Tricuspid Annular Plane Systolic Excursion Is a Robust Outcome Measure in Systemic Sclerosis-associated Pulmonary Arterial Hypertension

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ABSTRACT. ***Objective.*** The tricuspid annular plane systolic excursion (TAPSE) strongly reflects right ventricular (RV) function and predicts survival in idiopathic pulmonary arterial hypertension (PAH). But its role in systemic sclerosis (SSc)-associated PAH has not been established. Our objective was to validate the TAPSE in the assessment of RV function and prediction of survival in SSc-PAH.

Methods. Fifty consecutive patients with SSc-PAH who underwent echocardiography with TAPSE measurement within 1 h of clinically indicated right heart catheterization were followed prospectively. The relationship between TAPSE and measures of RV function and measures of survival was assessed.

Results. The majority of the cohort were women in New York Heart Association class III/IV with severe PAH (mean cardiac index 2.4 ± 0.8 l/min/m^2). RV function was significantly impaired (mean cardiac index 2.1 ± 0.7 vs 2.9 ± 0.8 l/min/m^2; $p < 0.01$) and RV afterload was significantly greater (mean pulmonary vascular resistance 11.1 ± 5.1 vs 5.8 ± 2.5 Wood units; $p < 0.01$) in subjects with a TAPSE ≤ 1.7 cm. The proportion surviving in the low TAPSE group was significantly lower [0.56 (95% CI 0.37–0.71) and 0.46 (95% CI 0.28–0.62) vs 0.87 (95% CI 0.55–0.96) and 0.79 (95% CI 0.49–0.93), 1- and 2-year survival, respectively]. TAPSE ≤ 1.7 cm conferred a nearly 4-fold increased risk of death (HR 3.81, 95% CI 1.31–11.1, $p < 0.01$).

Conclusion. TAPSE is a robust measure of RV function and strongly predicts survival in patients with PAH-SSc. Future studies are needed to identify the responsiveness of TAPSE to PAH-specific therapy and to assess its diagnostic utility in PAH-SSc. (First Release Oct 1 2011; J Rheumatol 2011;38: 2410–18; doi:10.3899/jrheum.110512)

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Pulmonary arterial hypertension (PAH) is a chronic disease of the pulmonary vasculature that leads to right ventricular failure and ultimately, death[1]. Patients with systemic sclerosis (SSc) are at increased risk for the development of PAH (SSc-PAH), which is a leading cause of death in this population[2]. Despite the advent of novel therapies that target putative molecular pathways involved in the pathogenesis of the disease, the response to therapy as assessed by functional capacity and survival remains poorer in SSc-PAH compared to other forms of PAH[3]. The reasons for these differences are unclear but may be related to the response of the right ventricle (RV) to increased afterload from the pulmonary vasculature.

The adaptation of the RV to increased cardiac load is a main determinant of survival in PAH in general and in SSc-PAH[4]. Traditional invasive measures of RV function, such as cardiac index and right atrial pressure (RAP), have been demonstrated to strongly predict survival in the idiopathic form of PAH (IPAH), but have been inconsistently associated with survival in SSc-PAH[3,5,6]. However, these hemodynamic measures may not adequately reflect the adaptive response of the RV to increasing load, especially in

SSc-PAH. We recently demonstrated that measures of both proximal and distal vascular resistance (pulmonary artery capacitance as estimated by stroke volume divided by pulmonary artery pulse pressure and pulmonary vascular resistance, respectively) independently predicted survival in a large, single-center cohort of patients with SSc-PAH[7]. Importantly, stroke volume index (SVI), a measure of RV function, was a strong, independent predictor of survival, portending a 2-fold increased risk of death for patients with an SVI < 30 ml/m^2. Neither cardiac index nor RAP independently predicted survival in this SSc-PAH cohort. This observation is strengthened by recent physiologic studies using pressure-volume relationships that have demonstrated differential responses to cardiac loads between IPAH and SSc-PAH, with decreased mean ventricular pressure at any given afterload in SSc-PAH[8]. Further, we have demonstrated increased N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone released in response to ventricular stretch, in SSc-PAH compared to patients with IPAH despite similar hemodynamic function as assessed by right heart catheterization[9]. Together, these findings suggest RV response to increased afterload may differ between IPAH and SSc-PAH.

While invasive hemodynamics have been essential to the assessment of RV function in PAH and SSc-PAH, noninvasive measures have not been consistently shown to be useful. Several echocardiographic measures have been studied in PAH, but have lacked sensitivity, reproducibility, or clinical utility[10,11,12]. This may be particularly relevant to SSc-PAH; studies have demonstrated limited ability to even obtain an adequate tricuspid regurgitant (TR) jet to estimate a right ventricular systolic pressure (RVSP)[13,14]. Further, we and others have demonstrated a poor correlation between pulmonary artery systolic pressure (PASP) estimated by echocardiography and measured invasively in PAH[15,16]. Accordingly, a recent systemic review by the Expert Panel on Outcome Measures in PAH related to Systemic Sclerosis (EPOSS Group) reported that echocardiography had yet to be fully validated as an outcome measure in SSc-PAH, as echocardiography lacked several components of the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter[17,18].

