic excursion (TAPSE), and fractional area change (FAC). PH patients had higher RV volumes, lower RV EF, lower free wall and septal RVLS, lower TAPSE, and lower FAC compared with normal controls (all $P < 0.001$). 3D RV EF, free wall RVLS, and FAC are predictors of adverse clinical outcomes [hazard ratio (confidence interval) 0.1 (0.03–0.27], $P < 0.001$; 0.17 (0.07–0.45), $P < 0.001$; 0.08 (0.03–0.22); $P < 0.001$, respectively).

Conclusion Paediatric PH patients have impaired RV function compared with normal children. 3D RV EF, volumes, FAC, and free wall RV strain serve as outcome predictors for paediatric PH patients.

Keywords 3D echocardiography • right ventricular function • paediatric pulmonary hypertension • myocardial strain • clinical outcomes

Introduction

Paediatric pulmonary hypertension (PH) is a progressive disease that results in right ventricular (RV) dysfunction; RV function is an important determinant of clinical status and survival in patients with PH.[1–4] Because of the complex RV geometry, 2D echocardiography (2DE) cannot capture the inflow and outflow portions of the RV in the same image acquisition and cannot determine comprehensive function in one beat. Real time 3D echocardiography (3DE) has emerged as a feasible tool to quantitate RV function as it captures the complex geometric shape and has been validated with cardiac magnetic resonance imaging.[5–10] Single beat 3DE of the RV is accurate and reproducible in quantifying the RV.[11–13] We previously demonstrated that this technique is feasible in paediatric PH patients and 3D RV EF correlated with invasive haemodynamics and severity of PH using biomarkers,[14] but these parameters have not been used to evaluate prognosis.

In addition to using 3D RV EF to quantify RV function, RV strain has been used in evaluating myocardial function and has predictive potential in both adult and paediatric PH population.[1,15–18] Although quantitative assessment of RV function using 3DE and strain are feasible, it frequently requires different vendors' software packages with transfer of images from different echocardiography machines to different offline packages that limit rapid clinical practice. Recently a vendor independent 3DE software (4D-RV Function 2) can generate RV size and functional parameters from one real-time 3DE dataset and enables an accurate, reproducible, and faster quantitation of RV function that requires less operator time.[19] In this study, we evaluated RV functional indices generated from 3DE datasets between normal controls and paediatric PH patients, and evaluated these indices as outcome predictors in children with PH.

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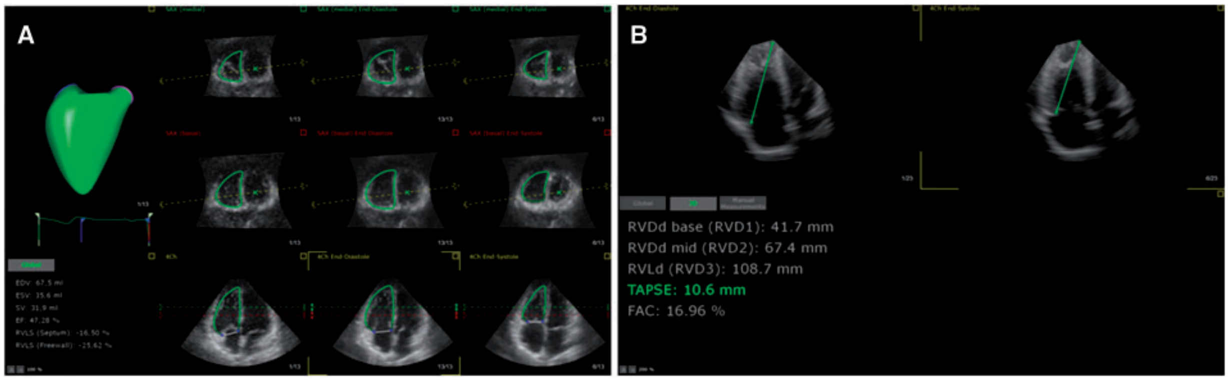


Figure 1 4D right ventricular function 2 software automatically generate 3D volumes, ejection fraction, right ventricular strain, tricuspid annular plane systolic excursion, and fractional area change.

