Right Ventricular Dysfunction in Systemic Sclerosis–Associated Pulmonary Arterial Hypertension

Ryan J. Tedford, MD; James O. Mudd, MD; Reda E. Girgis, MD; Stephen C. Mathai, MD, MHS; Ari L. Zaiman, MD; Traci Houston-Harris, MS, RN; Danielle Boyce, MPH; Benjamin W. Kelemen, BA; Anita C. Bacher, MSN, MPH, MA; Ami A. Shah, MD, MHS; Laura K. Hummers, MD; Fredrick M. Wigley, MD; Stuart D. Russell, MD; Rajeev Saggar, MD; Rajan Saggar, MD; W. Lowell Maughan, MD; Paul M. Hassoun, MD; David A. Kass, MD

Background—Systemic sclerosis–associated pulmonary artery hypertension (SScPAH) has a worse prognosis compared with idiopathic pulmonary arterial hypertension (IPAH), with a median survival of 3 years after diagnosis often caused by right ventricular (RV) failure. We tested whether SScPAH or systemic sclerosis–related pulmonary hypertension with interstitial lung disease imposes a greater pulmonary vascular load than IPAH and leads to worse RV contractile function.

Methods and Results—We analyzed pulmonary artery pressures and mean flow in 282 patients with pulmonary hypertension (166 SScPAH, 49 systemic sclerosis–related pulmonary hypertension with interstitial lung disease, and 67 IPAH). An inverse relation between pulmonary resistance and compliance was similar for all 3 groups, with a near constant resistance×compliance product. RV pressure–volume loops were measured in a subset, IPAH (n=5) and SScPAH (n=7), as well as SSc without PH (n=7) to derive contractile indexes (end-systolic elastance [E_s] and preload recruitable stroke work [M_s]), measures of RV load (arterial elastance [E_a]), and RV pulmonary artery coupling (Ees/Ea). RV afterload was similar in SScPAH and IPAH (pulmonary vascular resistance=7.0±4.5 versus 7.9±4.3 Wood units; E_a=0.9±0.4 versus 1.2±0.5 mm Hg/mL; pulmonary arterial compliance=2.4±1.5 versus 1.7±1.1 mL/mm Hg; P>0.3 for each). Although SScPAH did not have greater vascular stiffening compared with IPAH, RV contractility was more depressed (Ees=0.8±0.3 versus 2.3±1.1; P<0.01; M_s=21±11 versus 45±16; P=0.01), with differential RV-PA uncoupling (Ees/Ea=1.0±0.5 versus 2.1±1.0; P=0.03). This ratio was higher in SSc without PH (Ees/Ea=2.3±1.2; P=0.02 versus SScPAH).

Conclusions—RV dysfunction is worse in SScPAH compared with IPAH at similar afterload, and may be because of intrinsic systolic function rather than enhanced pulmonary vascular resistive and pulsatile loading. (Circ Heart Fail. 2013;6:953-963.)

Key Words: hypertension, pulmonary ■ scleroderma, systemic ■ vascular capacitance ■ vascular resistance ■ ventricular function, right

Systemic sclerosis (SSc; scleroderma) is a heterogeneous disorder characterized by microvasculopathy, immune abnormalities, and tissue fibrosis. Pulmonary arterial hypertension (PAH) is among its most serious complications and a leading cause of mortality.1 Pathologically, small vessel fibroproliferation ultimately leads to marked vascular narrowing or complete obliteration.2 The accompanying rise in pulmonary resistance stimulates right ventricular (RV) hypertrophy that initially helps maintain cardiac output, but over time can progress with RV dilution, dysfunction, and failure.3,4 Among causes of PAH, patients with systemic sclerosis (SScPAH) have the worst prognosis, with a median survival of 3 years after diagnosis,5,6 and RV failure is a primary cause of death. The incidence of PAH in SSc is ≈10%,7,8 and with ≈240 million patients with SSc in the United States alone,9 the population with SScPAH may indeed exceed that with idiopathic pulmonary arterial hypertension (IPAH).10 Our understanding of the underlying causes for worsened survival in SScPAH remains poor.