We have demonstrated that the tricuspid annular plane systolic excursion (TAPSE), an echocardiographic measure of RV function, has excellent sensitivity, reproducibility, and clinical utility, in a cohort of patients with various forms of PAH[19]. Therefore, we prospectively tested the hypothesis that TAPSE would be a useful noninvasive measure of RV function with prognostic value in patients with SSc-PAH. Some of these data were presented previously in abstract form[20].

MATERIALS AND METHODS

The Johns Hopkins Institutional Review Board approved our study. Written informed consent was obtained from all subjects prior to enrollment[19]. All research procedures were carried out in compliance with the Helsinki Declaration.

Patient population. Between March 2004 and July 2009, consecutive patients with known or suspected PAH evaluated at Johns Hopkins Hospital were screened for study enrollment at the time of referral for a clinically indicated right heart catheterization (RHC). A minority (18/50) of the cohort was recruited from our previous study of TAPSE in PAH[19]. Patients were considered eligible if RHC demonstrated PAH with a mean pulmonary artery pressure > 25 mm Hg and a pulmonary capillary wedge pressure ≤ 15 mm Hg in the absence of other known causes of pulmonary hypertension[21]. Pulmonary function tests (PFT) and computed tomography (CT) scans of the chest were obtained. Patients with significant obstructive or restrictive lung disease were excluded. Limited cutaneous and diffuse cutaneous SSc were defined as described[22].

Echocardiographic assessment. All subjects underwent 2-dimensional echocardiography with Doppler examination within 1 h following the RHC. To measure the TAPSE, an M-mode cursor was placed through the lateral aspect of the tricuspid annulus in real time, using the apical 4-chamber view. Five to 7 beats were recorded. A caliper was then placed from the leading edge to the leading edge of the M-mode signal from end-diastole to end-systole to measure the total systolic displacement of the tricuspid annulus toward the RV apex, measured in centimeters. The average TAPSE over 3 to 5 beats was reported.

The right and left atrial size were measured at end-systole, while right and left ventricular dimensions were obtained at end-diastole. Planimetered areas of the right atria (end-systole) and right and left ventricles (end-diastole, end-systole) were obtained, with right atrial and ventricular area indexed to patient height[11]. Right ventricular fractional area of change was calculated in the standard manner (RV end-diastolic area minus RV end-systolic area divided by RV end-diastolic area × 100). The eccentricity index was obtained from the parasternal short axis view, and expressed as described[23].

The maximal transtricuspid flow velocity was obtained in the usual manner, while TR was assessed semiquantitatively (graded 0–3)[24]. Pericardial effusions were graded 0–4 as described[23]. The physiology of left ventricular filling was assessed by transmitral Doppler velocity (E and A wave velocity) and diastolic Doppler tissue velocity at the interventricular septum using standard techniques[25].

Studies were analyzed offline in the core echocardiography laboratory using Prosolv Cardiovascular software (Klas Enterprises, Orem, UT, USA). Analyses were performed by 2 echocardiographers (PRF, CTS) who were blinded to the study subject's clinical and hemodynamic information.

Survival was ascertained by telephone contact and by reviewing the medical record as well as the Social Security Death Index.

Statistical analysis. Variables were summarized by mean ± SD or median (interquartile range), and were compared using an unpaired t test, Wilcoxon signed-rank test, or chi-square statistic, as appropriate. Pearson's correlation coefficient was used to analyze the relationship between TAPSE and other echocardiographic and hemodynamic measures.

Using TAPSE dichotomized by the median value in the cohort (1.7 cm), a time-to-event analysis was performed using the Kaplan-Meier product limit estimator. Multivariable Cox proportional hazards models were constructed using TAPSE as a continuous or dichotomous variable and included variables found to be significant in bivariable analyses (p value < 0.20) and variables previously shown to have prognostic significance in order to adjust for potential confounding factors. Subjects who underwent organ transplant were censored. Intraobserver and interobserver agreement of TAPSE was assessed by 2 sonographers blinded to the study participants' clinical data. Intraobserver and interobserver agreement was expressed by linear regression, with bias between observers calculated by the Bland-Altman method. All analyses were performed using Stata version 10.0 (StataCorp., College Station, TX, USA).

RESULTS

Fifty patients with SSc-PAH were enrolled and followed prospectively. Table 1 summarizes the clinical features of the cohort. In general, patients were white women, with an average age of 60 years, and with clinical symptoms consistent

Table 1. Demographic, clinical, and hemodynamic characteristics. All data are expressed as mean ± SD unless otherwise specified.

