Differences in Right Ventricular Functional Changes during Treatment between Systemic Sclerosis–associated Pulmonary Arterial Hypertension and Idiopathic Pulmonary Arterial Hypertension

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Abstract

Rationale: Patients with systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH) continue to have an unacceptably high mortality rate despite the progress achieved with pulmonary arterial vasodilator therapies.

Objectives: We sought to determine whether SSc-PAH is a clinically distinct pulmonary vascular disease phenotype when compared with idiopathic pulmonary arterial hypertension (IPAH) on the basis of progression of echocardiographic right ventricular (RV) dysfunction.

Methods: Retrospective analysis of echocardiographic data in 13 patients with SSc-PAH and 11 patients with IPAH was used to delineate the progression of RV dysfunction during single or combination pulmonary arterial vasodilator therapy. All patients had right heart catheterization–confirmed pulmonary arterial hypertension as well as complete baseline (at the time of diagnosis) and follow-up (most recent) echocardiograms. We excluded patients with significant scleroderma-associated interstitial lung disease. Adjusting for time of follow-up and disease duration, we performed mixed model regression analyses comparing

the changes between the two groups for different echocardiographic variables: tricuspid annular plane systolic excursion, tricuspid regurgitation jet velocity, right atrial area, and RV diameter.

Results: The mean ages for the SSc-PAH and IPAH groups were 60.8 and 48.2 years, respectively. The mean follow-up periods for the two groups were 3.8 and 1.95 years, respectively. Tricuspid annular plane systolic excursion did not improve in patients with SSc-PAH, whereas it increased in the patients with IPAH (-0.38 mm, $P = 0.87$; vs. $+5.6$ mm, $P = 0.02$). The other echocardiographic variables showed a trend toward worsening in the SSc-PAH group and improvement in the IPAH group.

Conclusions: Our results indicate that, in patients with SSc-PAH, echocardiographic RV function does not improve over time compared with that of patients with IPAH, despite institution of pulmonary artery vasodilator therapies.

Keywords: right ventricle; idiopathic pulmonary arterial hypertension; pulmonary arterial hypertension; disease progression; systemic sclerosis–associated pulmonary arterial hypertension

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Systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is the commonest form of connective tissue disease-associated pulmonary arterial hypertension. Indeed, SSc-PAH accounts for a significant proportion of all pulmonary arterial hypertension (PAH) cases (1, 2). SSc-PAH is the second leading cause of mortality in patients with systemic sclerosis (SSc) (3, 4). It is estimated that about 12 to 15% of patients with SSc have a lifetime risk of developing PAH (2, 5). The current 3-year survival rate for SSc-PAH is estimated to be between 39 and 67%, whereas the 3-year survival rate for patients with other forms of World Health Organization (WHO) group I PAH is around 84% (2, 4, 6). In a more recent prospective cohort analysis from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry in which researchers evaluated patients with SSc-PAH, the 3-year survival rate was 75% (7). However, the results derived from this analysis could have been affected by lead-time bias because patients were enrolled within 6 months of their right heart catheterization (RHC) and diagnosis of PAH.

PAH results in progressive pulmonary arterial remodeling with characteristic endothelial injury, intimal fibrosis, and smooth muscle hypertrophy. The resulting elevation of pulmonary vascular resistance (PVR) and right ventricular (RV) afterload may progress to RV failure and death. Therapy with different pulmonary arterial vasodilators has improved the survival and the quality of life of most patients with PAH. However, these trends have not been mirrored in patients with SSc-PAH (4). It is unclear why patients with SSc-PAH have such a high mortality rate despite therapy with pulmonary vasodilators. Some plausible mechanisms that could explain the poor survival in patients with SSc-PAH include (1) a more aggressive phenotype of pulmonary vascular disease with or without a significant presence of pulmonary venoocclusive disease (8) and (2) poor RV adaptation to the worsening PVR. Possible causes of poor RV adaptation include myocardial fibrosis (9), intracardiac conduction delays (10), or accelerated coronary atherosclerosis (11, 12). Because progressive RV dysfunction usually precedes death in patients with PAH, we sought to compare the progression of RV dysfunction in patients with idiopathic

pulmonary arterial hypertension (IPAH) with that of patients with SSc-PAH, as well as to delineate the differences in RV function change over time between these two groups.