Clinical Perspective on p 963

Given the importance of RV dysfunction in late-stage PAH, studies have begun focusing on features specific to SSc. Considered broadly, one can posit 2 major contributors for worse RV performance, greater pulmonary arterial load

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perhaps because of stiffening/sclerosis of the vessels that is missed by standard measures, or primary cardiac depression. A comparison of RV and left ventricular function in IPAH and SScPAH found similar global RV and left ventricular function by echocardiography at slightly lower RV afterload in 1 study, but similar right heart hemodynamics in another. Mathai et al examined tricuspid annular plane systolic excursion, a measure of RV systolic function, and found it predicted clinical mortality in patients with SScPAH. However, tricuspid annular plane systolic excursion also predicts survival in IPAH, making it less likely to have identified a specific feature of SSc. Tricuspid annular plane systolic excursion is also load dependent and influenced by overall cardiac motion. One study has suggested that RV depression is greater in SScPAH than in IPAH, but did not directly measure RV contractility. Accordingly, we tested whether the right ventricle of patients with SSc with pulmonary hypertension (PH), both in the presence and in the absence of interstitial lung disease (ILD), is subjected to greater total afterload as compared with IPAH, including pulsatile load that is not reflected in mean resistance. Right heart catheterization (RHC) data from PH databases at 2 institutions were analyzed to assess relations between pulmonary vascular compliance and resistance. Second, we tested whether the right ventricle in SScPAH displays reduced contractility as compared with IPAH, as well as SSc without PH using invasive RV pressure–volume (PV) relation analysis.

**Methods**

**Patient Groups**

This study was approved by institution review boards of each institution (JHM-IRB-1: NA_00027124, JHM-IRB-1: #NA_00014540, OPRS UCLA IRB #12-000738) and informed consent was obtained from all patients. The diagnosis of SSc was based on 1 of 3 definitions: the American College of Rheumatology criteria (formerly, the American Rheumatism Association); the presence of 3 of 5 features of the CREST (Calcinosis, Raynaud’s syndrome; Esophageal dysmotility; Sclerodactyly; Telangiectasia) syndrome; or definite Raynaud phenomenon, abnormal nailfold capillaries typical of scleroderma, and the presence of a specific scleroderma-related autoantibody. PAH was diagnosed by a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg and pulmonary capillary wedge pressure ≤ 15 mm Hg, measured by RHC. The diagnosis of SSc-related pulmonary hypertension with ILD (SSc-PH-ILD) was based on criteria previously reported. IPAH patients had all known causes of PAH excluded.

**Analysis of Pulmonary Resistance–Compliance Relations**

To analyze pulmonary vascular load, cohorts of SScPAH, SSc-ILD-PH, and IPAH patients with RHC and pulmonary function testing data were identified from the Johns Hopkins and University of California, Los Angeles (UCLA) PH databases, spanning the period from January 1, 1995, to May 31, 2012: SScPAH (77% Johns Hopkins, 23% UCLA), SSc-ILD-PH (100% UCLA), and IPAH (100% Johns Hopkins). For any patient with >1 RHC study in the database, the first study recorded was used. Pulmonary vascular resistance (Rv) was calculated from stroke volume/pulse pressure (mL·mm Hg⁻¹), the latter validated by several studies. Hyperbolic Rv–Cpa relations (expressed as mm Hg·seconds·mL⁻¹) were then derived for each group to assess whether compliance was less for any given resistance.

**PV Loop Analysis**

To measure RV contractile function and pulmonary vascular interaction, we prospectively studied patients referred for RHC at Johns Hopkins from November 2009 to February 2013 for diagnosis or...
management of PAH (with or without SSc). After completing the RHC, a PV catheter (model SPC-570-2, Millar Instruments, Houston, TX) was advanced through the internal jugular vein and positioned at the RV apex under fluoroscopic guidance. The catheter was connected to a digital stimulator micropressor (Sigma V, Leycom, The Netherlands) that supplied a high-frequency low amperage excitation current to electrodes at the RV apex and right atrium. Measured voltage differences between intervening electrode pairs were inversely proportional to segmental volume, and RV intracavitary segments were then added to yield total volume. This methodology is similar to that developed by our laboratory for the left ventricle.\(^23,24\) The RV conductance signal was calibrated to match independently determined RV ejection fraction (proximate study using MRI, \(n=14\); or echocardiography, \(n=5\)), and thermodilution cardiac output measured at time of catheterization (mean loop width was matched to stroke volume). To vary loading conditions and derive sets of PV relations, subjects performed a Valsalva maneuver. Phase 2 of the maneuver (period of preload decline) was used to generate PV relations. End-systolic PV points were determined by an iterative technique,\(^23\) and fit by perpendicular regression to derive the slope (end-systolic elastance \(E_{es}\), and intercept \(V_0\)). Preload recruitable stroke work (\(M_{sw}\)) was calculated as previously described.\(^23,24\) Effective arterial elastance (\(E_a\)) was calculated as the ratio of end-systolic pressure to stroke volume. \(E_{es}\) was also normalized to end-diastolic volume by the equation: \(E_{es\text{normal}} = E_{es} \times \text{end-diastolic volume}/100\).\(^25\) Data were analyzed with custom software (WinPV AN 3.5.10).