Characteristics	N = 50
Age, yrs	61 (11)
Sex, n (% women)	49 (98)
Race, n (% white)	45 (90)
NYHA FC, n (%)	
I:	2 (4)
II:	13 (26)
III:	30 (60)
IV:	5 (10)
Total lung capacity, n (% predicted)	82 (18)
DLCO, n (% predicted)	51 (18)
6MWT, m	325 (88)
Disease duration before index echocardiography, days	1147 (829)
PAH-specific therapy at index echocardiography, n (%)	25 (50)
Deaths, n (%)	25 (50)
Heart rate, bpm	82 (16)
Systolic blood pressure, mm Hg	125 (21)
Diastolic blood pressure, mm Hg	69 (13)
Systemic vascular resistance, dynes-s/cm^5	4722 (1821)
Right atrial pressure, mm Hg	9 (5)
Mean pulmonary artery pressure, mm Hg	42 (10)
Cardiac index, l/min/m^2	2.4 (0.8)
PCWP, mm Hg	10 (3)
Pulmonary vascular resistance, Wood units	9.2 (5.1)
Pulmonary artery saturation (%)	64.8 (9.1)
Stroke volume index, ml/m^2	32 (13)
RVSWI, g-m/m^2	13.5 (5.9)
SV/PP, mm Hg/ml	1.25 (0.73)

NYHA FC: New York Heart Association functional class; PCWP: pulmonary capillary wedge pressure, RVSWI: right ventricular stroke work index; SV/PP: stroke volume/pulse pressure.

with New York Heart Association functional class III or IV (35/50, 70%). Mean 6-min walk distance was 325 ± 88 m, suggesting significant functional impairment. Half the subjects were receiving PAH-specific therapy at the time of enrollment (25/50).

Pulmonary function testing revealed mild to moderate diffusion abnormalities. Hemodynamic measurements revealed moderate to severe pulmonary hypertension (PH) with a mean pulmonary artery pressure (mPAP) of 42 mm Hg, cardiac index (CI) 2.4 l/min/m^2, and pulmonary vascular resistance (PVR) 9.2 Wood units. Mean right ventricular stroke work index (MVSWI) was impaired (13.5 ± 5.9 g-m/m^2), suggesting significant RV dysfunction.

Baseline echocardiographic measurements are shown in Table 2. Measures of RV function revealed significant reduction in TAPSE (mean 1.7 cm vs 2.5 cm for normal subjects) and RV fractional area change (RVFAC; mean 30.9% vs ≥ 40% for normal subjects) comparable to previously reported values in PAH[10,23,26]. Both right atrium and RV were markedly enlarged in absolute dimension and in proportion to left heart size compared to normal subjects. LV systolic function was within the normal range, suggesting RV dysfunction as the primary etiology of the hemodynamic perturbations.

Table 2. Echocardiographic measures. All data expressed as mean ± SD unless otherwise specified.

Measure	
TAPSE, cm (n = 50)	1.7 (0.5)
RVFAC, % (n = 44)	30.9 (11.5)
Right atrium, cm (n = 42)	4.5 (0.8)
Left atrium, cm (n = 42)	3.6 (0.6)
RVIDd, cm (n = 39)	4.3 (0.8)
LVIDd, cm (n = 42)	3.8 (0.8)
RAA index, cm^2/m (n = 41)	14.0 (5.5)
RVAd index, cm^2/m (n = 34)	15.0 (3.7)
RA:LA area ratio (n = 42)	1.3 (0.4)
RV:LV end-diastolic area ratio (n = 39)	1.2 (0.4)
Diastolic eccentricity index (n = 48)	1.3 (0.3)
Systolic eccentricity index (n = 48)	1.4 (0.6)
Maximum TR velocity, m/s (n = 34)	3.7 (0.6)
TR severity (grade 0-3, %; n = 45)	
0	4 (9)
1	11 (24)
2	13 (29)
3	17 (38)
Pericardial effusion, n (%)	18 (35)
LV ejection fraction, % (n = 50)	60 (9)

TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular fractional area change; RA: right atrium; LA: left atrium; RVIDd: right ventricular area diastolic dimension; LVIDd: left ventricular diastolic dimension; RAA: right atrial area; RVAd: right ventricular area in diastole; RA:LA: right atrium to left atrium; RV:LV: right ventricle to left ventricle; TR: tricuspid regurgitant; LV: left ventricle.

Importantly, despite using 2 experienced echocardiographers in a research echocardiography protocol, we were unable to obtain several measurements, including maximum TR jet velocity, right atrium area index, RV area index, and right atrium and left atrium measurements, for a significant proportion of the cohort (Table 2). However, the intraobserver ($r = 0.96$, $p < 0.0001$, mean bias 0.02, 95% CI –0.23 to 0.27) and interobserver reproducibility ($r = 0.95$, $p < 0.0001$, mean bias –0.02, 95% CI of agreement, –0.11 to 0.06) were excellent, similar to previous studies[19,25,27].

