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Right ventricular function mirrors clinical improvement with use of prostacyclin analogues in pediatric pulmonary hypertension

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Abstract

Pulmonary hypertension (PH) causes significant morbidity and mortality in children due to right ventricular (RV) failure. We sought to determine the effect of prostacyclin analogues on RV function assessed by echocardiography in children with PH. We conducted a retrospective cohort study of children with PH treated with a prostacyclin analogue (epoprostenol or treprostinil) between January 2001 and August 2015 at our center. Data were collected before initiation of treatment (baseline) and at 1–3 and 6–12 months after. Protocolized echocardiogram measurements including tricuspid annular plane systolic excursion (TAPSE) and RV global longitudinal strain were made with blinding to clinical information. Forty-nine individuals (65% female), aged 0–29 years at the time of prostacyclin initiation were included. Disease types included pulmonary arterial hypertension (idiopathic [35%], heritable [2%], and congenital heart disease-associated [18%]), developmental lung disease (43%), and chronic thromboembolic PH (2%). Participants received intravenous (IV) epoprostenol (14%) and IV/subcutaneous (SQ) (67%) or inhaled (18%) treprostinil. Over the study period, prostacyclin analogues were associated with improvement in TAPSE ($P = 0.007$), RV strain ($P < 0.001$), and qualitative RV function ($P = 0.037$) by echocardiogram, and BNP ($P < 0.001$), functional class ($P = 0.047$) and 6-min walk distance ($P = 0.001$). TAPSE and strain improved at early follow up ($P = 0.05$ and $P = 0.002$, respectively) despite minimal RV pressure change. In children with PH, prostacyclin analogues are associated with an early and sustained improvement in RV function measured as TAPSE and strain as well as clinical markers of PH severity. RV strain may be a sensitive marker of RV function in this population.

Keywords

pulmonary hypertension, prostacyclin, pediatric, right ventricular function

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Pulmonary hypertension (PH) is associated with significant morbidity and mortality in the pediatric population.[1] If left untreated, this condition may progress rapidly to right ventricular (RV) failure and early death. Survival has improved with use of pulmonary vasodilators, specifically with prostacyclin analogs epoprostenol and treprostinil.[2–4] Recent registry data suggest that the current five-year survival is in the range of 62–90%, whereas the median survival of children was only ten months from time of diagnosis before development of these therapies.[5–8]

The gold standard for diagnosis and monitoring of PH is cardiac catheterization; however, there are risks associated

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with cardiac catheterization and anesthesia in children with PH.[9–11] Therefore, echocardiography is used as a non-invasive tool for assessing disease severity and predicting outcome in children with PH. However, there is little consensus regarding utility of specific echocardiographic parameters in pediatric PH, especially with respect to measurement of RV function.[12,13] Several quantitative measures have recently been developed to assess RV function, including tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC), and RV global longitudinal strain. Both RV FAC and RV global longitudinal strain have been shown to predict survival in children with PH.[14,15] In the pediatric and adult population with pulmonary arterial hypertension (PAH), RV global longitudinal strain has emerged as a more sensitive parameter of ventricular shortening. Not only is strain a more direct measurement of myocardial shortening, but it has been correlated with mortality in pediatric and adult PAH.[15–19]

The survival benefit associated with prostacyclin analogue use in children with PH may be related to improvement in RV function, possibly ascribed to a combination of decreased afterload as well as a potential direct effect of the drug on the RV. We hypothesized that prostacyclin therapy improves RV function, with increased benefit seen with longer duration of therapy. In this study, we sought to evaluate clinical and echocardiographic parameters of PH and RV function before initiation of prostacyclin and at early (1–3 months) and mid-term (6–12 months) follow-up.

Methods

We performed a retrospective cohort study of patients with PH treated with prostacyclin at our institution between 1 January 2001 and 31 August 2015. The study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia and informed consent was not required.

Study cohort: Patients were identified from existing clinical databases. Inclusion criteria were confirmed diagnosis of PH at age ≤ 21 years and treatment with a prostacyclin therapy (epoprostenol or treprostinil). Patients were excluded if there were no available echocardiogram images pre- and post-prostacyclin initiation. Patients with complex congenital heart disease, unrepaired significant congenital heart disease, or substantial left ventricular dysfunction were also excluded. Patients with simple shunts, such as small atrial septal defects or patent ductus arteriosus, were not excluded.