Validation of PV Relation Analysis During Valsalva

We used a Valsalva maneuver to assess PV relations rather than inferior vena caval occlusion as this previously used method would require femoral venous catheterization in a procedure otherwise performed via a jugular vein. Valsalva involves rapid elevation of intrathoracic pressure, which increases all intracardiac pressures, although so long as this is fairly constant for several seconds; subsequent cycles measured during the ensuing decline in preload are equally offset and the derived PV relations should be similar to that from inferior vena cava occlusion. We directly tested this in studies performed in the left ventricle in which both maneuvers were recorded (\(n=20\), patients with hypertrophy or normal ventricles). Figure 1 shows PV tracings...
from a patient with data measured by both methods. Valsalva induced an upward pressure shift, but this was well maintained as shown by the colinearity of the diastolic PV curves and the resulting systolic and diastolic PV relations comparable (other than the offset). For the 20 patients Ees and Msw were well correlated.

Statistics
Results are presented as the mean±SD. Curve fits (linear or nonlinear) were generated and statistical analysis was performed using commercial software (SigmaPlot 11.0/Systat 10.2). Comparisons between groups on continuous variables were performed by Student t test or Mann–Whitney rank-sum test. A χ² test or Fisher exact test was used to compare categorical variables. ANCOVA was used to compare resistance–compliance relations after log transformation (log [compliance]: dependent variable; covariates–log [resistance]). Comparison of resistance x compliance (RC) times between patient groups was performed using multiple linear regression (RC: dependent; covariates: resistance, age, pulmonary capillary wedge pressure, and mPAP). An F test was used to compare pulmonary and systemic RC time variances. A P value of <0.05 (2-sided) was considered statistically significant. There was no adjustment for multiple comparisons.

Results
Patient Characteristics
Table 1 summarizes the clinical characteristics and resting hemodynamics for IPAH (n=67), SScPAH (n=166), and SSc-ILD-PH (n=49) groups. Compared with SScPAH, IPAH patients were younger at the time of RHC (P<0.001) and had significantly higher mPAP and RPA, and lower CPA. Thus, overall resistive and reactive load was higher in the IPAH group. Both groups had a similar cardiac index (2.4±0.8 versus 2.6±0.8 L/min per m²; P=0.16), and there were no differences in pulmonary capillary wedge pressure. The SScPAH group had a shorter 6-minute walk distance (1056±332 feet [n=61] versus 1289±443 feet [n=41]; P=0.003).

Compared with SScPAH, SSc-ILD-PH patients were more likely to be men, had less of a white predominance, and were younger (Table 1). Other than heart rate, which was faster in the ILD cohort (88 versus 82 beats per minute; P=0.01), there were no statistically significant differences in hemodynamics. As expected, pulmonary function testing parameters were all significantly worse in the ILD cohort (online supplement 1 in the online-only Data Supplement; P<0.001).