TAPSE relation to RV function and remodeling. When stratified by the median TAPSE value of 1.7 cm, distinct differences between various measures of RV function were noted. As shown in Table 3, 33 of the 50 subjects had a TAPSE ≤ 1.7 cm. RV systolic function, as assessed by both invasive and noninvasive measures, was significantly lower in the group with TAPSE ≤ 1.7 cm. Cardiac index and SVI in the low TAPSE group were significantly lower than in the high TAPSE group (2.1 ± 0.7 vs 2.9 ± 0.8 l/min/m^2, $p < 0.01$, and 27.9 ± 13 vs 39.9 ± 11.4 ml/m^2, $p < 0.01$, respectively) and markedly lower than previously reported normal values. Pulmonary artery saturation was also reduced in the patients with TAPSE < 1.7 cm, consistent with poor cardiac function. RVFAC, an echocardiographic estimate of RV systolic function, also was depressed in the low TAPSE group compared to the high TAPSE group.

Table 3. Right ventricular (RV) measures stratified by TAPSE. All data are expressed as mean ± SD unless otherwise specified.

Measure	TAPSE ≤ 1.7 (n = 33)	TAPSE > 1.7 (n = 17)	p
RV systolic function			
CI, l/min/m^2	2.1 (0.7)	2.9 (0.8)	< 0.01
SVI, ml/m^2	27.9 (13.0)	39.9 (11.4)	< 0.01
PA saturation, %	60.7 (8.3)	72.5 (4.2)	< 0.01
RVSWI, g-m/m^2	13.1 (6.9)	14.2 (3.1)	0.51
RVFAC, %	26.6 (8.8)	39.3 (11.7)	< 0.01
Right heart remodeling			
RAA index, cm^2/m	15.9 (5.1)	9.8 (3.7)	< 0.01
RVAd index, cm^2/m	16.0 (3.6)	12.5 (2.9)	< 0.01
RV-LV relationship			
Diastolic eccentricity index	1.4 (0.3)	1.1 (0.2)	< 0.01
Systolic eccentricity index	1.6 (0.6)	1.1 (0.3)	< 0.01
RA/LA diameter	1.4 (0.4)	1.1 (0.3)	0.03
RV/LV diameter	1.2 (0.4)	1.1 (0.4)	0.56
RV afterload			
PVR, Wood units	11.1 (5.1)	5.8 (2.5)	< 0.01
SV/PP, ml/mm Hg	1.07 (0.64)	1.57 (0.78)	0.02

TAPSE: tricuspid annular plane systolic excursion; CI: cardiac index; SVI: stroke volume index; PA: pulmonary artery; RVSWI: right ventricular stroke work index; RVFAC: right ventricular fractional area change; RAA: right atrial area; RVAd: right ventricular area in diastole; RA:LA: right atrium to left atrium; LV:left ventricular; PVR: pulmonary vascular resistance; SV/PP: stroke volume/pulse pressure.

Similarly, right atrium area index (15.9 ± 5.1 vs 9.8 ± 3.7 cm^2/m; p < 0.01) and RV area index (16.0 ± 3.6 vs 12.5 ± 2.9 cm^2/m; p < 0.01), markers of right heart remodeling, were significantly higher in the low TAPSE group, suggesting more remodeling in this group. As expected, RV-LV relationships differed significantly between the low and high TAPSE groups, with both diastolic and systolic eccentricity indices being significantly higher in the low TAPSE group. Interestingly, while the right atrium-left atrium ratio was higher in the low TAPSE group, there was no difference in the RV-LV ratio between groups. RV afterload, as assessed by PVR and stroke volume/pulse pressure (SV/PP), was significantly increased in the low compared to the high TAPSE group, suggesting inadequate adaptation of the RV to both proximal and distal vascular load.

There were no significant differences between the low and high TAPSE groups in other measures of RV dysfunction, such as maximum TR jet velocity, severity of tricuspid regurgitation, and presence of pericardial effusion. However, TR jet velocity and severity of TR were obtainable on only 34 (68%) and 44 (88%) of the subjects, respectively.

TAPSE and outcomes. Patients were followed for a median of 15.7 months (IQR 8.7–38.8 mo). Twenty-five patients died during followup (50%). The cause of death was related to progressive right heart failure in 18 patients, sudden cardiac death in 5 patients, and gastrointestinal hemorrhage in 2 patients. No patients underwent lung transplant. Twenty-one of the 25 deaths (84%) occurred in the low TAPSE group (p = 0.01). The mean TAPSE was significantly higher in survivors compared to nonsurvivors (1.8 ± 0.5 cm vs 1.5 ± 0.4 cm; p = 0.01). When divided into tertiles, mortality was nearly 70% (11/16) in the lowest tertile (TAPSE < 1.4 cm) compared to 25% (4/16) in the highest tertile (TAPSE > 1.7 cm).

As shown in Figure 1, subjects who died were clustered in the low TAPSE group (TAPSE ≤ 1.7 cm). However, in contrast to the expected relationship between increasing PVR and survival in PAH-SSc[28], a significant proportion of subjects with a low TAPSE who died had a low PVR (less than the median value of 8 Wood units; bottom left quadrant in Figure 1A). Similarly, several subjects with a low TAPSE who died also had a relatively high estimated pulmonary artery compliance (greater than the median value of 1.06 mm Hg/ml; top left quadrant in Figure 1B). In fact, a low TAPSE was a better discriminator of mortality than PVR or SV/PP, as 84% of nonsurvivors had a TAPSE ≤ 1.7 cm; only 60% and 72% had a high PVR or low SV/PP, respectively. These findings suggest that low TAPSE reflects aspects of RV function that are independent of both proximal and distal vascular load.