Clinical data: Medical records were reviewed to confirm the diagnosis of PH, date of diagnosis, PH diagnostic classification, demographic information, survival/transplant status, and PH medical therapies (type and date of initial prostacyclin analogue therapy, maximum dose, and concomitant medications). Date of diagnosis was considered to be date of the first confirmatory cardiac catheterization or echocardiogram (if catheterization not performed). Study time points were determined as: baseline (before prostacyclin initiation), short term (1–3 months after initiation) and mid-term (6–12 months after initiation). Echocardiograms were identified for those time points. The results of 6-min walk test (6MWT), serum brain type natriuretic peptide (BNP), and Pediatric Panama functional class (FC) were recorded for each time point, if available. The pediatric Panama classification provides an age-based assessment of functional status from I to IV, with higher classes indicating more severe limitation.[20] PH diagnosis type was categorized by the World Health Organization (WHO) Nice Classification.[21] Post-treatment catheterization data were not included as catheterization was not performed within the study window for many patients and timing was highly variable.

Echocardiographic data: We reviewed images from clinically indicated echocardiograms performed using standard pediatric views in a Phillips IE33 machine (Phillips, Andover, MA, USA). Images were acquired with 3–8 MHz transducers, suited for patient's size and acoustic windows. Images were digitally stored using Syngo Dynamics (Siemens, Ann Arbor, MI, USA). Echocardiograms performed before and at 1–3 months and 6–12 months after prostacyclin initiation were reviewed offline in a blinded manner using a standardized research protocol. Parameters included: RV pressure estimate using the tricuspid valve regurgitation jet Doppler velocity (expressed as a ratio of the RV pressure estimate to the systemic systolic blood pressure), ventricular septal position in systole (graded as normal, flattened or bowing, reflecting sub-systemic, elevated and supra-systemic RV pressure, respectively), pulmonary artery acceleration time adjusted for ejection time (PAAT), RV hypertrophy, and RV function (qualitatively assessed as mild, moderate, or severe). Quantitative parameters of RV systolic function included TAPSE, RV FAC, and RV global longitudinal strain. TAPSE was measured by M-mode, as previously described.[22] Although Z-scores for TAPSE can be generated based on normative data, we indexed TAPSE to body surface area rather than using age-based Z-scores, as many pediatric PH patients are small for their age.[23] PAAT was obtained from a spectral Doppler measurement at the pulmonary valve annulus in the parasternal short-axis view and measured as the time interval between the onset of systolic pulmonary artery flow and peak velocity, divided by the RV ejection time. Corrected PAAT < 0.31 was considered abnormal.[24] RV FAC (%) was calculated from the apical four-chamber view as the end-diastolic area (EDA) minus the end-systolic area (ESA) divided by the EDA.[25] RV global longitudinal strain was assessed using TomTec software (Cardiac Performance Analysis, TomTec, Munich, Germany). A single observer (YW) blinded to clinical characteristics obtained measurements using speckle-tracking analysis on four-chamber cine-loop images that included the RV free wall and septum. The global longitudinal strain (i.e. the ventricular septum was included in the

assessment) was chosen to provide a more global assessment of the RV function, as opposed to just the free wall function that would be obtained with the RV free wall strain. Values were averaged to calculate RV global longitudinal strain (%) and strain was considered abnormal if $< -30\%$.[26] To ensure that strain measurements were reproducible, ten random studies were blindly reread with an intraclass correlation coefficient of 0.93 (interquartile range [IQR] = 0.85–1.0), indicating excellent reproducibility. Systolic strain is represented by negative values, where more negative values represent more myocardial deformation/strain and therefore better function.

Statistical analysis: Descriptive statistics were presented as frequency counts and percentages for categorical variables and mean ± standard deviation (SD) or median (range) for continuous variables. Logarithmic transformation was applied before performing analysis to the skewed data. Changes in the continuous (i.e. BNP and 6MWT distance), binary (RV function and FC), and ordinal (septal position) outcomes over time were investigated using mixed-effects linear, logistic, and ordinal regression models, respectively. Random intercepts were applied to these models. Mixed-effects regression models implemented via maximum likelihood account for correlations arising from the repeated measures and allow using all data from each individual under the assumption of missing at random.