Methods

Study population

This is a retrospective evaluation of paediatric PH patients from 2014 to 2016. PH patients were included if they had a diagnosis of idiopathic pulmonary arterial hypertension (IPAH) and associated pulmonary arterial hypertension with congenital heart disease (APAH-CHD) by cardiac catheterization with a mean pulmonary artery pressure >25 mmHg and were seen in PH clinic. World Health Organization Functional Classifications (WHO-FC) were identified in each patient at PH clinic visits. Patients were included if they had 2DE and 3DE on the same day. Patients were excluded if they were >18 years of age and if the echocardiographic images were poor for adequate tracing of the endocardial borders or if the entire RV could not be included in the apical four chamber view. Normal paediatric patients served as controls who had no cardiac defects or family history of cardiac disease or they were patients who were evaluated in the cardiology clinic for heart murmurs, chest pain, or syncope with normal structure hearts. This study was approved by the institutional review board at the University of Colorado.

2D and 3D echocardiography

2DE was performed on all children with PH and were digitally acquired using a standard protocol with appropriate sized transducers for patient size. Single beat full volume of 3DE RV datasets was acquired using the 4Z1c matrix-array transducer on the Siemens SC2000 cardiac ultrasound system (Siemens Healthcare, Erlangen, Germany). An apical four chamber view was acquired with the patient in the lateral decubitus position. The transducer position was modified for optimal simultaneous visualization of the tricuspid valve, cardiac apex, and right ventricular outflow tract. 3DE RV datasets were digitally analysed offline using the commercial software (4D RV-Function 2.0, TomTec, Germany) to generate RV functional indices automatically: 3D end-diastolic volume (EDV), 3D end-systolic volume (ESV), 3D stroke volume (SV), 3D EF, 2D septal and free wall RV longitudinal strain (LS), 2D tricuspid annular pane systolic excursion (TAPSE), and 2D fractional area change (FAC), calculated as calculated as [(end-diastolic area) - (end-systolic area)/end-diastolic area] × 100% (*Figure 1*). End-diastole is defined as the time just before the tricuspid valve closure with the greatest RV volume and end-systole is when the RV cavity is the smallest. TAPSE is measured from the apex of the RV to the tricuspid valve annulus in systole and diastole. FAC is also measured in systole and diastole with adjustable tracking lines. Intraobserver variability was performed on 10 randomly selected PH patients at an interval of 4 weeks apart by P.N.J. Interobserver variability was also performed by two investigators (P.N.J. and C.B.) at an interval of 4 weeks apart.

Clinical outcomes

Clinical outcomes were analysed in all PH patients with pre-defined adverse clinical events. An adverse clinical event was defined as (i) initiation of intravenous prostacyclin, (ii) PAH-related hospitalization with increased RV failure or haemoptysis, (iii) creation of an atrial septostomy, (iv) Pott's shunt, (v) lung transplant, or (vi) death. These adverse clinical outcomes were composite end points similar to previous medication trials in PAH.[20] All patients were followed up until the clinical event or the end of the study period.

Statistical analysis

Analyses were performed using JMP 13.0 (SAS Institute, Cary, NC, USA). Variables were checked for normality using normal plots, in addition to Kolmogorov–Smirnov and Shapiro–Wilks tests. All normally distributed data sets are reported as mean with standard deviations. Non-normally distributed values are reported as median values with interquartile ranges. Demographic and clinical characteristics among PH and control patients were compared using a student's *t*-test for normally distributed continuous variables, Wilcoxon ranked sum test for non-normally distributed variables, and χ^2 for categorical variables. Additional group comparisons were performed using Kruskal–Wallis or one-way analysis of variance tests between the PAH specific WHO-FC groups and PAH clinical diagnosis groups. Observer agreement was assessed using intraclass correlation (ICC) analysis.

Univariate Cox proportional hazards analysis assessed the predictive ability of 3DE variables in all PH patients. For variables that were found to be significantly associated with survival univariate analysis, Kaplan–Meier survival curves were constructed with specific log-rank test with the predictor dichotomized to describe event-free survival where the most optimal cut-off values were identified by performing receiver operating characteristic (ROC) analysis for detection of adverse clinical events, specifically by finding Youden index to achieve maximum sensitivity and specificity. All patients were followed up to the particular event or the end of the study (December 2016). As sensitivity analysis, the above models were applied to IPAH patients only to examine their robustness. A multivariate analysis using step-up model and score method was applied. Significance was based on an α-level of 0.05.