In Kaplan-Meier analysis, survival was significantly worse in the low TAPSE group (log-rank test, chi-square = 6.44, p < 0.01; Figure 2). One-year and 2-year survival estimates were 0.87 (95% CI 0.55–0.96) and 0.79 (95% CI 0.49–0.93) in the TAPSE > 1.7 group compared to 0.56 (95% CI 0.37–0.71) and 0.46 (95% CI 0.28–0.62) in the TAPSE < 1.7 group, respectively.

The unadjusted risk of death for patients with TAPSE ≤ 1.7 cm was nearly 4-fold higher than that for patients with TAPSE > 1.7 cm (HR 3.81, 95% CI 1.31–11.1, p = 0.01; Table 4). When examined as a continuous variable, for every 1-mm decrease in TAPSE, the unadjusted risk of death increased by 15% (HR 1.15, 95% CI 1.04–1.28, p < 0.01). In multivariable analyses that included variables found to be significant in univariable analyses and variables previously shown to have prognostic significance in PAH, TAPSE remained a significant predictor of survival (Table 5). Importantly, these relationships remained significant when stratified by treatment status at baseline.

Other clinical and hemodynamic variables, previously demonstrated to have prognostic significance in various forms of PAH, also predicted survival in this cohort. These variables included World Health Organization (WHO) class (HR 1.92, 95% CI 1.05–3.51, p = 0.03), RAP (HR 1.07, 95% CI 1.01–1.14, p = 0.02), PVR (HR 1.14, 95% CI 1.05–1.23, p < 0.01), and pulmonary artery saturation (HR 0.95, 95% CI 0.92–0.99, p = 0.03). Several echocardiographic measures were also predictive of survival in the cohort, including the right atrial area index (HR 1.11, 95% CI 1.02–1.19, p = 0.01) and the diastolic eccentricity index (HR 5.29, 95% CI 1.42–20.4, p = 0.01). However, we were unable to obtain right atrial area index measures on 9 (18%) of the subjects and diastolic eccentricity index on 3 (6%) subjects. Other previously validated measures in PAH, such as RV fractional area change

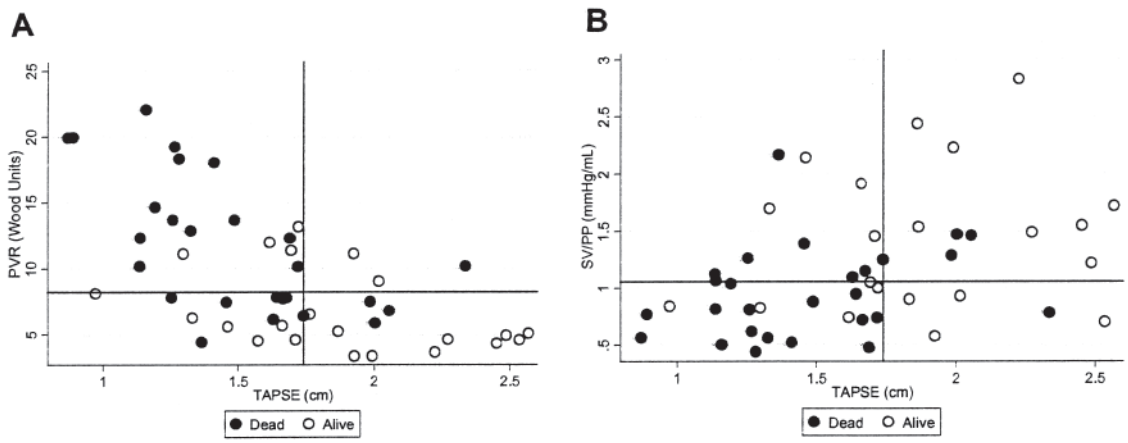
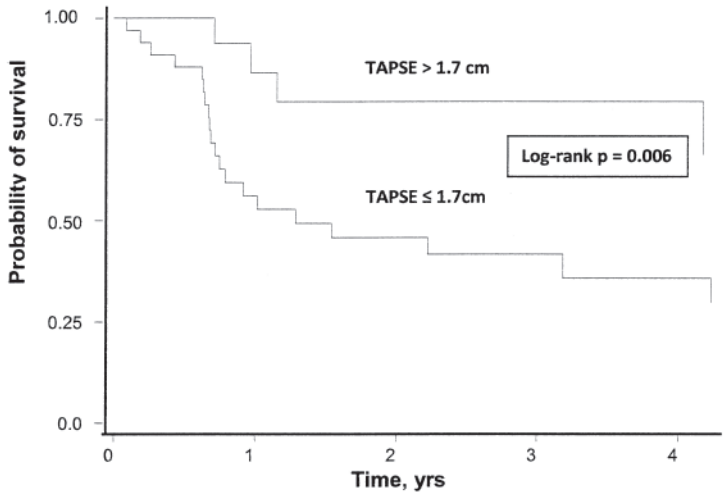


