Research Article

Pulmonary Circulation

Follow-up tricuspid annular plane systolic excursion predicts survival in pulmonary arterial hypertension

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Abstract

Few studies have examined the utility of serial echocardiography in the evaluation, management, and prognosis of patients with pulmonary arterial hypertension (PAH). Therefore, we sought to evaluate the prognostic significance of follow-up tricuspid annular plane systolic excursion (TAPSE) in PAH. We prospectively studied 70 consecutive patients with PAH who underwent baseline right heart catheterization (RHC) and transthoracic echocardiogram, who survived to follow-up echocardiogram after initiation of PAH therapy. Baseline TAPSE was 1.6 ± 0.5 cm which increased to 2.0 ± 0.4 cm on follow-up ($P < 0.0001$). The cohort was dichotomized by TAPSE at one-year follow-up: Group 1 ($n = 37$): follow-up TAPSE ≥ 2 cm; Group 2 ($n = 33$): follow-up TAPSE < 2 cm. Group 1 participants were significantly more likely to reach WHO functional class I–II status and achieve a higher six-minute walk distance on follow-up. Of the 68 patients who survived more than one year, 18 died (26.5%) over a median follow-up of 941 days (range, 3–2311 days), with significantly higher mortality in Group 2 versus Group 1 (41.9% vs. 13.5%; $P = 0.003$). While baseline TAPSE stratified at 2 cm did not predict survival in this cohort, TAPSE ≥ 2 cm at follow-up strongly predicted survival in bivariable models (hazard ratio, 0.21; 95% confidence interval, 0.08–0.60). In conclusion, follow-up TAPSE ≥ 2 cm is a prognostic marker and potential treatment target in a PAH population.

Keywords

pulmonary arterial hypertension (PAH), right ventricular function, tricuspid annular plane systolic excursion (TAPSE), survival, follow-up

Date received: 1 December 2016; accepted: 26 January 2017

Pulmonary Circulation 2017; 7(2) 361–371
DOI: 10.1177/2045893217694175

Despite significant advances in the understanding, treatment, and prognosis of pulmonary arterial hypertension (PAH), the morbidity and mortality of this condition remains high. Patient outcomes in PAH are strongly linked to the relative degree of adaptation or maladaptation of the right ventricle (RV) to the chronically elevated RV afterload that is inherent to the condition.[1,2] The inability to restore a relative balance between RV function and RV afterload is central to exercise intolerance, clinical RV failure, and death.[1]

As the treatment options for PAH have increased substantially over the last decade, expected response to therapy has likewise shifted.[3–8] Classically, invasive baseline hemodynamic markers including right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), mixed venous oxygen saturation (MVO2), and cardiac index (CI) have been shown to predict survival.[4,9] Other non-invasive parameters, including 6-minute walk distance (6MWD), World

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Health Organization functional class (WHO FC), and serum biomarkers (e.g. B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]), have been studied, and are currently used to assess both response to therapy as well as survival.[6,8,10–12]

These studies have focused on the prognostic ability of these measures either before or during active PAH treatment. However, more recently Nickel et al. found that while many of these parameters were predictive of survival at baseline, follow-up assessment of WHO FC, CI, MVO2, and NT-proBNP in response to therapy were more predictive of prognosis than baseline values.[13] Likewise, serial RV ejection fraction (RVEF) in response to PAH medical therapy was superior to baseline RVEF in assessing patient outcome in PAH.[14,15]

Previously, we have shown the prognostic significance of baseline tricuspid annular systolic plane excursion (TAPSE), a reproducible, echo-derived assessment of RV function, in a PAH population.[16] In that study, there was a three- to fourfold increased risk of death in patients with reduced TAPSE (<1.8 cm). However, TAPSE was assessed at one undefined time-point in the course of the disease, with over 50% of the patients having prevalent PAH. Thus, while this TAPSE cut-point identified patients with the highest risk of death, it did not reflect RV function in response to PAH medical therapy. To date, no study has evaluated the utility of follow-up TAPSE assessment, as opposed to baseline TAPSE measurement, in predicting survival in a PAH population, after initiation of PAH therapy. Thus, we sought to assess the prognostic role of follow-up TAPSE measurement, and specifically a treatment TAPSE goal of $\geq$2 cm, as previously proposed[17] and reflective of normal RV function,[18] in a PAH population after initiation of PAH therapy.

Methods

Study design

We prospectively enrolled consecutive patients referred to our pulmonary hypertension (PH) programs between January 2007 and March 2013 and diagnosed with PAH. All patients who underwent standard right heart catheterization (RHC) and two-dimensional (2D) echocardiography on initial encounter (baseline), had a repeat echocardiogram (follow-up) after at least six months from initial examination, and were initiated on PH-specific therapy were eligible for the study.

Patients were included if their RHC met PAH hemodynamic criteria (mPAP $\geq$ 25 mmHg, pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg, and pulmonary vascular resistance (PVR) $\geq$ 3 WU) in the absence of other known causes of PH. Seventy-five patients were screened and five were excluded: two were diagnosed with chronic thromboembolic PH, two had prior cardiac surgery for congenital heart disease, and one had significant parenchymal lung disease. Seventy patients comprised the study cohort (Fig. 1).