Methods

The Medical University of South Carolina (MUSC) Pulmonary Hypertension (PH) Clinic keeps an active therapy database of patients receiving PAH therapies through the clinic. The MUSC PH nurse coordinator (K.E.) regularly updates this database. Patients followed in the clinic who are no longer living are periodically removed from the database. With MUSC Institutional Review Board approval, we performed a retrospective observational analysis of all patients with IPAH and SSc-PAH seen between January 1, 1991, and January 12, 2015. Patients in this PH clinic database were all alive (as of January 12, 2015) and were actively being followed by providers in the MUSC PH Clinic.

Inclusion criteria for this study included (1) the absence of significant radiographic or spirometric (restrictive [FVC, <60% predicted] and/or severe obstructive [FEV₁/FVC, <70%; FEV₁, <50% predicted]) parenchymal pulmonary disease (Table 1), (2) the presence of two echocardiograms at least 6 months apart, (3) a definitive diagnosis of PAH by RHC, and (4) the absence of an alternative etiology of PAH. Patients with SSc met the American College of Rheumatology criteria for the diagnosis of systemic sclerosis

(Table 1). For patients without available baseline numerical data for FVC and FEV₁ (n = 2 in the IPAH group), we relied on subsequent pulmonary function testing (PFT) data as well as provider documentation from referral facilities, and we used available computed tomographic imaging data to rule out any significant parenchymal lung disease that could contribute to the development of PH.

Two patients (one each in the SSc-PAH and IPAH groups) had missing baseline RHC data, and whereas one had RHC data consistent with PAH available from subsequent years, we could not track down the original RHC data for the second patient. For this second patient, we had numerous PH attending notes documenting the diagnosis of SSc-PAH based on review of then-available RHC data from our institution.

The first available echocardiographic study at our institution was considered the baseline echocardiogram. The most recent one (prior to January 12, 2015) available at our institution was considered the “follow-up” echocardiogram. Disease duration was defined as the time from the diagnosis of PAH by RHC to the date of the follow-up echocardiogram. Follow-up time was defined as the time between the baseline and follow-up echocardiograms (Figure 1). All patients were receiving physician-determined, Food and Drug Administration–approved PAH therapies.

Echocardiography

Prerecorded and stored echocardiograms for each patient were accessed for the purposes of this study. The interpreting

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
RHC-confirmed PAH and alive as of follow-up echocardiogram Diagnosis of SSc-PAH or IPAH	Concomitant significant ILD (FVC <60%) or HRCT evidence of significant ILD Concomitant severe obstructive lung disease (FEV ₁ /FVC <70% and FEV ₁ <50%) Significant left heart disease indicated by a PCWP or LVEDP >15 mm Hg
Baseline and follow-up echocardiograms available and interpretable Follow-up echocardiogram separated by at least 6 mo from baseline echocardiogram	Overlap syndromes or undifferentiated connective tissue disease with SSc features

Definition of abbreviations: HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPAH = idiopathic pulmonary arterial hypertension; LVEDP = left ventricular end diastolic pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; RHC = right heart catheterization; SSc = systemic sclerosis; SSc-PAH = systemic sclerosis-associated pulmonary arterial hypertension.

Figure 1. Disease duration and follow-up time. Right heart catheterization (RHC) was used to diagnose pulmonary arterial hypertension. Baseline ECHO = first available echocardiogram; follow-up ECHO = most recent echocardiogram.

cardiologists (B.W.U. and D.G.) were blinded to the patient subgroup. Measurements were made consistent with the guidelines of the American Society of Echocardiography for assessment of the right ventricle (13). In brief, the tricuspid annular plane systolic excursion (TAPSE) for each patient was evaluated using the anatomical M-mode function in the EchoPAC* software system (GE Healthcare, Chicago, IL). Right atrial (RA) size was measured in the apical four-chamber view. Tricuspid regurgitation (TR) jet velocity was sampled in multiple views to optimize alignment with the jet, and the highest value was used. RA area was measured in the apical four-chamber view. The RV basal diameter during diastole in a right ventricle-focused view was used as the surrogate for the RV size. The changes in various echocardiographic parameters, including TAPSE, TR jet velocity, RA area, and RV basal diameter, from baseline to follow-up were compared between the SSc-PAH and IPAH groups.