Figure 1. A. Pulmonary vascular resistance (PVR) compared to TAPSE (tricuspid annular plane systolic excursion). Each circle denotes 1 study subject with PAH-SSc. Vertical line represents TAPSE = 1.7 cm and horizontal line represents the median value of pulmonary vascular resistance (PVR; 8 Wood units). B. Stroke volume/pulse pressure (SV/PP) compared to TAPSE. Each circle represents 1 study subject PAH-SSc. Vertical line represents TAPSE = 1.7 cm; horizontal line represents the median value of SV/PP (1.10 mm Hg/ml).



Number at risk

TAPSE > 1.7	17	15	15	7	7
TAPSE ≤ 1.7	33	20	14	7	2

Figure 2. Kaplan-Meier estimates of survival in study subjects with PAH-SSc, stratified by TAPSE (tricuspid annular plane systolic excursion).

and presence of pericardial effusion, were not significantly associated with survival.

DISCUSSION

We found that TAPSE, a simple, reproducible measure of RV function, was significantly associated with other noninvasive and invasive measures of RV function in a large cohort of patients with SSc-PAH. Patients with a TAPSE ≤ 1.7 cm had significantly worse RV function and evidence of increased RV remodeling and RV-LV disproportion compared to those with TAPSE > 1.7 cm. Further, TAPSE ≤ 1.7 cm was a strong predictor of survival, even adjusting for other previously validated echocardiographic and invasive hemodynamic predictors of outcome in PAH as well as treatment status. These results

Table 4. Univariable Cox proportional hazard models.

Measure	Unadjusted HR (95% CI)	p
Age	0.98 (0.96–1.01)	0.31
WHO class	1.92 (1.05–3.51)	0.03
Baseline therapy	0.99 (0.45–2.17)	0.98
Echocardiography		
RVFAC, %	0.99 (0.95–1.03)	0.47
RAA index	1.11 (1.02–1.19)	0.01
Diastolic eccentricity index	5.39 (1.42–20.4)	0.01
Maximum TR jet velocity	0.58 (0.31–1.10)	0.10
Pericardial effusion	1.11 (0.75–1.64)	0.59
TAPSE (dichotomous)	3.81 (1.31–11.1)	0.01
TAPSE (continuous)	0.87 (0.78–0.96)	< 0.01
Hemodynamics		
RAP	1.07 (1.01–1.14)	0.02
CI	0.62 (0.34–1.12)	0.12
PVR	1.14 (1.05–1.23)	< 0.01
SV/PP	0.35 (0.13–0.92)	0.03
SVI	0.97 (0.93–1.00)	0.10
PA saturation	0.95 (0.92–0.99)	0.03

WHO: World Health Organization; TAPSE: tricuspid annular plane systolic excursion; CI: cardiac index; SVI: stroke volume index; PA: pulmonary artery; RVSWI: right ventricular stroke work index; RVFAC: right ventricular fractional area change; RAA: right atrial area; TR: tricuspid regurgitant; RAP: right atrial pressure; PVR: pulmonary vascular resistance; SV/PP: stroke volume/pulse pressure.

Table 5. Multivariable Cox proportional hazard models. TAPSE adjusted for clinical, echocardiographic, and hemodynamic variables.

TAPSE	Adjusted HR for Death (95% CI)	p
Measure		
NYHA FC	3.35 (1.13–9.90)	0.03
Baseline therapy*	4.43 (1.46–13.4)	< 0.01
Echocardiography		
RVFAC, %	5.25 (1.41–19.4)	0.01
RAA index	2.44 (0.74–8.11)	0.14
Diastolic eccentricity index	2.61 (0.84–8.08)	0.09
Maximum TR jet velocity	4.54 (1.02–20.1)	0.05
Pericardial effusion	3.82 (1.31–11.2)	0.01
Hemodynamics		
RAP	3.12 (1.02–9.58)	0.05
CI	3.60 (1.09–11.9)	0.04
PVR	2.27 (0.69–7.48)	0.18
SV/PP	3.41 (1.12–10.4)	0.03
SVI	3.41 (1.10–10.6)	0.03
PA saturation	3.13 (0.90–10.8)	0.07

* Baseline therapy refers to use of PAH-specific therapy (phosphodiesterase type 5 inhibitor, endothelin receptor antagonist, prostacyclin analog). TAPSE: tricuspid annular plane systolic excursion; NYHA FC: New York Heart Association functional class; RVFAC: right ventricular fractional area change; RAA: right atrial area; TR: tricuspid regurgitant; RAP: right atrial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; SV/PP: stroke volume/pulse pressure; SVI: stroke volume index; PA: pulmonary artery.

suggest that TAPSE is a robust measure of RV function and an important predictor of survival in patients with SSc-PAH.