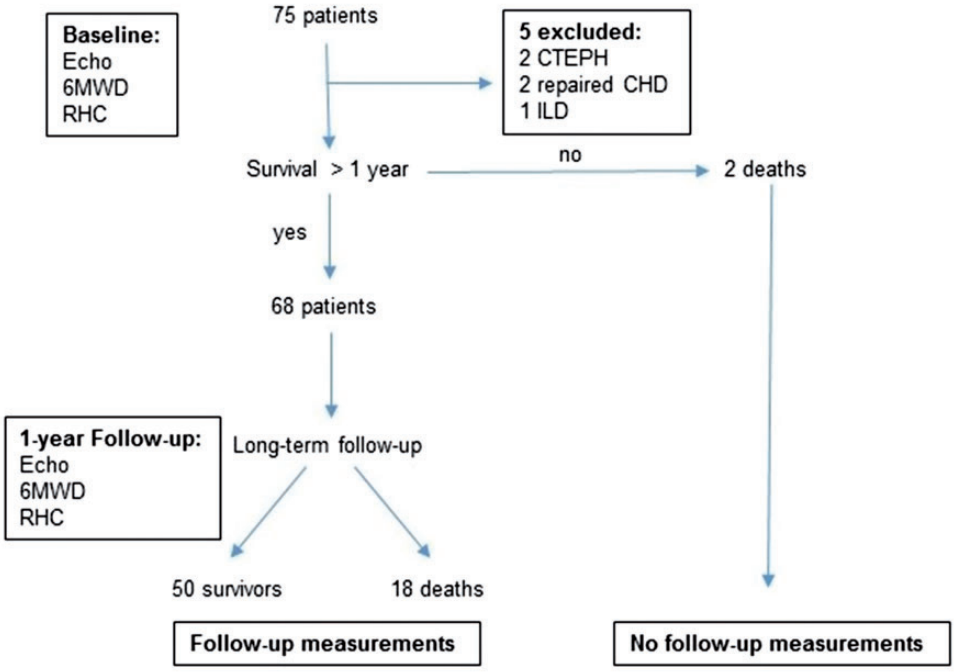

Fig. 1. Schematic of patient enrollment. Echo, echocardiogram; 6MWT, 6-minute walk test; RHC, right heart catheterization; CTEPH, chronic thromboembolic pulmonary hypertension; CHD, congenital heart disease; ILD, interstitial lung disease.

The primary endpoint was all-cause mortality. Vital status of each patient was confirmed by review of medical records, phone contact, and the Social Security Death Index. The study was approved by the institutional review boards at the Hospital of the University of Pennsylvania and Temple University Hospital.

Measurements

Hemodynamic assessment. All patients underwent standard hemodynamic assessment by RHC.

Echocardiography. All patients underwent a baseline echocardiogram as well as a follow-up examination at least six months after the baseline exam, after the initiation of PH-specific therapy.

To measure TAPSE, the apical four-chamber view was used, and an M-mode cursor was placed through the lateral tricuspid annulus, with TAPSE measured as the total displacement of the tricuspid annulus (cm) from end-diastole to end-systole, with values representing the average TAPSE of three to five beats, as previously described.[16,19] Alternatively, if an M-mode TAPSE was not available or of adequate quality, the 2D apical four-chamber view was used, with TAPSE measured by subtracting the distance of displacement of the lateral tricuspid annulus between end-systole and end-diastole, a technique that has been shown to tightly correlate with M-mode TAPSE, as previously described.[20,21]

Additional method details related to patient characteristics and hemodynamic and echocardiographic assessment are detailed in the online supplement.

Statistical analysis

Categorical variables were reported as percentages, with mean and standard deviation (SD) or median (interquartile range [IQR]) for normally and non-normally distributed continuous data, respectively. Comparisons were made using the student's t-test or Wilcoxon rank-sum test for continuous variables where appropriate, or Chi-square test or Fisher's exact test for categorical variables, as appropriate. A P value < 0.05 was considered significant.

The cohort was dichotomized by serial TAPSE value as follows: Group 1: follow-up TAPSE ≥ 2 cm; and Group 2: follow-up TAPSE < 2 cm. Univariable and bivariable Cox proportional hazards models were constructed using TAPSE as a continuous or dichotomous variable. Time-to-event analyses were performed using the Kaplan–Meier product limit estimator. Additional details on data analysis and modeling is provided in the online supplement.

Results

Fig. 1 shows the study design and enrollment. Demographic, clinical, and hemodynamic characteristics of the 70 patients in the total study cohort, and separated into follow-up TAPSE subgroups (Group 1: follow-up TAPSE ≥ 2 cm; Group 2: follow-up TAPSE < 2 cm), are summarized in Table 1.

Overall, the majority of patients were women (n = 55; 78.6%), with mean age of 55 ± 15 years, and 67% WHO FC III–IV. Between follow-up TAPSE subgroups, there were no significant differences in demographic variables, type of PAH, baseline WHO FC, baseline 6MWD, or hemodynamic variables ($P > 0.05$). At follow-up, 46 patients (66%) were on two or more PAH therapies. Overall, the use of oral phosphodiesterase-5-inhibitors (PDE-5i), endothelin receptor antagonists (ERA), and inhaled PAH therapies at time of follow-up echocardiogram were similar in both groups, however, more patients in Group 2 received parenteral prostacyclin therapy ($P = 0.04$). Median time to follow-up echocardiogram was 384 days, (range, 201–753 days).

Fifty-four of the 70 participants were incident cases, while the remainder (n = 16) were prevalent cases referred to our center for second opinions or intensification of management. The median time of the prevalent patients on PH medical therapy was 456 days (range, 214–1000 days). Of the prevalent cases, 69% (n = 11) were on oral monotherapy, with six patients on ERAs and five patients on PDE5i. In the remaining participants, four were on dual therapy and one was on triple therapy. Furthermore, 12 of the 16 prevalent patients (75%) had intensification of therapy after baseline measurement. Sensitivity analyses were performed on the treatment-naïve cohort alone and showed no significant differences from the results found in the larger cohort (data not shown).

Baseline hemodynamic data were similar across subgroups, and reflective of severe pre-capillary, pulmonary vascular disease as described in the PAH population, with a normal PAWP (11 ± 4 mmHg) and severely elevated PVR (11 ± 5 WU).

Baseline echocardiographic values are listed in Table 2 and further described in Supplemental Table 1 in the online data supplement. Baseline TAPSE was reduced for the total study cohort (1.6 ± 0.5 cm), but was statistically significantly higher in Group 1 compared with Group 2 (1.7 ± 0.5 cm vs. 1.5 ± 0.5, $P = 0.03$). Baseline RV fractional area change (RV FAC) was similarly reduced, and baseline measures of right atrial (RA) and RV size (absolute and relative to left-sided chambers) were significantly increased, consistent with prior data.[16]

In the overall cohort, follow-up echocardiographic assessment revealed a significant increase in TAPSE (1.6 ± 0.5 cm vs. 2.0 ± 0.4 cm; $P < 0.0001$). There was a marked difference in follow-up TAPSE observed in Group 1 versus Group 2 (2.3 ± 0.2 cm vs. 1.6 ± 0.3 cm; $P < 0.0001$). Importantly, 28 of 37 patients (76%) in Group 1 had a TAPSE < 2 cm at baseline, with 19 of 37 (51%) having a baseline TAPSE ≤ 1.6 cm, the mean TAPSE for the total cohort (Fig. 2). There were also serial improvements noted

Table 1. Baseline characteristics for the overall cohort and by follow-up TAPSE group.