Statistical Analysis

An unpaired *t* test was used to compare the continuously distributed variables between the SSc-PAH and IPAH groups. Categorical variables were compared between the two groups using chi-square tests. We then performed mixed model regression analyses comparing the changes between the two groups for the various transthoracic echocardiographic variables: TAPSE, TR jet, RA area, and RV diameter. Adjustments were made for the time of follow-up and disease duration. A *P* value less than 0.05 was considered significant. All statistical analyses were performed

using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

The Consolidated Standards of Reporting Trials (CONSORT) diagram for study enrollment is shown in Figure 2. There were a total of 142 patients with a diagnosis of PH listed in the database. Of these, 78 were identified as patients with potential PAH, and 64 patients were excluded because the primary etiology of their PH was non-WHO group I (WHO group II, III, IV, or V). Of the 78 WHO group I patients, 42 patients were excluded because they had concomitant restrictive lung disease (FVC, <60%) or obstruction (FEV₁/FVC, <70%; FEV₁, <50% predicted) or developed significant interstitial lung disease after their initial diagnosis of SSc-PAH (Figure 2). Of the 36 isolated patients with WHO group I PAH, we excluded 10 with other WHO group I causes of PAH (e.g., portopulmonary hypertension, undifferentiated connective tissue disease). Two patients were excluded because they did not have follow-up echocardiograms (i.e., echocardiographic studies done with outside nonMUSC providers).

For the final analysis, 24 patients were selected as belonging to either the IPAH group (*n* = 13) or the SSc-PAH group (*n* = 11). There were no differences with regard to intravenous prostacyclin use between the two groups (2 of 11 in SSc-PAH group vs. 3 of 13 in IPAH group). There was also no difference between the two groups with regard to oral vasodilator use (Table 2).

The baseline demographic and clinical features of the two cohorts are shown in Table 2. The SSc-PAH group was significantly older than the IPAH group (60.8 yr vs. 48.2 yr; *P* = 0.01). Diffusing capacity of the lung for carbon monoxide percent predicted was worse in the patients with SSc-PAH (39.8% vs. 59.1%; *P* = 0.014). There were no significant differences between the two groups with regard to other demographic and PFT variables. The disease duration, follow-up time, and therapeutic regimens were not significantly different between groups. Even though these differences were not statistically significant, we adjusted for follow-up time and disease duration in our analyses.

The baseline RHC and echocardiogram data are compared in Table 3. The baseline mean pulmonary arterial pressure (mPAP) was significantly higher in the patients with IPAH than in the patients with SSc-PAH (62.4 vs. 37.9 mm Hg; *P* < 0.001). The PVR was also higher in the IPAH group than in the SSc-PAH group (15.2 vs. 5.8 Wood units; *P* = 0.004). There were no differences with regard to cardiac output or cardiac index between the two groups. When we compared baseline echocardiogram data between the two groups, we observed that the RV basal diameter was larger in the IPAH group than in the SSc-PAH group (43.3 vs. 36.4 mm; *P* = 0.046). In summary, baseline RV function appeared slightly worse in the patients with IPAH.

From baseline to follow-up, the TAPSE improved in the IPAH group (15.48 vs. 21.09 mm; *P* = 0.01) but not in the SSc-PAH cohort (16.54 vs.

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram showing the selection of patients with systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH) and patients with idiopathic pulmonary arterial hypertension (IPAH) for this study. PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; UCTD = undifferentiated connective tissue disease; WHO = World Health Organization.