Sensitivity analyses were performed to examine the potential outliers and influential points. These measurements were assessed by visual examination of histograms and normal probability plots of residual from these models. STATA version 14.2 (StataCorp, College Station, TX, USA) software was used to conduct statistical analyses.

Results

This retrospective cohort included 49 pediatric patients with PH treated with prostacyclin therapy. Most participants were white (63%), non-Hispanic (78%), and women (65%) (Table 1). According to the WHO Nice Classification,[21] most individuals had PAH (group 1), classified as idiopathic (35%), heritable (2%), or associated with congenital heart disease (18%). PH related to developmental lung disease, including bronchopulmonary dysplasia and congenital diaphragmatic hernia, was seen in 43%. One patient had chronic thromboembolic PH (2%). Median age at diagnosis was 1.1 years (age range = 0–21 years) and median age at prostacyclin start was 2.6 years (age range = 0–29 years). Thirty-two patients (65%) underwent cardiac catheterization within one year of starting prostacyclin therapy, with median catheterization timing four days before the start of treatment. Hemodynamics indicated severe disease, with average mean pulmonary arterial pressure (mPAP) 65 mmHg and indexed pulmonary vascular resistance (PVR) 16.6 $WU \bullet m^2$, with preserved cardiac index (3.5 $L/min/m^2$). Most patients were treated with treprostinil (67% received continuous IV/SQ and 18% received the inhaled form). Seven patients (14%) were treated with epoprostenol IV. Nearly half the patients were treated concurrently with a phophodiesterase type V inhibitor (43% with sildenafil and 6% with tadalafil) and one-quarter with an endothelin receptor antagonist (12% each with bosentan and ambrisentan). At last known follow-up, 16% patients had died or undergone lung transplantation (Table 1).

Table 1. Demographics and medical history (n = 49).

	Total n (%)
Sex	
Male	17 (34.7)
Female	32 (65.3)
Race	
White	31 (63.3)
Black	10 (20.4)
Other	2 (4.1)
Unknown	6 (12.2)
Ethnicity	
Unknown	1 (2.0)
Hispanic/Latino	10 (20.4)
Not Hispanic/Latino	38 (77.6)
PAH diagnosis	
1.1 Idiopathic PAH	17 (34.7)
1.2 Heritable PAH	1 (2.0)
1.4 Associated PAH	9 (18.4)
3.7 Developmental lung disease	21 (42.9)
4 Chronic thromboembolic PH	1 (2.0)
Age at PH diagnosis (years) (median (range))	1.1 (0–21.2)
Baseline hemodynamics	32 (65.3)
Cath before prostacyclin (days) (median (range))	4 (0–295)
mPAP (mmHg) (mean (SD))	65 (23.7)
PVR ($WU*m^2$) (mean (SD))	16.6 (9.9)
Cardiac index ($L/min/m^2$) (mean (SD))	3.5 (1)
Age at prostacylin start (years) (median (range))	2.6 (0.02–29)
Prostacyclin therapy type	
Treprostinil IV/SQ	33 (67.3)
Treprostinil Inhaled	9 (18.4)
Epoprostenol IV	7 (14.3)
Concurrent PH therapies	
Sildenafil	21 (42.9)
Tadalafil	3 (6.1)
Bosentan	6 (12.2)
Ambrisentan	6 (12.2)
Outcome	
Alive	41 (83.7)
Death	7 (14.3)
Lung transplant	1 (2.0)

Data are presented as frequencies and percentages for categorical variables or mean ± standard deviation (SD) for continuous variables and unless indicated.

Table 2. Echocardiographic and clinical parameters assessed at baseline, 1–3 months, and 6–12 months following prostacyclin initiation.