Table 1 Patient clinical characteristics

	PH (*n* = 96)	Control (*n* = 40)	*P*-value
Age (years)	8.1 ± 5.2	9.4 ± 4.0	0.1339
Sex (female)	53 (55%)	20 (50%)	0.6261
BSA (m^2)	1.04 ± 0.42	1.18 ± 0.46	0.0210
WHO-FC			
I	47 (49%)		
II	34 (29%)		
III	12 (12%)		
IV	3 (2%)		
IPAH	34 (35%)		
APAH-CHD	62 (65%)		
ASD s/p repair	15 (16%)		
VSD s/p repair	14 (15%)		
AVSD s/p repair	10 (10%)		
PDA s/p repair	8 (8%)		
CoA s/p repair	2 (2%)		
Absent RPA or LPA s/p repair	5 (5%)		
TGA s/p repair	1 (1%)		
PAPVR s/p repair	2 (2%)		
PVS s/p repair	2 (2%)		
Tricuspid valve dysplasia s/p repair	1 (1%)		
TAPVR s/p repair	2 (%)		
Medications			
PDE5i	65 (67%)		
IV Treprostinil	10 (10%)		
SC Treprostinil	4 (3%)		
Inhaled Treprostinil	6 (5%)		
IV Epoprostenol	2 (2%)		
ERA	43 (45%)		
CCB	13 (14%)		
RV functional indices			
EDVi (mL/m^2)	83 (49–111)	60 (45–66)	0.0002
ESVi (mL/m^2)	41 (33–56)	25 (21–31)	<0.0001
SVi (mL/m^2)	37 ± 13	31 ± 8	0.0036
EF (%)	46 ± 5	55 ± 4	<0.0001
RVLS septum (%)	-15 ± 6	-20 ± 4	<0.0001
RVLS free wall (%)	-21 ± 5	-28 ± 4	<0.0001
TAPSE (mm)	14 ± 4	17 ± 3	0.0043
FAC (%)	37 ± 7	44 ± 5	0.0001

Data are represented as mean ± SD.
ASD, atrial septal defect; AVSD, atrioventricular septal defect; CCB, calcium channel blockers; CHD, congenital heart disease; CoA, coarctation of the aorta; EDVi, end-diastolic volume indexed; EF, ejection fraction; ERA, endothelin receptor antagonist; ESVi, end-systolic volume indexed; IPAH, idiopathic pulmonary arterial hypertension; LPA, left pulmonary artery; PAPVR, partially anomalous pulmonary venous return; PDA, patent ductus arteriosus; PDEi, phosphodiesterase enzyme inhibitors; PVS, pulmonary venous stenosis; RPA, right pulmonary artery; RVLS, right ventricular longitudinal strain; SVi, stroke volume indexed; TGA, transposition of great arteries; VSD, ventricular septal defect; WHO-FC, World Health Organization—Functional Class; SD, standard deviation.

Results

PH patients and controls

There were 104 paediatric PH patients with IPAH and APAH-CHD from 2014 to 2016 with 8 (7%) PH patients excluded due to poor image quality, thus leaving 96 PH patients for analysis. Forty normal paediatric patients served as controls. *Table 1* shows the clinical characteristics of PH patients and controls. There were 35% IPAH and 65% APAH-CHD patients. PH patients had higher volumes, lower EF, and lower free wall and septal RVLS, TAPSE, and FAC compared with normal controls (*Table 1*). IPAH patients had higher volumes and lower EF compared with APAH-CHD patients (all $P < 0.01$) as demonstrated in *Table 2*. IPAH group had worse PH with higher mean pulmonary artery pressure and higher pulmonary