16.16 mm; $P = 0.87$) (Figure 3). Other echocardiographic indicators (TR jet velocity, RA size, RV size) of RV function trended worse for the SSc-PAH group and favorably for the IPAH group, but the differences were not statistically significant (Table 4). There was no significant change in TR jet velocity for the SSc-PAH group (3.81 vs. 3.81 m/s; $P = 0.80$) or the IPAH group (4.90 vs. 4.42 m/s; $P = 0.58$). Interestingly, the left atrial (LA)

size (left atrial end-systolic volume index) trended lower in the SSc-PAH group (24.69 vs. 19.75 ml/m²; $P = 0.39$), but it significantly increased in the IPAH group (15.99 vs. 26.34 ml/m²; $P = 0.01$). Because the age, mPAP, and PVR were significantly different between the two groups at baseline, we included these three variables in a subsequent analysis. In this analysis, we noted that although age did not impact the outcome, the

between-group differences in TAPSE trends lost statistical significance when mPAP and PVR were included (data not shown).

Discussion

Our analysis showed that whereas patients with IPAH demonstrated an improvement in TAPSE on a follow-up echocardiogram after the institution of single or combination pulmonary arterial vasodilator therapies, patients with SSc-PAH had no change in TAPSE. The cause did not appear to be left ventricular (LV) dysfunction, because the LA size (an indicator of LV filling pressure) and the LV ejection fraction did not change significantly in the SSc-PAH group, whereas the LA size increased significantly in the IPAH group. This improvement in TAPSE persisted despite adjustment for age. However, after adjustment for PVR and mPAP, the between-group differences in the TAPSE trends lost statistical significance (data not shown). On one hand, this could well be due to the small number of patients in our analysis. On the other hand, this could be due to worse PVR in the IPAH group at baseline, which could imply a greater potential for pulmonary arterial vasodilation and RV afterload reduction in the IPAH group, and consequently a greater possibility for improvement of RV function with vasodilator therapies, in the IPAH group.

Although pulmonary arterial vasodilators improve the hemodynamics and the quality of life of patients with PAH, the response to these therapies in patients with connective tissue disease associated PAH is poor and has been described previously (14). Our analysis suggests that RV function differences between these two groups (SSc-PAH vs. IPAH) could be one plausible explanation for the heterogeneity in treatment responses between patients with IPAH and patients with SSc-PAH.

Mortality in SSc-PAH continues to be high compared with other forms of PAH despite the availability of many therapies (4). Others have attempted to determine whether this is because of worse vasculopathy for a given degree of clinical presentation, a treatment-unresponsive vasculopathy (8), or an independent effect of the disease on the right ventricle (15).

Table 2. Demographic and clinical features of the systemic sclerosis–associated pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension cohorts

	SSc-PAH (n = 11)	IPAH (n = 13)	P Value
Age, yr	60.8 (±10.2)	48.2 (±11.6)	0.01
Sex, F/M, n	10/1	11/2	0.64
Ethnicity, AA/C/H, n	5/5/1	6/7/0	0.53
Baseline FVC, L (n = 3 IPAH missing)	2.7 (±0.9)	3.1 (±1.2)	0.36
Baseline FVC, % predicted (n = 4 IPAH missing)	82.9 (±12.7)	82.3 (±14.8)	0.97
Baseline DL _{CO} , ml/mm Hg/min (n = 5 IPAH missing)	7.9 (±2.3)	14.96 (±6.9)	0.005
Baseline DL _{CO} , % predicted (n = 5 IPAH missing)	39.8 (±9.1)	59.1 (±21.3)	0.014
Follow-up time, yr	3.8 (±3.1)	1.95 (±1.3)	0.12
Baseline 6MWT, m (n = 5 IPAH missing, n = 2 Scl missing)	360.8 (±97.4)	333.8 (±152.9)	0.67
Prostacyclin use at baseline, n	2	3	0.80
Vasodilator 1 at follow-up,* n (bosentan/ambisentan/sildenafil/tadalafil)	3/4/3/1	1/2/8/0	0.18
Vasodilator 2 at follow-up, n (bosentan/ambisentan/sildenafil/tadalafil)	1/0/1/1	0/1/1/0	0.41

Definition of abbreviations: 6MWT = 6-minute walk test distance; AA = African American; C = white; DL_{CO} = diffusing capacity of the lung for carbon monoxide; H = Hispanic; IPAH = idiopathic pulmonary arterial hypertension; Scl = scleroderma; SSc-PAH = systemic sclerosis–associated pulmonary arterial hypertension.