Characteristic	Total cohort (n = 70)	TAPSE ≥ 2 cm (n = 37)	TAPSE < 2 cm (n = 33)	*P* value
Age (years)	55 ± 15	52 ± 16	57 ± 14	0.19
Sex (n (% women))	55 (78.6)	32 (86.5)	23 (69.7)	0.09
Race (n (% White))	49 (70.0)	27 (72.9)	22 (66.7)	0.26
BMI (kg/m^2)	28.8 ± 6.7	29.3 ± 6.6	28.2 ± 6.8	0.52
Baseline functional class (n (%))				0.55
WHO FC I–II	23 (32.9)	11 (29.7)	12 (36.4)	
WHO FC III–IV	47 (67.1)	26 (70.3)	21 (63.6)	
Follow-up functional class (n (%))				0.03
WHO FC I–II	33 (47.1)	22 (59.5)	11 (33.3)	
WHO FC III–IV	37 (52.9)	15 (40.5)	22 (66.7)	
Diagnoses (n (%))				0.53
IPAH	36 (51.4)	21 (56.8)	15 (45.5)	
CTD	23 (32.9)	10 (27.0)	13 (39.4)	
Other	11 (15.7)	6 (16.2)	5 (15.2)	
Treatment (n (%))*				
PDE5-i	58 (82.9)	32 (86.5)	26 (78.8)	0.39
ERA	48 (68.6)	26 (70.3)	22 (66.7)	0.75
Inhaled PG	14 (20.0)	8 (21.6)	6 (18.2)	0.72
Parenteral PG	14 (20.0)	4 (10.8)	10 (30.3)	0.04
Combination therapy (n (%))*				0.67
Monotherapy	23 (32.9)	13 (35.1)	10 (31.3)	
Dual therapy	27 (38.6)	15 (40.5)	12 (37.5)	
Triple therapy	19 (27.1)	9 (24.3)	10 (31.3)	
Baseline 6MWD (m)	284 ± 134	296 ± 132	271 ± 137	0.42
Follow-up 6MWD (m)	356 ± 132	394 ± 113	313 ± 141	0.01
Change in 6MWD (m)	71 ± 94	97 ± 91	43 ± 90	0.01
Baseline hemodynamics				
HR (beats/min)	81 ± 16	79 ± 16	84 ± 16	0.24
Systolic BP (mmHg)	129 ± 19	128 ± 19	130 ± 20	0.81
RAP (mmHg)	10 ± 5	9 ± 5	11 ± 5	0.09
PASP (mmHg)	86 ± 21	90 ± 22	82 ± 20	0.13
mPAP (mmHg)	53 ± 12	55 ± 13	50 ± 11	0.13
PAWP (mmHg)	11 ± 4	11 ± 4	10 ± 4	0.63
PVR (Wood Units)	11 ± 5	12 ± 6	11 ± 4	0.73
CI (L/min/m^2)	2.2 ± 0.6	2.2 ± 0.6	2.3 ± 0.6	0.92
SVI (mL/m^2)	28 ± 8	30 ± 9	27 ± 8	0.25
MVO2 (%)	63.5 ± 11.5	63.8 ± 13.4	63.2 ± 7.9	0.90

*Therapy at follow-up.

BMI, body mass index; BP, blood pressure; CI, cardiac index; CTD, connective tissue disease; ERA, endothelin receptor antagonist; HR, heart rate; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; MVO2, mixed venous oxygen saturation; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PDE5-I, phosphodiesterase inhibitor; PG, prostaglandin; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walk distance.

in several indices of right heart size and function, and right to left heart proportion, with improvements largely appreciated in those who achieved a follow-up TAPSE ≥ 2 cm (Supplemental Table 1). Group 1 participants had a significantly longer pulmonary artery acceleration time (AcT) on follow-up, consistent with a relatively greater reduction in RV afterload in Group 1 versus Group 2 (Table 1). We did not observe an overall change in RV

Table 2. Echocardiographic parameters for the overall cohort and by follow-up TAPSE group.

Echo parameter	Total cohort (n = 70)	TAPSE ≥ 2 cm (n = 37)	TAPSE < 2 cm (n = 33)	*P* value
Baseline TAPSE (cm)	1.6 ± 0.5	1.7 ± 0.5	1.5 ± 0.5	**0.03**
Follow-up TAPSE (cm)	2.0 ± 0.4	2.3 ± 0.2	1.7 ± 0.3	**<0.0001**
Baseline RV fractional area change (%)	26 ± 10	25 ± 9.0	27 ± 12	0.62
Follow-up RV fractional area change (%)	26 ± 11	28 ± 10	25 ± 12	0.25
Baseline RA (cm)	4.8 ± 1.0	4.8 ± 0.9	4.9 ± 1.2	0.74
Follow-up RA (cm)	4. 5 ± 1.1	4.3 ± 0.9	4.7 ± 1.2	0.24
Baseline LA (cm)	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	0.94
Follow-up LA (cm)	3.7 ± 0.6	3.8 ± 0.6	3.6 ± 0.6	0.17
Baseline RVIDd (cm)	5.0 ± 0.9	4.8 ± 0.8	5.2 ± 0.9	**0.02**
Follow-up RVIDd (cm)	4.8 ± 0.9	4.6 ± 0.8	5.0 ± 1.0	**0.04**
Baseline LVIDd (cm)	3.8 ± 0.6	3.8 ± 0.6	3.8 ± 0.6	0.81
Follow-up LVIDd (cm)	4.2 ± 0.7	4.4 ± 0.6	4.0 ± 0.7	**0.01**
Baseline RVIDd:LVIDd	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.4	0.08
Follow-up RVIDd:LVIDd	1.2 ± 0.4	1.1 ± 0.2	1.3 ± 0.5	**0.004**
Baseline RAA index (cm^2/m)	13.0 ± 4.4	12.8 ± 3.8	13.1 ± 5.1	0.56
Follow-up RAA index (cm^2/m)	12.1 ± 4.2	11.6 ± 3.3	12.7 ± 5.1	0.32
Baseline RVAd index (cm^2/m)	14.8 ± 4.4	14.2 ± 3.4	15.5 ± 5.3	0.24
Follow-up RVAd index (cm^2/m)	13.6 ± 4.5	12.7 ± 3.9	14.7 ± 4.9	0.06
Baseline systolic eccentricity index	1.4 ± 0.7	1.3 ± 0.6	1.5 ± 0.7	0.21
Follow-up systolic eccentricity index	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.5	0.29
Baseline RV-PA gradient (mmHg)	65 ± 29	68 ± 35	62 ± 21	0.42
Follow-up RV-PA gradient (mmHg)	52 ± 23	48 ± 26	58 ± 17	0.09
Baseline TR severity (grade ≥ 3+) (n (%))	19 (27)	10 (27)	9 (27)	1.0
Follow-up TR severity (grade ≥ 3+) (n (%))	20 (29)	7 (19)	13 (39)	0.36
Baseline RVOT VTI (cm)	11 ± 3.2	12 ± 2.7	10 ± 3.4	**0.01**
Follow-up RVOT VTI (cm)	15 ± 4.5	17 ± 4.1	13 ± 3.9	**0.001**
Baseline Notch (n (%))	None: 3 (4) LSN: 27 (39) MSN: 39 (57)	None: 1 (2.7) LSN: 16 (43) MSN: 20 (54)	None: 2 (6.3) LSN: 11 (34) MSN: 19 (59)	0.67
Follow-up Notch (n (%))	None: 14 (20) LSN: 27 (39) MSN: 28 (41)	None: 10 (27) LSN: 15 (41) MSN: 12 (32)	None: 4 (13) LSN: 12 (38) MSN: 16 (50)	0.21
Baseline AcT (ms)	69 ± 18	69 ± 19	69 ± 18	0.89
Follow-up AcT (ms)	85 ± 19	90 ± 19	79 ± 18	**0.01**
Baseline LVEF (%)	67 ± 7.9	68 ± 7.6	67 ± 8.2	0.53
Follow-up LVEF (%)	68 ± 7.1	68 ± 4.9	67 ± 8.9	0.40