Table 2 Right ventricular functional indices between IPAH and APAH-CHD

	IPAH (n = 34)	APAH-CHD (n = 62)	P-value
EDVi (mL/m^2)	101 (66–131)	61 (42–99)	<0.0001
ESVi (mL/m^2)	42 (33–70)	39 (32–47)	<0.0001
SVi (mL/m^2)	39 ± 12	36 ± 12	0.2629
EF (%)	43 ± 4	46 ± 5	0.0123
RVLS septum (%)	-15 ± 6	-16 ± 6	0.3450
RVLS free wall (%)	-20 ± 4	-22 ± 4	0.1137
mPAP (mmHg)	42 ± 19	25 ± 11	<0.0001
PVRi (WU.m^2)	11 ± 7	5 ± 3	<0.0001
PAWP (mmHg)	8 ± 2	9 ± 3	0.0563
mRAP (mmHg)	7 ± 2	7 ± 2	0.4757
CI (L/min/m^2)	3.5 ± 0.8	4.6 ± 2.8	0.0161

Data are represented as mean ± SD or medians with interquantile ranges.
CI, cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PAWP, pulmonary arterial wedge pressure; PVRi, pulmonary vascular resistance index; SD, standard deviation; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; EF, ejection fraction.

Table 3 3D right ventricular indices and haemodynamics in pulmonary hypertension patients with and without adverse clinical events

		Adverse clinical events		
	All patients (n = 96)	Event free (n = 78)	With event (n = 18)	P-value
EDVi (mL/m^2)	83 (49–111)	75 (45–105)	101 (69–153)	0.0312
ESVi (mL/m^2)	41 (33–56)	40 (33–53)	44 (33–72)	0.0817
SVi (mL/m^2)	37 ± 13	36 ± 12	42 ± 16	0.1542
EF (%)	46 ± 5	47 ± 4	39 ± 7	0.0002
RVLS septum (%)	-15 ± 6	-16 ± 6	-13 ± 5	0.0553
RVLS free wall (%)	-21 ± 5	-21 ± 4	-18 ± 5	0.0135
mPAP (mmHg)	32 ± 17	27 ± 13	48 ± 18	0.0002
PVRi (WU.m^2)	7 ± 6	6 ± 4	12 ± 8	0.0075
PAWP (mmHg)	9 ± 3	8 ± 2	9 ± 5	0.6769
mRAP (mmHg)	7 ± 2	7 ± 2	7 ± 3	0.5621
CI (L/min/m^2)	4.1 ± 1.9	4.3 ± 2.1	3.3 ± 0.7	0.0075

Data are represented as mean ± SD or medians with interquantile ranges. Please see abbreviations from Tables 1 and 2.

vascular resistance compared with APAH-CHD group. The myocardial strain between IPAH and APAH patients was not statistically different but the IPAH patients tended to have lower RV strain compared with APAH patient. Patients with different WHO-FC groups were different in their 3D functional indices (see Supplementary data online, *Table S1*). Patients with WHO-FC III and IV had higher RV volumes compared with WHO-FC I (all $P < 0.01$) and lower 3D RV EF compared with WHO-FC I or II ($P < 0.001$). Free wall RVLS was also worse in WHO-FC III and IV compared with WHO-FC II and I ($P < 0.001$).

Clinical outcome analysis

Over a follow-up of 24 months, there were 18 adverse clinical events. Two patients died, three underwent Pott's shunt, one underwent clinically indicated septostomy, seven were started on IV prostacyclin therapy, and five had PAH related hospitalization. RV functional indices and haemodynamics of the 96 patients with and without adverse clinical events are shown in *Table 3*. There are significant differences between RV EDVi, RV EF, and free wall RVLS between the patients with and without clinical adverse events. The mean pulmonary artery pressures and pulmonary vascular resistance indices were higher in patients with adverse clinical events and the cardiac index was lower in patient with adverse clinical events. The RV functional indices that predicted hard clinical outcomes were 3D volumes, 3D RV EF, free wall RVLS, and 2D FAC in *Figure 2* [reported as hazard ratio (95% CI)]. ROC curves for all RV functional indices are demonstrated in *Figure 3*. Kaplan–Meyer survival curves for observed predictors are shown in *Figure 4* and confidence intervals in Supplementary data online, *Figure S1*. An EDVi ≥ 102 mL/m^2, ESVi ≥ 54 mL/m^2, SVi ≤ 37 mL/m^2, 3D EF ≤ 43%, free wall RVLS ≤ -16, and FAC ≤ 32% were significantly associated with increased risk of adverse clinical events.