	Baseline		1–3 months		6–12 months		
	n	Statistics	n	Statistics	n	Statistics	*P*
RVPE(TR):SBP	29	0.95 ± 0.37	18	0.80 ± 0.39	18	0.76 ± 0.50	0.1
Septal position							
Normal	2	5.0%	5	13.9%	6	18.2%	0.59
Flattened	23	57.5%	18	50.0%	15	45.5%	
Bowing	15	37.5%	13	36.1%	12	36.4%	
PAAT:Ejection time	41	0.32 ± 0.09	31	0.36 ± 0.09	31	0.33 ± 0.09	0.26
RV function							
Normal/mildly diminished	25	59.5%	24	66.7%	29	82.9%	**0.037**
Moderately/severely diminished	17	40.5%	12	33.3%	6	17.1%	
TAPSE M-mode (mm)*	27	11.67 ± 4.42	29	13.20 ± 3.51	26	14.97 ± 3.80	**0.007**
RV FAC	43	0.30 ± 0.12	38	0.32 ± 0.14	33	0.35 ± 0.12	0.22
RV global longitudinal strain (%)	37	−13.61 ± 4.69	33	−16.39 ± 5.37	28	−17.97 ± 4.15	<**0.0001**
LV SF (%)	42	42.44 ± 10.77	37	44.27 ± 9.68	32	44.08 ± 9.64	0.41
BNP†	39	201.8 (11–3892)	35	86.5 (10–4207)	36	34.9 (10–2238)	<**0.0001**
6MWT distance (m)	11	457.8 ± 144.71	11	514.5 ± 107.43	10	491.3 ± 134.05	**0.0001**
FC (Panama)							
I or II	16	53.3%	18	66.7%	27	79.4%	**0.047**
IIIa, IIIb, or IV	14	46.7%	9	33.3%	7	20.6%	

Data are presented as mean ± standard deviation for continuous variables and frequencies and percentages for categorical variables unless indicated. *P* value is reported from the mixed-effects linear/logistic/ordinal regression models for testing the changes over time.

*Mixed-effects linear regression model was adjusted for body surface area.

†Median (range) presented and logarithmic transformation was applied before performing analysis due to skewed data.

RVPE (TR), right ventricular pressure estimate assessed by tricuspid valve regurgitation Doppler, expressed as a ratio to systemic systolic blood pressure (SBP); LVSF, shortening fraction of the left ventricle.

Echocardiographic changes with prostacyclin therapy

Estimates of RV systolic pressure: The estimated RV pressure was elevated at baseline at near systemic levels, as assessed by tricuspid valve regurgitation jet, with a trend towards a significant decrease to about two-thirds systemic at mid-term follow-up. Most patients (95%) had either systolic flattening or bowing of the ventricular septum at baseline. At mid-term follow-up, there was an increase in the proportion of participants with normal septal curvature but no significant change in the proportion of participants with bowing of the septum, such that the overall septal changes were not significant. Similarly, adjusted PAAT was borderline low at 0.32, with no significant improvement after prostacyclin treatment (Table 2).

Changes in RV function with prostacyclin therapy: There was significant improvement in multiple parameters of RV function in response to prostacyclin therapy over the study period. On qualitative assessment, 17 patients (41%) had moderately or severely diminished RV function at baseline, while the remainder had normal or mildly diminished function. The proportion of participants with moderate or severely diminished RV function decreased from 41% to 17% over the course of the study period ($P = 0.037$) (Table 2). While there was no significant improvement from baseline to 1–3 months, there was interim improvement between 1–3 and 6–12 months ($P = 0.5$ and 0.04, respectively) (Fig. 1).

Quantitative parameters of RV function also improved over the study period. TAPSE, adjusted for body surface area in analysis, was low at baseline (mean = 11.7 mm, corresponding to Z-score –2.6 ± 2) and improved significantly over the study period ($P = 0.007$) (Table 2). TAPSE increased at the early time point (13.2 mm, $P = 0.05$), with no additional interval improvement between early and mid-term assessments (Fig. 1).

RV strain was abnormally low at baseline (–13.6%) and significantly improved over the study period ($P < 0.001$) (Table 2). The majority of improvement was seen by 1–3 months with a trend toward additional improvement between 1–3 and 6–12 months (–16.4% and −18%, $P = 0.005$ and 0.05, respectively) (Fig. 1).