AcT, acceleration time; LA, left atrial; LVIDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; PA, pulmonary arterial; RA, right atrial; RAAi, right atrial area indexed to patient height; RV, right ventricular; RVAd, right ventricular area indexed to patient height; RVIDd, right ventricular diastolic dimension; RVOT VTI, right ventricular outflow tract velocity time integral; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

FAC in response to PAH treatment (26 ± 10 vs. 26 ± 11, $P = 0.51$). Overall, there was excellent intra-observer (reader 1: intraclass correlation coefficient [ICC] = 0.98; 95% confidence interval [CI], 0.97–0.99; reader 2: ICC = 0.99; 95% CI, 0.98–0.99) and inter-observer reliability (ICC = 0.98; 95% CI, 0.97–0.99) of TAPSE, as previously shown.[22]

Of note, a significantly higher proportion of participants in Group 1 reached WHO FC I–II status versus Group 2 (60% vs. 33%; Table 1). In addition, Group 1 participants experienced a greater than twofold higher increase in 6MWD from baseline (+97 ± 91 vs. + 43 ± 90 m; $P = 0.01$), as well as a significantly higher absolute 6MWD on follow-up versus Group 2 (394 ± 113 vs. 313 ± 141 m; $P = 0.01$).

Follow-up hemodynamics were available in a subset of 35 patients obtained at a median of 350 days (IQR, 265–415) after the initial RHC. Overall, follow-up cardiac output

(CO; 6.0 ± 1.7 vs. 4.8 ± 1.4 L/min) and stroke volume index (SVI; 47 ± 15 vs. 37 ± 13) were significantly higher in Group 1 compared with Group 2 ($P = 0.03$ and $P = 0.05$, respectively), with otherwise similar follow-up hemodynamic parameters across both groups (Fig. 3 and Supplemental Table 2 in the online data supplement).

Complete NT-proBNP data were available in 36 patients (51%), with 19 patients in Group 1 and 17 patients in Group 2. At baseline, median NT-proBNP was 813 (IQR, 278–2493) pg/mL and 1568 (IQR, 892–3970) pg/mL in Group 1 and Group 2, respectively ($P = 0.10$). At follow-up, median NT-proBNP decreased significantly in Group 1 (269 [94–575] pg/mL; $P = 0.03$) with no significant change in follow-up NT-proBNP in Group 2 (1913 [798–3052] pg/mL; $P = 0.87$). At follow-up, the NT-proBNP level was significantly lower (86%) in Group 1 versus Group 2 (269 [94–575] vs. 1913 [798–3052] pg/mL; $P < 0.0001$).

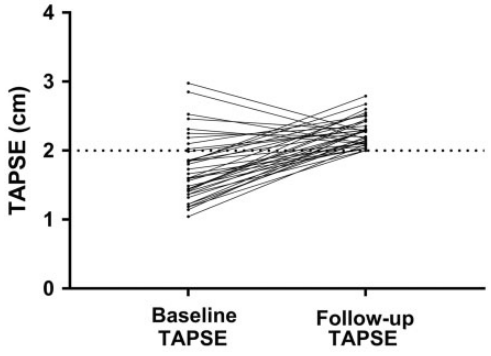

Fig. 2. Line plot of TAPSE trend. Individual baseline and follow-up TAPSE for patients with follow-up TAPSE ≥ 2 cm.

TAPSE and survival

Of the 70 patients included in the study, 68 patients survived more than one year, with a median follow-up time of 941 days (range, 3–2311 days). Overall, 18 of the 68 participants died (26.5% mortality) with significantly higher mortality in Group 2 compared with Group 1 ($P = 0.003$; five deaths in Group 1 [13.5%] vs. 13 deaths in Group 2 [41.9%]).

As seen in Fig. 3, on Kaplan–Meier analysis, while there was no difference in survival based on baseline TAPSE ≥ 2 cm vs. < 2 cm (Fig. 4a; one-, two-, and three-year actual survival rates: TAPSE ≥ 2 cm: 0.86, 0.86, 0.86 and TAPSE < 2 cm: 0.82, 0.78, 0.70), there was a marked difference in survival after stratifying by follow-up TAPSE ≥ 2 cm versus < 2 cm (Fig. 4b; one-, two-, and three-year actual survival rates: TAPSE ≥ 2 cm: 0.95, 0.95, 0.88 and TAPSE < 2 cm: 0.71, 0.63, 0.57). Those in Group 1 (follow-up TAPSE ≥ 2 cm) had significantly longer survival compared with those in Group 2 (follow-up TAPSE < 2 cm; log-rank $P = 0.004$).