Pulmonary Resistance–Compliance Relationship
Unlike the systemic vasculature, $R_{PA}$ and $C_{PA}$ display a consistent inverse relationship indicating a codependence between them. Importantly, this inverse relationship is not mathematically determined (eg, by a shared stroke volume in the numerator of $C_{PA}$ and denominator of $R_{PA}$).
If SScPAH disproportionately impacted vessel stiffness, and therefore, vessel compliance independent of resistance, then the relation should shift downward compared with that for IPAH. Figure 2A displays relations for each group showing them to be well fit by hyperbolic decays (SScPAH: \( y = 0.70/(0.082+x) \); \( r^2 = 0.80 \); and IPAH: \( 0.73/(0.086+x) \); \( r^2 = 0.86 \) that were virtually superimposable. Log-transformation of both variables yielded linear plots (Figure 2B), and ANCOVA found no difference between the SScPAH and IPAH groups (\( P = 0.71 \)). The product of \( R_{PA} \times C_{PA} \) (the RC time) provides a time constant for pulmonary arterial diastolic pressure decay. The RC time was slightly lower in patients with SScPAH, but this disparity was lost after adjusting for patient age, consistent with a recent study.\(^{22}\) Plots of \( R_{PA} \times C_{PA} \) versus mean pulmonary or systemic pressure showed both groups to have superimposable data, with the pulmonary value highly constrained (Figure 2C), and the systemic value quite variable (Figure 2D; \( P < 10^{-7} \) for F test of variance difference between RC time in Figure 2C and 2D). As expected, there was a small but significant rise in pulmonary and systemic RC times with greater respective mean pressures. \( R_{PA} \times C_{PA} \) relations and the RC product were also similar in patients with SScPAH and SSc-ILD-PH (Figure 3A–3D).

**PV Loop Analysis**

PV analysis was attempted on 30 patients referred for invasive RHC to assess dyspnea and PAH (online supplement 2 in the online-only Data Supplement). Twenty-two patients had analyzable PV loops, and 12 of 22 met hemodynamic criteria for PAH: IPAH (\( n=5; 100\% \) women, 100\% white) and SScPAH (\( n=7; 86\% \) women, 71\% white, and 29\% black). Preload reduction in the right ventricle occurred almost immediately on initiation of Valsalva and maximal reduction occurred within 10 beats. The mean preload (end-diastolic volume) reduction by Valsalva was 23±14 mL. Heart rate did not appreciably change during phases 1–2 (0.4±3.7 beats per minute) or phase 3 (−0.6±5.3 beats per minute), and thus overall (−0.2±5.3 beats per minute; online supplement 3 in the online-only Data Supplement). Chronic medications for the 3 patient groups are provided in online supplement 4 in the online-only Data Supplement.

Table 2 provides routine hemodynamic parameters including \( R_{PA} \) in these cohorts and shows no significant difference between them. However, PV analysis revealed a significant disparity in RV contractile function between groups. Figure 4 displays example PV loops and relations from both groups. The steady-state data (left panels) were similar in shape, with...
RV pressure rising throughout ejection and peaking at end-systole, consistent with increased RV afterload from pulmonary hypertension. Net afterload ($E_a$) was similar between cohorts (Table 2). Of note, although right atrial pressure and corresponding RV diastolic pressures were somewhat elevated, the diastolic PV relations were relatively flat, with little difference in pressure from the onset to end of chamber filling. Loops generated from all patients in both cohorts are shown in Figure 5.

Figure 4 (right panels) also shows corresponding PV data obtained during Valsalva. The upward pressure shift reflects the rise in intrathoracic pressure because of Valsalva (phase 1), but this is held as constant as possible during the beat-to-beat decline in filling volume (phase 2). The end-systolic PV relation is shown in each graph and its slope ($E_{es}$) was reduced in SScPAH subjects compared with IPAH patients. As $E_{es}$ is known to be chamber volume dependent, we also normalized the value to end-diastolic volume (Table 2); for the group, $E_{es(norm)}$ was ≈70% lower in SScPAH versus IPAH ($P<0.01$). $V_x$ (the volume intercept) was lower in the SScPAH than IPAH, consistent with the reduced $E_{es}$ at similar chamber volumes characterizing the former group. The decline in contractile function in SScPAH compared with IPAH was further confirmed by a lower preload-recruitable stroke work (Msw; $P=0.011$), an index that is chamber size independent. The ratio of $E_{es}$ to $E_a$, an index of ventricular-PA coupling, was lower in the SScPAH group (1.0±0.5 versus 2.1±1.0), suggesting differential coupling, with an inability of the right ventricle in SScPAH to compensate for the higher afterload. Diastolic function assessed by isovolumetric relaxation rate, end-diastolic pressure, and peak filling rate was similar between groups.