Of the 18 adverse clinical events, 15 events occurred in IPAH patients and 3 events occurred in APAH-CHD patients. Our sub-analysis of outcomes in IPAH patients demonstrated the same RV functional indices (3D volumes, 3D RV EF, free wall RVLS, and 2D FAC) that predicted hard outcomes when combining the two groups (see Supplementary data online, *Table S2*). A multivariate analysis in IPAH patients revealed that the ESVi was an independent predictor of clinical events. SVi and EF were the two predictors with the highest Fisher's score. Due to limited number of adverse clinical events ($n = 3$) in 62 APAH-CHD patients, we were unable to perform multivariate analysis in this group.

Intraobserver and interobserver variability

The ICC showed good agreements on RV EDV, ESV, SV, EF, RV septal and free wall strain, TAPSE, and FAC (0.96, 0.99, 0.75, 0.97, 0.83, 0.84, 0.78, and 0.96, respectively) for intraobserver variability comparisons in RV functional indices. The ICC showed good agreement for RV EDV, ESV, SV, EF, and RVLS free wall (0.80, 0.83, 0.78, 0.93, and 0.82, respectively) and showed moderate agreement in RVLS septal, TAPSE, and FAC (0.63, 0.66, and 0.64, respectively) for interobserver comparisons in RV functional indices.

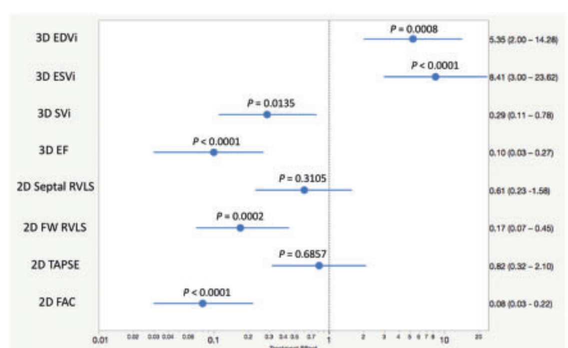
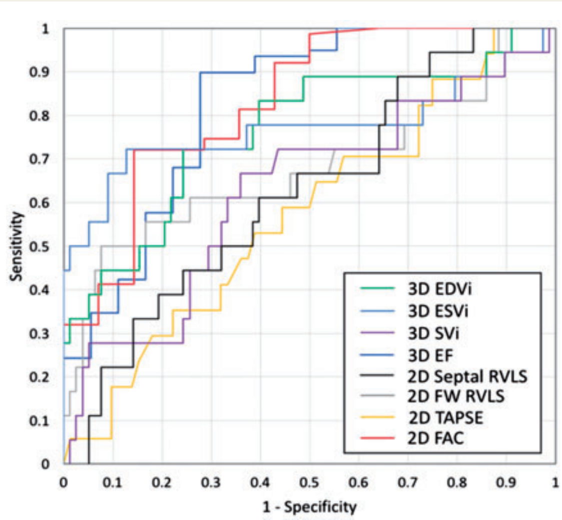


Figure 2 Univariate Cox proportional analysis of right ventricular indices in PH patients. Data are reported as hazard ratios with 95% confidence intervals per one standard deviation increase per given parameter.

Discussion

This study demonstrated the prognostic significance of 3D RV functional indices in paediatric PH patients. Paediatric PH patients have impaired RV function compared with normal children. We found that 3D volumes, 3D RV EF, FAC, and free wall RVLS were significant outcome predictors for paediatric PH patients.

Previously, we demonstrated that 3D RV EF correlated well with invasive haemodynamics and biomarkers of severity in paediatric PH population.[14] 3DE minimizes geometric assumptions of RV and is more accurate in evaluating ventricular function. Our study demonstrated that PH patients have larger RV volumes with low EF and longitudinal strain compared with normal controls. Within the two different PH groups, we observed that IPAH patients have worse RV functional indices compared with APAH-CHD patients. In our sub-analysis of IPAH patients, the outcome predictors remained the same as the entire group of 96 PH patients. Using a multivariate analysis, we demonstrated that ESVi was an independent predictor of adverse clinical events in IPAH patients and that using the Fisher's score method, we found that the model with SVi and EF as predictors is better than any other models with two predictors. As expected in PH patients with worse functional class and disease severity, their RV volumes were larger with prominent decrease in RV EF. Vitarelli *et al.*[21,22] demonstrated that 3D RV EF provided better diagnostic accuracy in predicting RV failure haemodynamics compared with conventional echocardiography in adult patients with chronic PH and that RV EF decreases in patients with acute pulmonary embolism and