On univariable Cox-proportional hazards analysis, male gender and connective tissue disease (CTD)-associated PAH were strongly predictive of death (HR [hazard ratio], 3.55; 95% CI, 1.43–8.84; and HR, 3.10; 95% CI, 1.27–7.51), respectively; both $P < 0.01$), as shown in other cohorts.[23–25] Other baseline variables previously shown to be associated with outcomes in PAH were not predictive of survival in this analysis (Table 3). Follow-up TAPSE ≥ 2 cm, as opposed to baseline TAPSE, was strongly predictive of survival

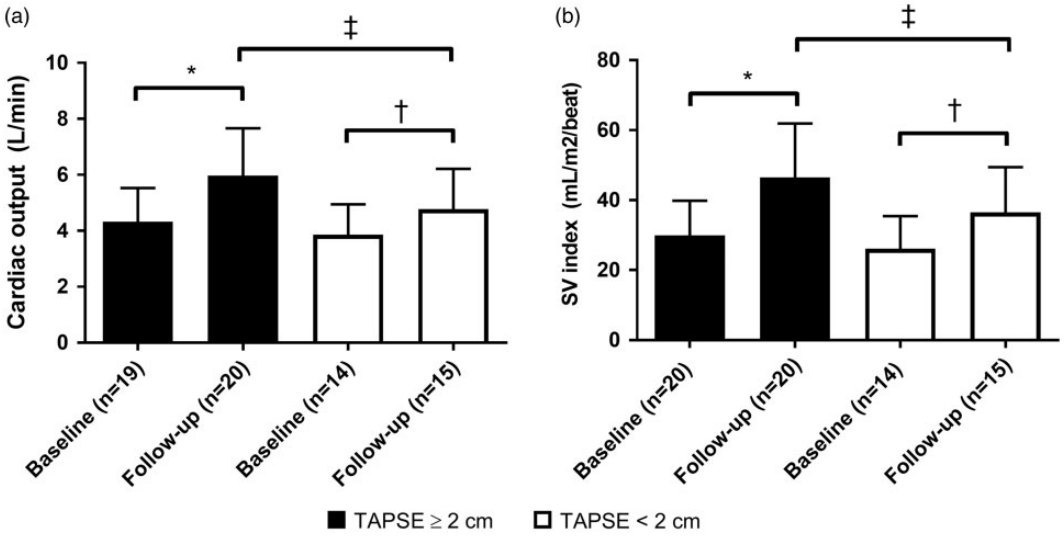

Fig. 3. Baseline and follow-up CO and SVI and TAPSE subgroups. (a) Bar graphs compare baseline and follow-up CO within and between the follow-up TAPSE subgroups. *$P = 0.001$, †$P =$ not significant, ‡$P = 0.03$. (b) Bar graphs compare baseline and follow-up SVI within and between the follow-up TAPSE subgroups. *$P < 0.001$, †$P = 0.02$, ‡$P = 0.05$. CO, cardiac output; TAPSE, tricuspid annular plane systolic excursion; SVI, stroke volume index.

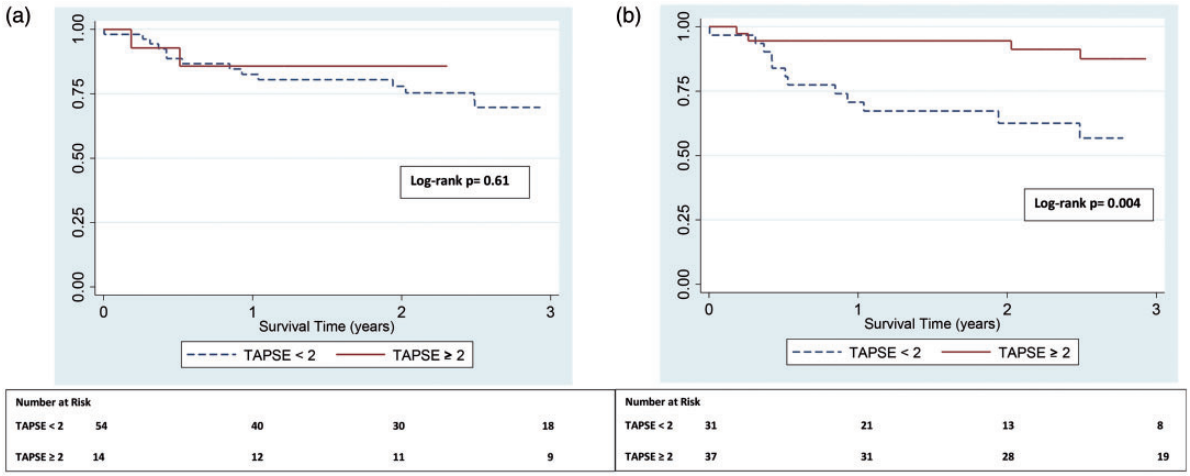

Fig. 4. Kaplan–Meier estimates of survival stratified by TAPSE values. (a) Survival stratified by baseline TAPSE value < 2 cm or ≥ 2 cm. (b) Survival stratified by follow-up TAPSE value < 2 cm or ≥ 2 cm. Numbers below each figure represent the number of patients at risk for death at each time point.

Table 3. Univariable Cox proportional hazards model.