Finally, we compared the SScPAH group to SSc without PH (n=7; 71% women, 86% white, and 14% black). As expected, steady-state loops were more rectangular in patients without PH (Figure 6), with RV pressure fairly constant or slightly

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<thead>
<tr>
<th>Table 2. Pressure–Volume Loop Data and Hemodynamics</th>
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Hemodynamics and volumes

- Mean pulmonary artery pressure, mm Hg: 49±21 vs 37±12
- Cardiac index, L/min per m²: 2.4±0.6 vs 2.4±0.8
- Pulmonary artery oxygen saturation, %: 67±7 vs 62±3
- Right atrial pressure, mm Hg: 7±3 vs 8±4
- Pulmonary capillary wedge pressure, mm Hg: 11±3 vs 10±4
- Mean systemic artery pressure, mm Hg: 86±15 vs 86±8
- Right ventricular end-diastolic volume, mL: 161±47 vs 130±45

RV afterload

- Pulmonary arterial compliance, mL mm Hg⁻¹: 1.7±1.1 vs 2.4±1.5
- Pulmonary vascular resistance, Wood units: 7.9±4.3 vs 7.0±4.5
- Pulmonary vascular resistance, mm Hg·S·mL⁻¹: 0.47±0.26 vs 0.42±0.27
- Effective arterial elastance: 1.2±0.5 vs 0.9±0.4

RV systolic function (contractility)

- RV ejection fraction, %: 43±13 vs 47±12
- RVSWI, mm Hg·m⁻³·L⁻¹: 18.8±9.7 vs 12.5±5.9
- End-systolic elastance ($E_{es}$): 2.3±1.1 vs 0.8±0.3
- $V_x$ (x-intercept of end-systolic elastance): 46±37 vs −31±49
- End-systolic elastance (normalized; $E_{es(norm)}$): 3.1±1.4 vs 0.9±0.3
- Preload recruitable stroke work (Msw): 45±16 vs 21±11

RV diastolic function

- Peak fill rate/end-diastolic volume, ms/mL: 2.7±0.9 vs 2.9±0.9
- Tau (Glantz), ms: 105±47 vs 106±18
- Tau (Suga), ms: 36±9 vs 39±6
- $dp/dt$, mm Hg/ms: −867±274 vs −420±120

RV pulmonary artery coupling

- $E_{es}/E_{a}$: 2.1±1.0 vs 1.0±0.5

IPAH indicates idiopathic pulmonary arterial hypertension; RVSWI, Right Ventricular Stroke Work Index; SSc-no-PH, SSc without PH; SScPAH, systemic sclerosis–associated pulmonary artery hypertension; and WHO, World Health Organization.

Continuous variables shown as mean±SD. Student t test or Mann–Whitney rank-sum test as appropriate.
declining during systole. Despite the lower afterload, contractile function was essentially the same as in SScPAH subjects (Table 2), thus RV-PA coupling was similar to IPAH. The maximal rate of pressure decline was greater in SScPAH as compared with SSc without PH, likely reflecting the higher end-systolic pressures with the former, but other measures of diastolic function were similar.

Discussion

The present study tested whether pulmonary arterial loading or intrinsic RV function differs between patients with SScPAH and IPAH. The results support intrinsic RV systolic dysfunction in SSc and an inability of the right ventricle to compensate for higher afterload, rather than differences in load. These findings may offer a potential explanation for poor survival observed in SScPAH.