TAPSE and RV function. The unique functional anatomy of the RV allows assessment of RV function using TAPSE. As shown by Rushmer and colleagues, RV contraction occurs primarily along the longitudinal axis[29]. Thus, assessment of the systolic displacement of the tricuspid annulus toward the RV apex along the longitudinal plane has been shown to accurately reflect RV systolic function, as measured by RV ejection fraction[26]. Previously, we demonstrated the close relationship between TAPSE and RV function as assessed by echocardiography and invasive hemodynamics in a cohort of patients with various forms of PAH[19]. Further, we found TAPSE to be a strong predictor of survival in multivariable analyses, with a 7-fold increased risk of death in patients whose TAPSE was < 1.8 cm.

In our current cohort of patients with SSc-PAH, TAPSE was closely related to indices of RV function. As shown in Table 3, significant differences were noted in indices of RV systolic function (CI, SVI, pulmonary artery saturation, and RVFAC), right heart remodeling (right atrium area index, RV area index), RV-LV interdependence (eccentricity index and right atrium/left atrium diameter), and RV afterload (PVR and SV/PP) between subjects with TAPSE > 1.7 cm and those with TAPSE ≤ 1.7 cm. Lower TAPSE identified patients with severely compromised RV function as assessed by several metrics of global function: systolic function, right heart remodeling, RV-LV disproportion, and RV afterload. For example, outcomes were more strongly associated with low TAPSE than with high PVR, suggesting that TAPSE reveals multiple facets of RV function, not only afterload (Figure 1). Further, patients with a lower TAPSE tended to have a higher heart rate (88 ± 17 vs 79 ± 11 beats per min; p = 0.06), lower systolic blood pressure (121 ± 20 vs 132 ± 23 mm Hg; p = 0.10), and higher systemic vascular resistance (3001 ± 1145 vs 2573 ± 725 dynes-s/cm^5/m^2; p = 0.14), suggesting increased systemic hemodynamic compensation, and thus reduced hemodynamic reserve, compared to patients with a higher TAPSE. Therefore, TAPSE seems to accurately reflect multiple components of RV function in patients with SSc-PAH.

Displacement of the tricuspid annulus is afterload-dependent. We and others have demonstrated the strong inverse relationship between TAPSE and RV afterload in a cohort of patients with various forms of PAH[19,30]. In our current study, we have also found a strong relationship between TAPSE and measures of both proximal and distal resistance. Patients with TAPSE ≤ 1.7 cm had significantly lower estimated pulmonary artery capacitance, a measure of proximal pulsatile flow in the pulmonary vasculature, and higher PVR, representing resistance in the distal portion of the pulmonary vasculature. These relationships suggest that TAPSE is also afterload-dependent in SSc-PAH.

In a recent study of a large cohort of patients with

SSc-PAH, we found measures of afterload (SV/PP and PVR) to be strong independent predictors of survival in multivariable analyses[28]. Interestingly, measures of cardiac function such as cardiac index were not associated with survival, suggesting that traditional hemodynamic predictors used in other forms of PAH may not be applicable in SSc-PAH. Although TAPSE was not rigorously assessed in all subjects in this cohort and thus could not be evaluated as a predictor of survival, our results suggest that TAPSE may be a robust noninvasive measure of RV function in response to increased afterload.

As discussed, our prior TAPSE study demonstrated the close relationship between TAPSE and measures of RV function in a mixed cohort of patients with PAH, and found TAPSE to be a strong predictor of survival in this cohort. We compared TAPSE between our current cohort of patients with SSc-PAH and the IPAH subgroup (n = 23) from our prior study (data not shown). We found TAPSE was significantly different [mean TAPSE 1.7 ± 0.5 vs 2.0 ± 0.7 cm (p = 0.04), SSc-PAH vs IPAH, respectively], despite significantly lower mPAP in the SSc-PAH group (42 ± 10 vs 50 ± 15 mm Hg; p = 0.02), similar CI (2.3 ± 0.7 vs 2.2 ± 0.5 l/min/m^2; p = 0.40), and similar PVR (9.5 ± 2.0 vs 10.4 ± 6.0 Wood units; p = 0.31). These data suggest that the RV response to increased afterload may differ between SSc-PAH and IPAH, and is consistent with prior studies comparing invasively measured ventricular response to increased afterload in IPAH and SSc-PAH[8] and noninvasive markers of ventricular strain (NT-proBNP)[9].

TAPSE and outcome. Overall mortality was high in the cohort, with a median survival around 3 years[5,28]. Crude mortality was associated with TAPSE when divided into tertiles, with a nearly 3-fold increase in mortality between the highest and lowest groups. Further, TAPSE ≤ 1.7 cm portended a nearly 4-fold increased risk of death compared to patients with TAPSE > 1.7 cm. When considered as a continuous variable, a decrease of 1 mm in TAPSE was associated with a 15% increased risk of death. Indeed, a low TAPSE appeared to be a more reliable predictor of mortality than a high PVR and low SV/PP (Figures 1A and 1B), hemodynamic measures that we have recently shown to be very strong predictors of outcomes in SSc-PAH[28]. Importantly, the association between TAPSE and survival was not appreciably altered when adjusting for potential confounders in multivariable analyses. Further, TAPSE remained strongly predictive of survival when controlling for other measures of RV function, both invasive and noninvasive.