At baseline, RV FAC was diminished at 30% with a trend toward improvement after 6–12 months of prostacyclin therapy. There was no change in left ventricular function across the study period assessed by shortening fraction (Table 2).

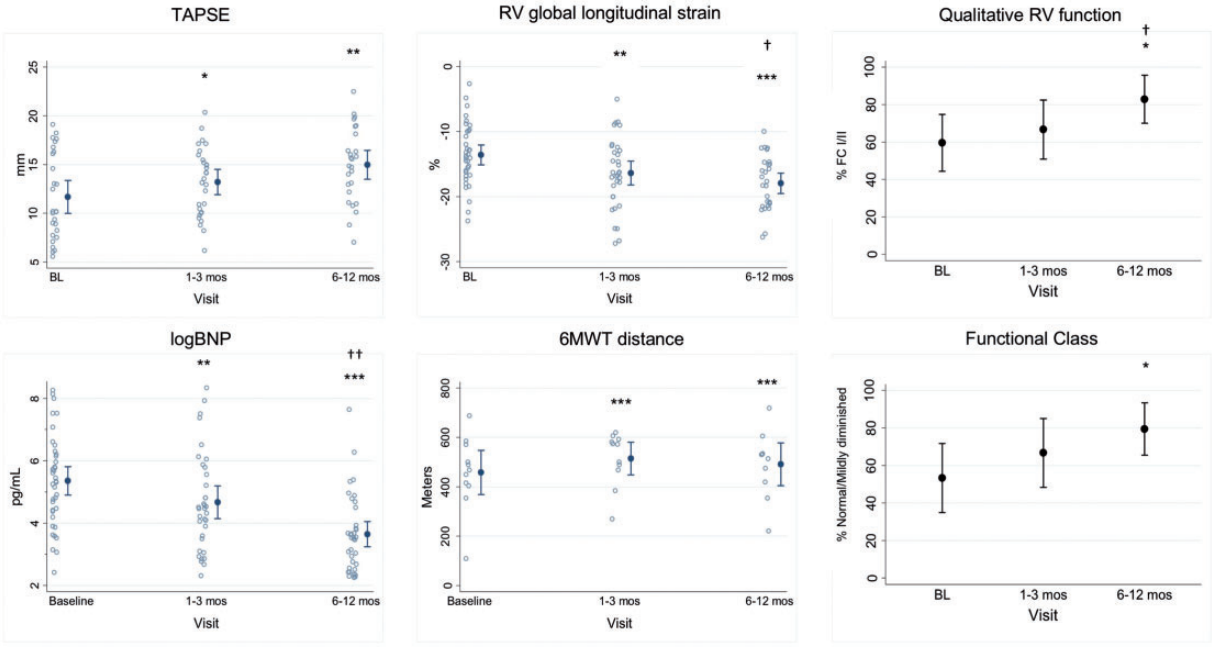

Fig. 1. Parameters significantly improved over the study period shown at baseline, and early, and late follow-up after initiation of prostacyclin therapy in children with PH. BNP (log), 6MWT distance, TAPSE, RV global longitudinal strain shown as mean ± standard deviation. FC (Panama) and qualitative RV function assessment represented as percent (FC I/II or normal/mildly diminished, respectively) with 95% confidence interval. *$P \leq 0.05$ (for TAPSE, $P = 0.05$), **$P < 0.01$, ***$P < 0.001$ relative to baseline (BL). †$P < 0.05$, (for strain, P=0.05) ††$P < 0.001$ relative to 1–3 months.

Clinical response to prostacyclin

Median BNP was elevated at baseline, with significant improvement (reduction) at 1–3 months and further improvement at 6–12 months ($P < 0.01$ and < 0.0001, respectively) (Fig. 1). Mean 6MWT distance improved significantly from baseline to 1–3 months ($P < 0.001$) with further improvement at 6–12 months ($P < 0.001$) (Fig. 1). This result was available in fewer patients given the inability of infants and young children to perform the test. In patients for whom the Panama FC assessment was available, about half (47%) showed severe functional limitation at baseline (class IIIa, IIIb, or IV) with improvement by the 6–12 month time point seen by with a reduction in class IIIa, IIIb, or IV to 21% ($P = 0.013$) (Table 2, Fig. 1).