	AUC	Sensitivity (%)	Specificity (%)	Cut-off
3D EDVi (mL/m²)	0.76	55	91	102
3D ESVi (mL/m²)	0.76	72	87	54
3D SVi (mL/m²)	0.62	66	64	37
3D EF (%)	0.83	90	67	43
2D Septal RVLS (%)	0.62	61	64	-15
2D Free wall LS (%)	0.68	48	93	-16
2D TAPSE (mm)	0.68	60	57	14
2D FAC (%)	0.80	97	57	32

Figure 3 Receiver operating characteristics of 3D right ventricular functional indices.

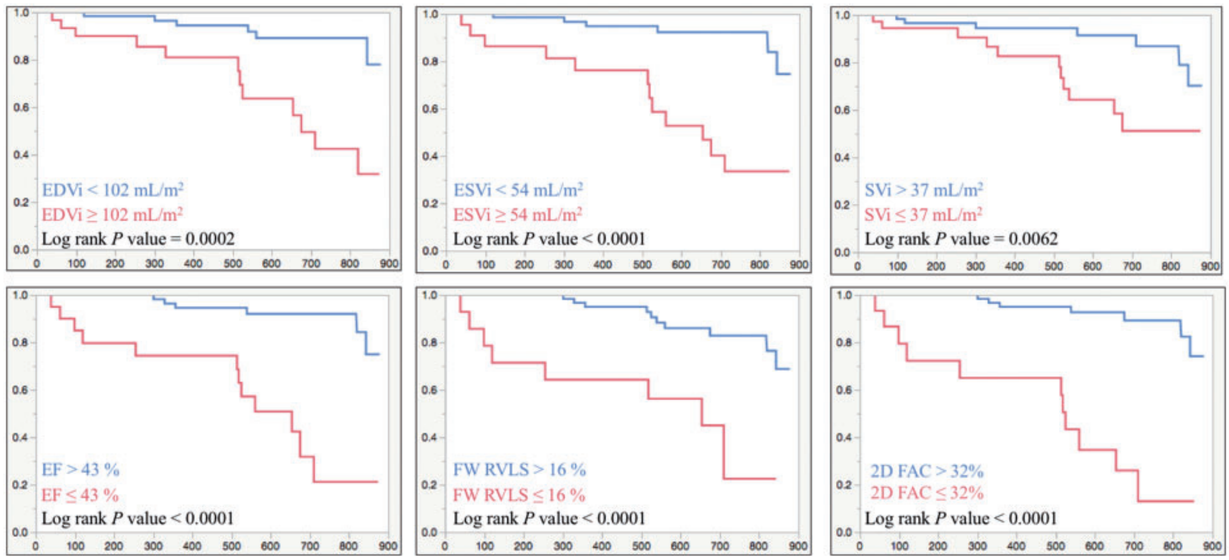


Figure 4 Kaplan–Meyer curves for adverse clinical events.

correlated with unfavourable outcomes. 3DE has incremental value over 2DE in identifying RV dysfunction in patients with pressure or volume overload.[11] Murata *et al.*[23] demonstrated that 3D RV EF was superior to mean pulmonary artery pressure in predicting associated clinical events. As the RV volumes get progressively bigger, the RV function declines with decreased RV EF. Ryo *et al.*[24] also demonstrated that quantitative 3DE in adult PH patients was associated with clinical outcomes and that 3D RV EF was a predictive parameter for combined end point. Our study demonstrates that 3D RV EF can be used to evaluate paediatric PH patients clinically.