	Overall*		Landmark (1 year)†	
Parameter	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (0.99–1.06)	0.11	1.02 (0.99–1.06)	0.16
Sex (men vs. women)	3.55 (1.43–8.84)	<0.01	2.75 (1.02–7.39)	0.04
Race (Black/other vs. White)	0.42 (0.12–1.44)	0.17	0.30 (0.07–1.30)	0.11
BMI	0.99 (0.93–1.06)	0.74	1.00 (0.94–1.07)	0.93
PAH Type (CTD vs. IPAH/other)	3.10 (1.27–7.51)	0.01	3.23 (1.27–8.23)	0.01
Baseline WHO FC	1.56 (0.94–2.60)	0.08	1.54 (0.90–2.63)	0.11
Baseline 6MWD	0.99 (0.99–1.00)	0.08	0.99 (0.99–1.00)	0.14
Hemodynamics (baseline)				
RAP	1.08 (0.99–1.17)	0.08	1.05 (0.96–1.15)	0.29
mPAP	0.99 (0.95–1.02)	0.51	0.98 (0.95–1.02)	0.42
Cardiac output	0.91 (0.59–1.39)	0.66	0.94 (0.60–1.47)	0.78
Cardiac index	0.88 (0.42–1.84)	0.73	0.98 (0.42–1.99)	0.83
PVR	0.97 (0.88–1.06)	0.48	0.96 (0.87–1.06)	0.44
Echocardiogram				
TAPSE (baseline)	0.64 (0.23–1.73)	0.38	0.80 (0.28–2.23)	0.67
TAPSE ≥ 2 vs. < 2 cm at 1 year	0.21 (0.08–0.60)	<0.01	0.24 (0.08–0.68)	<0.01
RVFAC (baseline)	2.35 (0.02–228.4)	0.71	4.91 (0.04–579.5)	0.51
RA size (baseline)	0.98 (0.62–1.56)	0.94	1.00 (0.61–1.64)	0.99
RVIDd (baseline)	1.60 (0.99–2.58)	0.06	1.43 (0.86–2.38)	0.17
RV:LV (baseline)	1.50 (0.42–5.31)	0.53	1.00 (0.25–4.02)	0.99
Systolic EI (baseline)	0.67 (0.29–1.57)	0.36	0.75 (0.31–1.78)	0.51

*Data shown represents univariable model for the overall cohort.

†Data shown represents univariable model for the landmark analysis for the subjects who survived at least one year.

BMI, body mass index; BP, blood pressure; CI, confidence interval; CTD, connective tissue disease; EI, eccentricity index; HR, hazard ratio; IPAH, idiopathic pulmonary arterial hypertension; LV, left ventricular; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVFAC, right ventricular fractional area change; RVIDd, right ventricular diastolic dimension; TAPSE, tricuspid annular plane systolic excursion; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walk distance.

Table 4. Bivariable Cox proportional hazards model.

Parameter	Overall*		Landmark (1 year)†	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
TAPSE ≥ 2 vs. < 2 cm	0.21 (0.08–0.60)	<0.01	0.24 (0.08–0.68)	<0.01
TAPSE ≥ 2 vs. < 2 cm controlling for				
Age	0.22 (0.08–0.62)	<0.01	0.25 (0.09–0.71)	0.01
Sex (men vs. women)	0.25 (0.09–0.72)	0.01	0.27 (0.09–0.78)	0.02
Race (Black/other vs. White)	0.21 (0.07–0.59)	<0.01	0.20 (0.07–0.59)	<0.01
PAH type (CTD vs. IPAH/other)	0.23 (0.08–0.66)	<0.01	0.26 (0.09–0.76)	0.01
Baseline WHO FC	0.19 (0.07–0.54)	<0.01	0.21 (0.07–0.61)	<0.01
Baseline 6MWD	0.21 (0.07–0.59)	<0.01	0.23 (0.08–0.68)	<0.01
Total number of medications	0.22 (0.08–0.60)	<0.01	0.25 (0.09–0.70)	<0.01
Hemodynamics (baseline)				
RAP	0.23 (0.08–0.65)	<0.01	0.25 (0.09–0.72)	0.01
mPAP			0.24 (0.08–0.71)	0.01
Cardiac index	0.18 (0.06–0.57)	<0.01	0.20 (0.06–0.66)	<0.01
PVR	0.19 (0.06–0.59)	<0.01	0.22 (0.07–0.68)	<0.01
Echo (baseline)				
RVFAC	0.22 (0.08–0.63)	<0.01	0.26 (0.09–0.75)	0.01
RVIDd	0.25 (0.09–0.71)	<0.01	0.27 (0.09–0.80)	0.02
Systolic EI	0.23 (0.08–0.65)	<0.01	0.25 (0.09–0.74)	0.01

*Data shown represents bivariable model for the overall cohort.
†Data shown represents bivariable model for the landmark analysis for the subjects who survived at least one year.
CI, confidence interval; CTD, connective tissue disease; EI, eccentricity index; HR, hazard ratio; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVFAC, right ventricular fractional area change; RVIDd, right ventricular diastolic dimension; TAPSE, tricuspid annular plane systolic excursion; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walk distance.

Table 5. Association of change in TAPSE and risk of death.

Variable	Continuous		Dichotomous*		Dichotomous†	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted	0.37 (0.14–0.96)	0.04	0.36 (0.13–1.00)	0.05	0.38 (0.12–1.16)	0.09
Age	0.36 (0.14–0.85)	0.02	0.30 (0.10–0.85)	0.02	0.28 (0.09–0.89)	0.03
Sex	0.36 (0.14–0.97)	0.04	0.35 (0.12–0.98)	0.05	0.44 (0.14–1.36)	0.16
Race	0.38 (0.16–0.92)	0.03	0.30 (0.11–0.85)	0.02	0.29 (0.09–0.90)	0.03
PAH Type	0.35 (0.14–0.92)	0.03	0.37 (0.13–1.03)	0.06	0.37 (0.12–1.13)	0.08
Baseline WHO FC	0.28 (0.10–0.78)	0.01	0.33 (0.11–0.94)	0.04	0.32 (0.10–0.98)	0.05
Baseline 6MWD	0.32 (0.12–0.84)	0.02	0.34 (0.12–0.97)	0.04	0.32 (0.10–0.98)	0.04
Total number med	0.43 (0.16–1.19)	0.10	0.40 (0.14–1.18)	0.10	0.45 (0.14–1.46)	0.19
Baseline RAP	0.27 (0.09–0.76)	0.01	0.31 (0.11–0.89)	0.03	0.33 (0.10–1.02)	0.05
Baseline mPAP	0.39 (0.14–1.03)	0.06	0.37 (0.13–1.05	0.06	0.40 (0.13–1.25)	0.11
Baseline CI	0.27 (0.09–0.75)	0.01	0.28 (0.08–0.90)	0.03	0.28 (0.08–1.03)	0.06
Baseline PVR	0.30 (0.10–0.89)	0.03	0.33 (0.10–1.02)	0.06	0.33 (0.09–1.20)	0.09
Baseline RVFAC	0.42 (0.16–1.17)	0.11	0.39 (0.13–1.13)	0.08	0.41 (0.13–1.33)	0.14
Baseline RVIDd	0.29 (0.09–0.90)	0.03	0.33 (0.11–0.95)	0.04	0.38 (0.12–1.17)	0.09
Baseline EIS	0.43 (0.17–1.10)	0.08	0.38 (0.13–1.08)	0.07	0.38 (0.12–1.16)	0.09

*TAPSE dichotomized by change > or < than median change in cohort (0.37 cm).
†TAPSE dichotomized by change > or < 0.5 cm (n = 28 with TAPSE > 0.5 cm change).