The pulmonary load analysis used a simple yet elegant approach first presented by Lankhaar et al and Saouti et al involving the $R_{pa}/C_{pa}$ relationship. They showed this to be little altered in patients with or without PAH, PH from chronic thromboembolic disease, and PAH before and after pulmonary vasodilator treatment. We recently confirmed this relationship in a large group of patients with or without PH. No prior study has specifically investigated the potential impact of SSc on the $R_{pa}/C_{pa}$ relationship. Prior estimates have put the contribution of proximal to total C$_{pa}$ at $\approx 19\%$, although this value was derived from patients without SScPAH. In SSc, deposition of collagen and other matrix components in the vascular walls has been proposed to increase arterial stiffening and is correlated with worse prognosis. However, if true, then the calculated C$_{pa}$ should decline for any corresponding $R_{pa}$, shifting the $R_{pa}/C_{pa}$ curve down and to the left; yet this was not observed. As with other forms of PH, the pulsatile load is dependent principally on factors that influence mean $R_{pa}$. The small but statistically significant rise in RC time with increasing mPAP is related to the finding that even...
in the pathophysiological range of elevated pulmonary pressures, total compliance does not fall to zero, requiring inclusion of a positive constant in the denominator of the hyperbolic decay equation. Our prior analysis also showed no change in the $R_{pa}-C_{pa}$ relation in patients with severe ILD, although most of those patients had pulmonary pressures in the normal range. The new SSc-ILD-PH cohort presented here had pulmonary hypertension with an average $R_{pa}$ of 7.4 Wood units, yet still no change was observed. Although pulmonary artery impedance spectra analysis is recognized as the gold standard for assessing pulsatile vascular loading, $C_{pa}$ and $E_{a}$ are useful lumped parameters that combine components because of vascular stiffening, characteristic impedance (mean impedance at high frequencies), and wave reflections into a single term. In sum, these data do not support the speculation that the mechanical properties of the pulmonary vasculature are fundamentally different in SSc.

While admittedly a small patient group, to our knowledge the present data represent the first effort to date to assess chronic RV function in the presence of PAH by invasive PV analysis, and first to show PV relations generated using the Valsalva maneuver. The conductance catheter signal calibration relied and first to show PV relations generated using the Valsalva maneuver. The conductance catheter signal calibration relied

Figure 5. Steady-state signal-averaged right ventricular (RV) pressure–volume loops for idiopathic pulmonary arterial hypertension (IPAH; top) and systemic sclerosis–associated pulmonary artery hypertension (SScPAH; bottom). Pressure rises throughout ejection consistent with increased afterload.

were designed to minimize the impact of any error in absolute volume estimation. For example, $M_{sw}$ has units of force and is insensitive to absolute volumes (one obtains a similar value in the normal heart of small rodents and other mammals as in humans). Normalization of $E_{a}$ to volume also reduced the impact of calibration error in this regard. PV analysis also depended on the Valsalva response, and although the magnitude of loading induced by this maneuver varied between individuals, it was sufficient to derive the relations. Work by Wang et al recently highlighted the effects of Valsalva on RV preload, and compared with the left ventricle, the more rapid preload decline is similar to what we observed. Just as with inferior vena caval occlusion, the extent of load change during Valsalva will vary among patients depending on RV contractility, vascular load, and Valsalva effort. However, this does not have to be the same to determine PV relationships.

The PV analysis found similar total RV afterload between groups, confirming our RC analysis, but did reveal systolic impairment in SScPAH without apparent differences in diastolic function. Only 1 prior study has reported on RV contractility in SScPAH, but this analysis was heavily based on theoretical calculations (eg, estimation of peak RV pressure at infinite afterload and maximal ejection at zero load, neither of which can be measured). Lower contractile function relative to pulmonary afterload in SScPAH, reflected by a reduced

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Ees/Ea ratio, suggests a blunting of the adaptive process that is normally observed. Prior studies support enhanced contractile function at least initially in response to high chronic RV afterload, and similar findings are reported in the left ventricle exposed to chronic hypertension. The underlying cause for RV systolic dysfunction in SScPAH remains unknown, although its coupling to relatively unaltered relaxation may hint at changes in myofilament function. Inability of the right ventricle to hypertrophy to compensate for elevated afterload is another possibility. Further studies are clearly needed to explore this finding.

We did not observe major differences in diastolic function between our patient groups. Prior studies using echo-Doppler analysis have revealed diastolic abnormalities in patients with SSc versus healthy controls. These may relate to RV load in 1 study but could not in another. The current data are the most reported to date on direct intracavitary measurements, and no prior studies have compared groups with PAH with or without SSc.

The clinical characteristics, including demographics, hemodynamics, and functional data of the IPAH and SScPAH cohorts, are very consistent with those of subgroups of similar patients we have previously reported. Despite less severe baseline hemodynamic impairment, SScPAH has more functional impairment as assessed by the 6-minute walk distance and a 2- to 3-fold elevation in serum NT-proBNP. The latter finding remains unexplained but is consistent with the current results that SScPAH has intrinsic myocardial dysfunction.