Values in parentheses represent SD.

*Only one patient in the IPAH group was taking a calcium channel blocker at follow-up (nifedipine).

Using RV pressure–volume loops from heart catheterization in 19 patients, patients with SSc-PAH and patients with SSc without PAH were shown to have worse

contractile indices than patients with IPAH as measured by end-systolic elastance and preload recruitable stroke work for similar degrees of PVR. Interestingly,

patients with SSc-PAH had remarkably similar RV function characteristics to those of patients with SSc without PAH (15). This suggests a two-hit hypothesis in which patients with SSc could have preexisting RV dysfunction (presumably due to myocardial fibrosis or small vessel disease) and could be more prone to RV maladaptation in the face of a second insult in the form of rising PVR. Kelemen and colleagues, in their comparison of right ventricles between patients with SSc-PAH and patients with IPAH, showed an attenuated RV hypertrophic remodeling response to rising PVR in patients with SSc-PAH compared with patients with IPAH (16). This also points to a heterogeneous and maladaptive response in the SSc-PAH right ventricle compared with the IPAH right ventricle.

Fisher and associates compared echocardiograms of patients with IPAH and patients with SSc-PAH at baseline (17). By identifying higher LV filling pressures and larger LA diameters as surrogates, they reported a significantly greater LV dysfunction in their cohort with SSc-PAH when compared to their patients with IPAH. However, they did not note any differences in pulmonary capillary wedge pressure determined by RHC between these two groups. The PVR was significantly

Table 3. Baseline hemodynamic parameters of the systemic sclerosis–associated pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension cohorts

RHC/Echocardiogram Variable		SSc-PAH (n = 11)	IPAH (n = 13)	P Value
RHC variables	Mean RAP, mm Hg (n = 2 SSc-PAH and n = 2 IPAH missing)	10 (±5.4)	10 (±5.3)	1.00
	mPAP, mm Hg (1 SSc-PAH missing)	37.9 (±9.7)	62.4 (±9.1)	<0.001
	PCWP, mm Hg (n = 1 SSc-PAH missing and n = 1 IPAH missing)	11.2 (±2.6)	12.2 (±3.4)	0.46
	TPG, mm Hg (n = 1 SSc-PAH missing and n = 1 IPAH missing)	26.7 (±10.2)	48.5 (±5.9)	<0.001
	CO, L/min (Fick)	5.04 (±1.4)	4.2 (±2.2)	0.34
	CI, L/min/m ² (Fick)	2.8 (±0.6)	2.2 (±1.1)	0.18
	TPR, wood units (n = 1 SSc-PAH and n = 2 IPAH missing)	8.1 (±4.7)	16.4 (±5.9)	0.002
	PVR, wood units (n = 2 SSc-PAH and n = 2 IPAH missing)	5.8 (±3.0)	15.2 (±8.2)	0.004
	LVEF, % by echocardiography	63.1 (±9.5)	67.3 (±16.1)	0.46
	LAESVI, ml/m ² (n = 6 SSc-PAH missing)	24.6 (±12.4)	17.2 (±6.6)	0.13
Transthoracic echocardiogram variables	RV diameter, mm (n = 1 SSc-PAH missing)	36.4 (±8.5)	43.3 (±7.2)	0.046
	RA size, mm ² (n = 1 SSc-PAH and n = 1 IPAH missing)	19.1 (±4.9)	22.8 (±8.2)	0.23
	TR jet velocity, m/s	3.8 (±0.9)	4.7 (±0.9)	0.05
	TAPSE, mm	17.3 (±6.3)	16.1 (±3.6)	0.59
	RAP, mm Hg	8.1 (±5)	7 (±5.6)	0.64
	Pericardial effusion, n	5	2	0.11

Definition of abbreviations: CI = cardiac index; CO = cardiac output; IPAH = idiopathic pulmonary arterial hypertension; LAESVI = left atrial end-systolic volume index; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrium; RAP = right atrial pressure; RHC = right heart catheterization; RV = right ventricle; SSc-PAH = systemic sclerosis–associated pulmonary arterial hypertension; TAPSE = tricuspid annular plane systolic excursion; TPG = transpulmonary gradient (mPAP–PCWP); TPR = total pulmonary resistance; TR = tricuspid regurgitant.