(HR, 0.21; 95% CI, 0.08–0.60) on both univariable and bivariable analyses (Tables 3 and 4).

Sensitivity analyses evaluating delta TAPSE as a continuous variable, dichotomized by the median value of change in TAPSE (0.37 cm), and dichotomized by change in TAPSE at $>$ or >0.5 cm, revealed similar point estimates across models (Table 5). Additionally, more conservative baseline TAPSE cut-points of 1.5 cm and 1.8 cm were both not significantly associated with survival (data not shown). Lastly, additional analyses assessing the prognostic value of follow-up 6MWD >400 m and RV:LV ratio compared with follow-up TAPSE ≥ 2 cm were performed and are detailed in the online supplement (Supplemental Figure 1).

Discussion

Our study highlights the utility of follow-up TAPSE measurement in a cohort of patients with PAH after initiation of therapy. We show that a follow-up TAPSE ≥ 2 cm, as opposed to baseline TAPSE, is highly predictive of survival in this population.

To our knowledge, this is the first study to evaluate the prognostic role of follow-up TAPSE in a PAH population. As recently highlighted in the proceedings of the Fifth World Symposium on PH in Nice, France, ''the need to identify clinically relevant treatment goals that correlate with long-term outcome has emerged as one of the most critical tasks.''[9] The current study provides important initial insight into the functional and prognostic role of serial echocardiographic assessment of RV function, and that a follow-up TAPSE ≥ 2.0 cm may represent an important treatment target in PAH. Furthermore, our data show that a follow-up TAPSE ≥ 2.0 cm is achievable, as 76% of those who met this target on follow-up had a TAPSE < 2.0 cm at baseline.

This study builds on previous data demonstrating the reliability and significance of serial TAPSE assessment in response to PAH therapy, as well as prior data relating TAPSE to survival in patients with PH and SSc-associated PAH.[16,26] Our prior reports relating TAPSE to survival (and using a lower TAPSE cut-point) were in largely prevalent cohorts and noted the prognostic value of TAPSE as a ''snapshot in time'' and not specifically in response to therapy. Furthermore, over a decade has passed with significant changes in availability and approach to PAH therapy. Specifically, while 76% of patients were on monotherapy in the prior study, only 33% were on monotherapy at follow-up in this study. Additionally, this study reflects a more modern and aggressive treatment approach, as 35 of the 54 treatment-naïve patients (65%) were initiated on a second drug within a median of 39 days (range, 25–78 days) from initial encounter. This current study underscores the distinction between ''snapshot in time'' and serial RV function assessment, highlighting the importance of follow-up as opposed to baseline measurements in predicting survival in response to modern PAH therapy.

This is consistent with the findings of Nickel et al. who evaluated the utility of prognostic markers at baseline and follow-up in patients with idiopathic PAH.[13] While they confirmed the independent prognostic utility of several baseline markers, it was the follow-up values on PAH therapy that predicted outcomes. For example, in that study, those with a follow-up CI of 2.5 L/min/m^2 experienced excellent outcomes, with similar survival at one, three, and five years, regardless of whether their baseline CI was $<$ or $\geq$2.5 L/min/m^2. In our study, repeat hemodynamics were available in a subset of participants (limiting statistical power); we found that patients with a follow-up TAPSE ≥ 2.0 cm had significantly higher CO and SVI on follow-up compared with those with a follow-up TAPSE < 2.0 cm.

Previously, van de Veerdonk et al.[14] demonstrated that on serial assessment of patients on PAH therapy, a follow-up cardiac magnetic resonance imaging (CMRI)-derived RVEF $> 35\%$ was associated with the lowest mortality rates. The survival advantage of an RVEF $> 35\%$ was observed independent of PVR. Thus, as RV failure is the final common pathway for death from PAH, it is important to assess RV function overtime, and in response to therapy.[1] The current study indicates that RV function can be effectively assessed serially by echocardiography as well. Prior work has shown that, in particular, longitudinal measures of RV function, including TAPSE, improve in response to PH medical therapy[22,27] with a TAPSE of ≥ 2 cm on serial CMRI, highly predictive of a preserved RVEF.[18] Taken together, these findings make a TAPSE cut-point ≥ 2 cm a rational choice as a serial echocardiographic measure of normal RV function in response to therapy.[17,18]

Importantly, and similar to Nickel et al. and van de Veerdonk et al., a cut-point is not only useful for prognostication, but also serves as a treatment target. This is in distinction to change in TAPSE with therapy which, while important for reflecting trajectory, does not convey sufficient prognostic information, likely relating to the fact that reaching a defined threshold informs more to the absolute degree of RV function on therapy. In fact, nine patients achieved $\geq$ mean improvement in TAPSE (0.37 ± 0.5cm) but remained with a follow-up TAPSE < 2 cm, of which four (44%) died. Thus, despite achieving a statistically significant improvement in TAPSE, those with sustained TAPSE < 2 cm on follow-up remained at a significant risk of death. Conversely, of the 15 patients with a baseline TAPSE < 1.5 cm who achieved a follow-up TAPSE > 2 cm, none died during the follow-up period. Lastly, and consistent with recent data, in our cohort, echo-derived RV FAC did not show an improvement on follow-up,[28] and likely relates to echocardiographic limitations in adequately visualizing and measuring the RV in PAH.[2,29]

Interestingly, participants with a follow-up 6MWD < 400 m had a much lower mortality rate if their TAPSE was $\geq$2.0 cm compared to those with a 6MWD < 400 m and a low TAPSE. These findings suggest that the prognostic

significance of a decreased 6MWD is heavily influenced by RV function, which is logical given that measures of RV function are far more disease-specific in PAH than distance walked per time.