2D TAPSE was not a good clinical predictor of adverse events in our patients. This may be because TAPSE is a measure of basal part of the heart with displacement in 1D and does not account for the entire RV volume that contributes to the RV EF.[25] TAPSE does not account for the mid and apical RV function of the lateral free wall that is more significantly affected than RV basal segment.[15] Okumura *et al.*[15] has demonstrated that the mid and apical RV strain segments in PH patients are more affected than the basal RV function. TAPSE is not reflective of global RV function and is influenced by the passive translational or tethering forces.[26] TAPSE is not sensitive in detecting RV dysfunction in adult PH patients compared with 3D RV EF and FAC.[11,21,27] Lastly, TAPSE seemed to be preserved in paediatric PH except in children with repaired congenital heart disease.[28] 2D FAC is a predictor of adverse events in our patients. This is consistent with adult PH studies where FAC has been shown to be an outcome predictor.[22,29,30]

In addition to decreased 3D RV EF as an outcome predictor, free wall RVLS is a predictor of adverse clinical event in our paediatric PH patients. RV strain is a more sensitive indicator of function and a direct measure of myocardial performance.[1,15–17,31–34] Although there were no statistically significant differences in RV strain between our IPAH and APAH-CHD patients, there were significant differences of RV strain from the entire PH cohort when compared with normal controls. APAH-CHD patients likely have decreased RV function from their CHD surgeries despite having better haemodynamics than IPAH patients. Our study showed that free wall RVLS was a strong predictor of adverse clinical events. Adult PH studies showed that RV free wall strain was the best predictor of cardiovascular events and a powerful predictor of clinical outcomes.[1,33] Paediatric studies have demonstrated that free wall RV strain can be used as a prediction of worsening WHO-FC and global RV longitudinal strain was reduced in children with IPAH and that it worsened over time in patients who required transplant or died.[15,34] Septal RVLS was not a predictor of adverse clinical event in our study. The ventricular septum is shared between the two ventricles and reflects both RV and left ventricle contractility, thus making the septal RVLS values difficult to interpret. Free wall RVLS however is a predictor of adverse clinical events because the free wall RV is not shared with the left ventricle and is the predominant ventricular component contributing to RV contractile function.

4D RV function 2 software generates functional parameters from single 3DE dataset making this an easier use in clinical practice and reducing the amount of time spent using multiple software to analyse 3D dataset and speckle-tracking echocardiography separately. Real-time 3DE can be incorporated into routine clinical use as it provides quantitative assessment of RV without the time and cost associated with cardiac magnetic resonance imaging or the invasiveness of the right heart catheterization. Importantly, we have demonstrated that functional measurements derived from one 3D dataset can be used to predict adverse clinical events.

Limitations

This study has the following limitations. First, we used single beat 3DE because it does not require breath hold in paediatric patients. This single beat 3DE is limited technically because of the big size of the probe that does not fit in between the intercostal spaces of small children. Despite this limitation, single beat 3DE acquisition generated from the Siemens machine has a higher volume rate than other vendor machines and is advantageous over traditional disk summation that require serial heartbeat acquisitions resulting in stitch artifacts. The development of a paediatric 3D transthoracic probe for single beat acquisition could help resolve the technical limitations. Because this is a vendor neutral package that can derive RV functional indices from real-time 3D datasets, the acquisition of 3D dataset is not limited to a specific vendor. Second, limitations to this study include those inherent to a retrospective study. We included patients with two specific aetiologies of PH so that we have two consistent groups of patients who have PAH. We were unable to perform an outcome sub-analysis in APAH-CHD patients due to low adverse events. Lastly, there are no established normal paediatric values for RV EF, FAC, and RV strain. Future studies to establish these values in normal paediatric populations may be helpful as paediatric reference values in echocardiography can be different from adult values.

Conclusions

Paediatric PH patients have impaired RV function compared with normal children. 3D RV EF, volumes, FAC, and free wall RV strain serve as outcome predictors for paediatric PH patients. Future studies to evaluate changes in these functional parameters as treatment goals with treatment induced improvements would help in future management of these paediatric PH patients.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Acknowledgements

We would like to thank Berthold Klas for his help with the 4D-RV Function 2 software.

Conflict of interest: None declared.

Funding

This study was supported by the Jayden DeLuca Foundation; the Leah Bult Foundation; and the Frederick and Margaret L Weyerhaeuser Foundation.

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