While numerous studies have demonstrated the importance of RV function in survival in PAH, most of them used invasive hemodynamic measures to assess cardiac function, such as RAP, CI, and PVR, which have an inconsistent association with outcome in SSc-PAH[5,28]. Our results are consistent with prior studies of TAPSE in patients with other disease states, such as dilated cardiomyopathy, acute inferior myocardial infarction, and cardiogenic shock[27,31,32,33]. A recent study by Ghio and colleagues in a large cohort of patients with IPAH also found TAPSE to have prognostic value[34]. In that study, patients with IPAH in WHO classes III and IV who were admitted to the hospital underwent an echocardiography and RHC and were prospectively followed for a median of 52 months. Subjects whose TAPSE was ≤ 1.5 cm had a more than 2-fold increased risk of death compared to those with TAPSE > 1.5 cm. Other echocardiographic measures of RV function, such as Tei index and TR jet velocity, were not associated with outcomes.

Few studies have examined the relationship between echocardiographic measures of RV function and outcomes in SSc-PAH. Rather, most studies in SSc have focused on diagnosis of PH in this high-risk population. However, the relationship between echo-derived estimated PASP and directly measured PASP is poor, with r^2 values around 0.5, suggesting limited use of this measure to accurately diagnose PH in SSc[13,35]. Further, echocardiographic estimates of PASP require an adequate acoustic window and presence of an analyzable TR jet; several studies have demonstrated that a high proportion (up to 62%) of patients with SSc do not have TR[13,14]. Similarly, the Tei index (right ventricular myocardial performance index), which has been studied extensively in various forms of PH, demonstrated poor correlation with mean PAP measured by RHC in a cohort of 35 patients with SSc[36]. Despite the limitations of echocardiographic measures such as PASP, MacGregor and colleagues demonstrated poorer survival in patients with SSc who had a PASP > 60 mm Hg in a large population of patients with SSc[37]. Unfortunately, PH was defined by echocardiographic evidence of PASP > 30 mm Hg, which limits the inferences that can be drawn from that study. Similarly, another study of patients with SSc who also had PH defined as PASP > 30 mm Hg found TAPSE at baseline to be predictive of the need for hospitalizations at 1 year[38]. Other echocardiographic measures of RV function, such as presence of pericardial effusion, have been shown to be predictive of survival in SSc-PAH (HR 2.35, 95% CI 1.06–5.2, p = 0.04)[3]. However, in our most recent study of 76 patients with SSc-PAH, presence of pericardial effusion was not associated with survival[28]. Thus, in contrast to TAPSE, echo-derived measures of RV function such as PASP, Tei index, and pericardial effusion demonstrate limited use in the assessment of RV function and inconsistent relationships with outcomes in SSc-PAH.

Limitations. First, all subjects were referred to our PH program and thus selection bias is likely toward inclusion of those patients who were most ill. Second, lead-time bias may influence the survival analyses; because half the subjects were receiving PAH-specific therapy at the index echocardiography, patients with established disease may have been more likely to die during followup. However, the relationship between TAPSE and survival remained significant even when controlling for treatment status at baseline. Further, when

examining treatment-naive subjects alone, TAPSE ≤ 1.7 cm portended > 5-fold increased risk of death (HR 5.11, 95% CI 1.38–18.9, p = 0.01). Third, while patients with significant interstitial lung disease (ILD) were excluded from the cohort, it is possible that patients with subclinical disease were included. Since survival in patients with SSc who have PH related to ILD is worse than that of patients with SSc-PAH, survival estimates may be influenced by the inclusion of such patients[39]. Further, it is possible that our results have been influenced by confounders for which we have not accounted.

Previous studies of echocardiography in various forms of PH have been limited by extensive time intervals between echocardiography and RHC, thereby drawing into question whether the echo-derived measures accurately represent invasive hemodynamic measures collected months before. While echocardiography was not performed in "real-time" during the RHC in our study, all echocardiograms were obtained within 1 h of RHC. Thus, TAPSE and other noninvasive measures of RV function are likely to truly reflect the hemodynamic state of the subjects at the time of RHC[40]. Additionally, as discussed, other measures of RV function such as PASP may not be obtainable in patients with SSc-PAH because of technical factors. In our study, TAPSE was obtainable on all 50 subjects; other measures were obtained in 68%–96% of the cohort. Further, TAPSE demonstrated excellent intraobserver and interobserver reproducibility.

We found TAPSE to be strongly associated with various noninvasive and invasive measures of RV function in patients with SSc-PAH. Further, TAPSE strongly predicted survival in this cohort of patients with RHC-proven SSc-PAH, suggesting that TAPSE may be an invaluable, noninvasive measure in the evaluation of SSc-PAH. Further studies are needed to validate these findings in larger SSc-PAH populations and to assess the responsiveness of TAPSE to therapy.

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