Values in parentheses represent standard deviations.

Figure 3. Change in mean tricuspid annular plane systolic excursion (TAPSE) from baseline to follow-up. The error bars represent the SEM. IPAH = idiopathic pulmonary arterial hypertension; SSc-PAH = systemic sclerosis-associated pulmonary arterial hypertension.

higher in the IPAH group than in the SSc-PAH group, similar to the data derived from our analysis. Although our analysis did not include measures of LV diastolic function, the LA size significantly increased in the IPAH group from baseline to follow-up echocardiography. This could have been due to the improvement in cardiac output and left-sided filling after institution of vasodilator therapies.

Interestingly, Hassoun and coauthors showed that upfront combination therapy with two vasodilators improved RV function and stroke work index (measured using magnetic resonance imaging) in therapy-naïve patients with SSc-PAH. RV ejection fraction improved with upfront combination therapy, suggesting that improvement in RV function is possible from baseline with aggressive, upfront, dual-

combination therapy (18). However, the follow-up time in their study was significantly shorter than the follow-up time in our analysis, and furthermore, comparisons between patients with IPAH and patients with SSc-PAH were not available to see if the improvements in RV function in the SSc-PAH group were comparable to patients with IPAH receiving upfront dual-combination therapy. It also remains to be determined whether the impressive improvements in RV function noted in the patients with SSc-PAH receiving upfront dual-combination therapies in their study will persist in the following years.

Hsu and colleagues showed that exercise responses in RV function and RV contractile reserves differ between patients with SSc-PAH and patients with IPAH (19). In their study, they also noted distinctly

different exercise responses in the pressure-volume loops between the two groups. In their analysis, patients with SSc-PAH could not increase their RV contractility in response to exercise, whereas the patients with IPAH could. They also noted that the patients with SSc-PAH exhibited a significant increase in end-systolic and end-diastolic volumes with exercise, whereas the patients with IPAH did not exhibit such “dilatatory” tendencies with exercise. They reasoned that these differences could be due to impaired calcium recycling in the sarcoplasmic reticula in the myocytes of patients with SSc-PAH compared with patients with IPAH, suggesting intrinsic myocardial differences between SSc-PAH and the IPAH right ventricles (19).

Autopsy studies, with the earliest study dating back nearly 75 years (20), have demonstrated the presence of myocardial fibrosis in up to 70% of patients with SSc without PAH (21). Patients with SSc have a higher prevalence of intracardiac conduction delays (10, 22, 23), atherosclerosis (12), and magnetic resonance imaging–documented fibrosis as noted by delayed enhancement or contrast uptake into the myocardium (9). These factors could predispose patients with SSc to RV maladaptation when these patients develop a new-onset pulmonary vasculopathy. Additionally, RV function independent of the PVR significantly influenced mortality prediction models in one PAH observational cohort (24).

Limitations

There are a number of limitations to our study. This is a retrospective, observational study and therefore represents a

Table 4. Changes in echocardiographic right ventricle parameters for the systemic sclerosis–associated pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension cohorts