Taken together, the results from the current study provide evidence that follow-up TAPSE assessment provides important prognostic information in PAH. Moreover, the associations between a TAPSE $\geq$ 2.0 cm on follow-up with improved WHO FC, 6MWD, NT-proBNP, and hemodynamics lend to the robust nature of TAPSE as a serial marker of clinical response in PAH and also support the notion that improving RV function in PAH is central to reaching the prescribed functional, biomarker, and hemodynamic goals felt to be important in this condition.[9]

This study is limited by its modest sample size and is not multi-centered, which may have limited more robust multivariable assessment as well as the generalizability of our findings to other PAH cohorts. Importantly, however, study inclusion maintained strict clinical criteria for PAH, with the population displaying characteristics of severe PAH, with one-third of the cohort with CTD-PAH. Furthermore, as this was a study to investigate the prognostic role of follow-up TAPSE, the study population was defined a priori as having had baseline TAPSE assessment and follow-up assessment at least six months from initial study. Thus, only patients who survived to follow-up evaluation were included, further limiting the total study population as well as explaining one-year survival of 97% (despite severe PAH). Additionally, this may explain why several baseline parameters previously described to be predictive of outcome in PAH were not found to be predictive of survival in this study. Nevertheless, this study suggests that while baseline TAPSE impacts follow-up TAPSE, it is the follow-up measure (in those who survive to follow-up) that predicts survival. Also, while the majority of patients had incident PAH (n = 54), inclusion of prevalent cases may introduce survivor bias in our analyses.[30] However, this bias is mitigated by use of landmark analysis; namely, inclusion of participants into the survival analysis who survived at least one year from enrollment.[31] Importantly, on sensitivity analysis no differences in outcome were found between the treatment-naïve group and the overall cohort. This may be explained by the fact that the prevalent patients in this study represent an ''intensified therapy'' group with 75% of these patients having PAH medications added to their regimen after baseline assessment.

In conclusion, the findings from the current study strengthen the notion that serial assessment of specific markers in response to treatment (''dynamic assessment'') are more relevant than static or baseline values for prognostication in the era of modern PAH therapy. We find that follow-up TAPSE $\geq$ 2 cm is a robust functional and prognostic marker associated with improved survival in a largely incidental PAH population. This study supports the use of TAPSE as a non-invasive means in assessing response to treatment and proposes that TAPSE $\geq$ 2 cm may serve as an important treatment target in this population.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

Funding for this project was provided by NHLBI K23 HL093387, Pulmonary Hypertension Association K23 Supplemental Award, Scleroderma Foundation (SCM).

References

1. Vonk-Noordegraaf A, Haddad F, Chin KM, et al. Right heart adaptation to pulmonary arterial hypertension: Physiology and pathobiology. *J Am Coll Cardiol* 2013; 62(Suppl. 25): D22–33.
2. Mazurek JA and Forfia PR. Enhancing the accuracy of echocardiography in the diagnosis of pulmonary arterial hypertension: Looking at the heart to learn about the lungs. *Curr Opin Pulm Med* 2013; 19: 437–445.
3. Girgis RE. Predicting long-term survival in pulmonary arterial hypertension: More than just pulmonary vascular resistance. *J Am Coll Cardiol* 2011; 58: 2520–2521.
4. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
5. Thenappan T, Shah SJ, Rich S, et al. A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J* 2007; 30: 1103–1110.
6. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in france: Results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
7. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: Baseline characteristics from the reveal registry. *Chest* 2010; 137: 376–387.
8. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (reveal). *Circulation* 2010; 122: 164–172.
9. McLaughlin VV, Gaine SP, Howard LS, et al. Treatment goals of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(Suppl. 25): D73–81.
10. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.
11. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; 102: 865–870.
12. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.
13. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39: 589–596.

14. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011; 58: 2511–2519.
15. Peacock AJ, Crawley S, McLure L, et al. Changes in right ventricular function measured by cardiac magnetic resonance imaging in patients receiving pulmonary arterial hypertension-targeted therapy: The EURO-MR study. *Circ Cardiovasc Imaging* 2014; 7: 107–114.
16. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006; 174: 1034–1041.
17. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation Galie N, Hoeper MM, et al (eds) Guidelines for the diagnosis and treatment of pulmonary hypertension. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.
18. Sato T, Tsujino I, Oyama-Manabe N, et al. Simple prediction of right ventricular ejection fraction using tricuspid annular plane systolic excursion in pulmonary hypertension. *Int J Cardiovasc Imaging* 2013; 29: 1799–1805.
19. Samad BA, Alam M and Jensen-Urstad K. Prognostic impact of right ventricular involvement as assessed by tricuspid annular motion in patients with acute myocardial infarction. *Am J Cardiol* 2002; 90: 778–781.
20. Mohammed SF, Hussain I, Abou Ezzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: A community-based study. *Circulation* 2014; 130: 2310–2320.
21. Mercer-Rosa L, Parnell A, Forfia PR, et al. Tricuspid annular plane systolic excursion in the assessment of right ventricular function in children and adolescents after repair of tetralogy of fallot. *J Am Soc Echocardiogr* 2013; 26: 1322–1329.
22. Spruijt OA, Di Pasqua MC, Bogaard HJ, et al. Serial assessment of right ventricular systolic function in patients with precapillary pulmonary hypertension using simple echocardiographic parameters: A comparison with cardiac magnetic resonance imaging. *J Cardiol* 2017; 69: 182–188.
23. Shapiro S, Traiger GL, Turner M, et al. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Chest* 2012; 141: 363–373.
24. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006; 54: 3043–3050.
25. Chung L, Liu J, Parsons L, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from reveal: Identifying systemic sclerosis as a unique phenotype. *Chest* 2010; 138: 1383–1394.
26. Mathai SC, Sibley CT, Forfia PR, et al. Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. *J Rheumatol* 2011; 38: 2410–2418.
27. Brown SB, Raina A, Katz D, et al. Longitudinal shortening accounts for the majority of right ventricular contraction and improves after pulmonary vasodilator therapy in normal subjects and patients with pulmonary arterial hypertension. *Chest* 2011; 140: 27–33.
28. Mauritz GJ, Kind T, Marcus JT, et al. Progressive changes in right ventricular geometric shortening and long-term survival in pulmonary arterial hypertension. *Chest* 2012; 141: 935–943.
29. Bano M, Kanaan UB, Ehrlich AC, et al. Improvement in tricuspid annular plane systolic excursion with pulmonary hypertension therapy in pediatric patients. *Echocardiography* 2015; 32: 1228–1232.
30. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
31. Dafni U. Landmark analysis at the 25-year landmark point. *Circ Cardiovasc Qual Outcomes* 2011; 4: 363–371.