Effect of age and other therapies

Because small participant numbers precluded meaningful subgroup analysis, we performed an adjustement to our mixed-effects linear/logistic regression analysis adjusting for age < 1 year. 6MWT is unavailable in the infant population so the P value remains unchanged, but Panama FC, TAPSE, strain and RV function all remained significantly improved over the study period regardless of age (Supplementary Table 1).

We performed an additional mixed-effects linear/logistic regression analysis adjusting for the presence of phosphodiesterase type 5 therapy (sildenafil or tadalafil) and endothelin receptor antagonist (bosentan or ambrisentan) (Supplementary Table 2). In the analysis, BNP and 6MWT distance remained significantly improved over the study period ($P < 0.0001$ for both). Similarly, there remained significant improvement in RV strain over the study period ($P = 0.0001$). TAPSE and RV function improved from baseline to 6–12 months ($P = 0.02$ for both) but the overall P values were no longer significant. With this adjustment for other drugs, Panama FC was not significantly changed over the study period, suggesting less of a direct effect of prostacyclin therapy on this parameter (Supplementary Table 2).

Discussion

In this retrospective cohort study, we investigated the potential clinical applicability of speckle tracking echocardiography to assess the response of the RV to treatment with prostacyclin analogues in pediatric PH. The main findings of the study were that after initiation of prostacyclin, there was early and sustained improvement in TAPSE and RV strain in most participants, which mirrored improvement in established clinical markers including BNP, 6MWT distance, and the Panama FC assessment, and a late improvement in qualitative assessment of RV function. Strain also detected interim improvement in RV function while TAPSE did not. These findings suggest that both TAPSE and strain are sensitive parameters to track RV function following initiation of prostacyclin therapy. The effect of prostacyclin on TAPSE and strain was significant after adjusting for other PH therapies, suggesting that most of the effect on RV

function is due to prostacyclin. The improvement seen in clinical parameters lends further credence to the use of these methods to assess RV function in pediatric PH.

RV function

Quantitative echocardiographic assessment of RV function is challenging due to the RV's complex geometric shape, anterior position in the chest, and potential changes in contractility pattern that occur in disease states. In this study, there was significant improvement in RV qualitative function assessment, TAPSE, and RV global longitudinal strain. TAPSE is a simple, two-dimensional parameter that has been widely used in PAH.[27,28] It has proven an important parameter with which to assess function and predict outcome in the adult PH population.[27,28] There is growing evidence to support use of TAPSE in pediatric PH, as it has been shown to be abnormal in children with PH, has shown improvement in response to PH treatment, and is considered a sensitive and specific predictor of mortality in this disease.[15,29–31] Despite this, one study showed TAPSE was preserved except in children with repaired congenital heart disease, suggesting superior RV adaptation and preservation of function except with severe disease.[32] Here we show that TAPSE is abnormal in children with PH and may be used for serial assessment of RV function, and suggest that it may prove valuable in combination with additional parameters, such as strain.

In our study, RV global longitudinal strain was reduced before initiation of treatment when considering published values in children.[26] Although we did not study a comparison of strain and TAPSE, we demonstrate that strain had early and interim improvement during the study observation period, while TAPSE did not show incremental improvement. Longitudinal strain measures the longitudinal contraction of the RV, and appears to be less load- and heart rate-dependent, and correlates with RV ejection fraction as assessed by MRI.[33] RV strain is inversely associated with PVR and PH severity in adults and children.[11,27,28] In adults with PH, improvements in RV strain are associated with therapy and with lower mortality.[14] In patients with Eisenmenger syndrome, RV strain and clinical parameters improve after initiation of prostacyclin analogue therapy.[36] A small study in term newborns showed improvement in RV strain following treatment with milrinone and inhaled nitric oxide.[37] In a longitudinal study examining the association of RV function and outcome in pediatric PAH, RV strain at presentation was worse in non-survivors than in survivors, and lower than TAPSE. Moreover, during the follow-up period, strain worsened in greater magnitude between non-survivors and survivors than changes seen in TAPSE.[15] Similar to our study, these results suggest that strain is a sensitive parameter with which to detect changes in RV function in PH and might be a more sensitive parameter than TAPSE.