Echocardiogram Parameter	SSc-PAH				IPAH			
	Baseline	Follow-Up	Difference	P Value	Baseline	Follow-Up	Difference	P Value
RV diameter, mm	36.37 (8.54)	37.25 (10.73)	+0.88	0.84	42.16 (7.68)	38.97 (9.21)	−3.19	0.44
RA size, mm ²	19.11 (4.92)	21.42 (10.10)	+2.31	0.51	23.09 (9.15)	20.68 (10.55)	−2.41	0.49
TR jet, m/s	3.81 (0.96)	3.81 (0.77)	+0.00	0.81	4.90 (0.99)	4.42 (0.53)	−0.48	0.58
TAPSE, mm	16.54 (6.41)	16.16 (3.64)	−0.38	0.87	15.48 (3.48)	21.09 (5.17)	+5.61	0.01
RAP, mm Hg	7.60 (5.27)	5.90 (5.04)	−1.70	0.80	7.63 (6.19)	5.50 (3.78)	−2.13	0.18
LA size, LAESVI, ml/m ²	24.69 (12.45)	19.75 (10.54)	−4.94	0.40	15.99 (5.75)	26.34 (8.96)	+10.35	0.01
LVEF, %	62.55 (10.30)	66.65 (6.28)	+4.10	0.30	66.42 (17.58)	66.48 (7.28)	+0.06	0.99

Definition of abbreviations: IPAH = idiopathic pulmonary arterial hypertension; LA = left atrium; LAESVI = left atrial end-systolic volume index; LVEF = left ventricular ejection fraction; RA = right atrium; RAP = right atrial pressure; RV = right ventricle; SSc-PAH = systemic sclerosis–associated pulmonary arterial hypertension; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation. Values in parentheses represent SD.

convenience sample of patients in our active therapy user database. Two patients in the IPAH cohort had no numerical PFT values available, and one patient in the SSc-PAH cohort did not have numerical baseline RHC data available; however, by using provider notes and outside hospital pulmonary function data, as well as available imaging studies, we were able to confirm their diagnoses to the best of our knowledge.

Owing to the limitations of the convenience sample of the PH clinic database that we used, patients with more severe disease in both the SSc-PAH and IPAH cohorts were most probably excluded. Owing to the limitations of the clinic database, only living patients with IPAH and SSc-PAH were available for the analysis. This could also have led to an oversampling of “prevalent” patients with PAH over “incident” patients with PAH in both the SSc-PAH and IPAH cohorts. This is an important aspect to consider because it was previously demonstrated that prevalent patients had an overall better prognosis than an incident cohort of patients with PAH (25). To restrict the analysis to an American College of Rheumatology criteria-defined SSc phenotype, we also excluded patients with an undifferentiated

connective tissue disease and some SSc clinical features.

Disease duration was calculated from the first day of the year (of the RHC) for patients who did not have the exact date of their diagnosis (RHC). The small sample size could have affected the power to detect small differences in other echocardiographic parameters. We did not have follow-up RHC data to prove incontrovertibly whether the change in RV function was independent of the severity of pulmonary vascular dysfunction.

We recognize that TAPSE is a two-dimensional variable and is not the only available modality for the evaluation of global RV function. In choosing patients with long-term stability of their disease for this analysis, we recognize that the patients with SSc-PAH in our analysis may have had lower mPAP and PVR than the values encountered in many of the patients who died. We also recognize that the attenuation of the differences in RV function trends over time after adjusting for mPAP and PVR (data not shown) could be an indicator that SSc-PAH is a different vasculopathy that is less responsive to vasodilator therapy than IPAH. Because death in PAH is often caused by an increase in PVR resulting in RV failure, serial cardiac

catheterizations, by virtue of adjustment for changes in PVR, could have demonstrated the mechanistic etiology underlying the differences in RV function between the two groups. Unfortunately, repeat cardiac catheterization data were not available for all the patients.

Conclusions

To our knowledge, this is the first such analysis done at an academic PH center to compare the change in echocardiographic RV function over time between patients with SSc-PAH and patients with IPAH treated with vasodilator therapies. We adjusted for the follow-up and disease duration times to reduce the impact of these variables on the change in RV function. Our data are consistent with existing information concerning RV function in patients with SSc-PAH. Although the exact etiology of the differential response in RV function to pulmonary arterial vasodilators between these two groups (SSc-PAH vs. IPAH) cannot be defined on the basis of our study, the RV function trends over time in IPAH and SSc-PAH appear to be markedly different. ■

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