While all three parameters improved over the course of the study, TAPSE and RV global longitudinal strain were significantly improved at the early time point, while qualitative RV function assessment was not, suggesting that TAPSE and strain may be more sensitive markers of early RV changes in function in response to treatment in pediatric PH (Fig. 1). Qualitative assessment was significantly improved at the later time point with significant improvement from early to late follow-up. Qualitative assessment of RV function remains a valuable tool in addition to quantitative parameters.

While the late FAC was on average five points higher than at baseline, there was no significant improvement in RV FAC over the study period. This could be attributed to several factors: FAC is a two-dimensional measure that takes into account end-systolic and end-diastolic areas and therefore incorporates the RV free wall's smaller contribution to shortening.[38] It is possible that therapy exerts most of its effect on the longitudinal motion of the RV, and therefore parameters that specifically assess longitudinal motion are most informative. A recent pediatric study found RV FAC correlated with indexed RV stroke work and TAPSE.[39] However, RV FAC may be limited by incomplete visualization of the RV and its dependence on loading conditions.[25] There is a trend toward improvement that does not reach statistical significance, but may be limited by small sample size.

Clinical parameters

TAPSE and RV global longitudinal strain may present distinct advantages for clinical usefulness in tracking RV performance over time in children with PH. BNP is an established and useful biomarker of marker of disease severity in pediatric PH and correlates with exercise capacity and hemodynamics.[40–42] However, despite these advantages, BNP requires phlebotomy, is not specific to the RV, and can be confounded by additional factors (renal function, fluid status, etc.).[43] In this study, we showed that BNP levels decreased in similar fashion to strain, i.e. an early and an interim improvement during the study observation. This gives further credence to the changes observed in RV strain.

The improvement in 6MWT was identified at the early follow-up, but no additional interim improvement. Although the 6MWT is an important metric to assess physical capacity in the setting of PH, it has limitations including age/size, developmental status, and physical disabilities. Similarly, FC assessment, even using a pediatric-specific scale, can also be obscured by developmental status or comorbidities. Therefore, in pediatric PH, TAPSE and strain may represent useful additions to the arsenal of non-invasive monitoring techniques.

Other parameters of pulmonary hypertension

Despite improvement in RV function and clinical assessments, there were not significant changes in RV systolic pressure estimate assessed by TR jet Doppler, interventricular septal position or PAAT adjusted for RV ejection time,

and a trend toward improvement in the ratio of RV to systemic systolic pressure (likely limited by small numbers due to lack of measurable tricuspid regurgitation in many patients). This may suggest the RV systolic pressure change with prostacyclin therapy may be modest over the first 6–12 months of therapy, not sufficient to be detected by echocardiogram, or may represent limited correlation between echocardiographic pressure assessments and hemodynamics measured by cardiac catheterization in children. Bano et al. also observed improvement in TAPSE with PH therapy with no change in PAAT.[44] Mourani et al. previously showed that echo assessment of PH severity was not strongly related to invasive hemodynamic measures in children with PH related to chronic lung disease suggesting there may be limitations to echocardiographic parameters of PH in this population.[45] Alternatively, there may be a direct effect of prostacyclin on RV myocardium, as has been reported in animal models of PH, explaining why function improvement can precede potential changes in pressure.[46]

Limitations to this study include the small sample size, heterogeneous population with respect to PH diagnosis type, and retrospective nature of data collection. Not all clinical or echocardiographic measures were available for all patients at the desired time points. We also lack information on correlation of echocardiographic findings with cardiac catheterization data (due to variable clinical practice) to determine how the echo findings relate to changes in mPAP, PVR, and cardiac output. Small numbers prohibited subgroup analysis for variability of effect by age, PH type, or prostacyclin therapy. Despite these limitations, this study shows consistent improvement in RV function as assessed by TAPSE and RV global longitudinal strain in children with PH in response to prostacyclin therapy that correlates with clinical improvement in BNP, 6MWT distance, and FC. Larger prospective studies are needed to validate these measurements in the general pediatric PH population. Our findings support the utility of TAPSE and RV global longitudinal strain for serial assessment of children with PH and highlights RV strain as a promising parameter that should be considered for clinical use.

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Conflict of interest

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