Among the limitations of the PV analysis is that we do not have true control data for comparison (ie, patients with normal right ventricles and without SSc or PH). Thus, truly normal values for human RV Ees or Ms remain unknown. However, animal studies support the use of both metrics to assess RV contractility independent of loading change. The conductance catheter method works for the right ventricle, although placement can be somewhat challenging because of heavy trabeculation and difficulties in advancing the distal pigtail toward the RV apex. With increasing experience, however, our success rate is exceeding 90%. A simplified approach using single-beat data to estimate Ees has also been described, but is yet to be validated in humans. Importantly, our study adds further support that the volume intercept of RV Ees cannot be assumed to be zero in patients with PH when using single-beat estimate techniques. Although statistically significant differences were observed in the PV analysis, we recognize that because of

**Figure 6.** Steady-state signal-averaged right ventricular (RV) pressure–volume loops for patients without pulmonary hypertension (PH), systemic sclerosis (SSc; top, n=7) and without SSc (bottom, n=1). The loops are more rectangular in shape than those in Figure 5, as pressure stays constant or decreases during ejection.
the small cohort size, the results may be subject to a type II error. Finally, some patients in both the resistance–compliance analysis and the PV loop analysis (online supplement 4 in the online-only Data Supplement) were on PAH-specific treatment at the time of hemodynamic measurements. It has previously been shown that treatment of PAH does not alter the $R_{pa} - C_{pa}$ relationship,$^{21}$ and although such therapies are not known to principally alter RV contractility, some contribution cannot be ruled out. The SScPAH and SSC without PH cohorts each had only 1 patient on chronic vasodilator therapy at the time of PV loop measures and had identical measures of contractile function, despite marked differences in afterload. The failure of the SScPAH patients to augment contractility in response to higher afterload which is the anticipated response,$^{22,23}$ again points to an intrinsic myocardial deficit in this cohort, rather than drug-induced enhancement of RV function in the IPAH group.

In conclusion, patients with SScPAH have relatively depressed RV function, despite similarly augmented pulmonary afterload compared with IPAH. The similarity between pulmonary $R_{pa} - C_{pa}$ relations among all patient groups, including patients with SSC with PH, and interstitial fibrosis indicates that exacerbated pulsatile afterload is unlikely a cause for the worsened cardiac function and outcome in patients with SScPAH. The similar contractile function in patients with SSC with or without PAH further suggests a lack of adaptations to enhanced loading in this syndrome. The factors that cause this impairment remain to be determined, but the findings likely contribute to the worsened prognosis in this patient group.

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**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

Among causes of pulmonary arterial hypertension (PAH), patients with systemic sclerosis (SSc)–associated PAH have the worst prognosis, and right ventricular (RV) failure is a primary cause of death. We tested whether this clinical observation was secondary to higher RV afterload (including pulsatile components not measured in a standard right heart catheterization) and intrinsic myocardial dysfunction. We show no difference in afterload in SScPAH or SSc-related pulmonary hypertension with interstitial lung disease compared with idiopathic PAH. Instead, using invasive RV pressure–volume relations, our data show differences in RV contractile function and an inability of the right ventricle to compensate for higher afterload in the SScPAH group. The RV pressure–volume loops are the first to be reported in humans with PAH, as is use of the Valsalva maneuver to lower preload and generate end-systolic pressure–volume relationships effectively. These techniques offer a potential way to better study this disease and to develop better noninvasive measures of RV function. The findings of this study should shift the focus of future research onto understanding the mechanisms of RV dysfunction in the SSc population.
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SUPPLEMENTAL MATERIAL
### Online Supplement 1.
#### Pulmonary Function Parameters

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SScPAH (n=166)</th>
<th>SSc-ILD-PH (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>1.91 ± 0.60 (n=144)</td>
<td>1.47 ± 0.44 (n=45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>78 ± 18 (n=129)</td>
<td>53 ± 13 (n=46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC</td>
<td>2.52 ± 0.82 (n=145)</td>
<td>1.75 ± 0.58 (n=45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>80 ± 18 (n=131)</td>
<td>50 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>76.4 ± 7.8 (n=144)</td>
<td>84.9 ± 8.3 (n=46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLCO</td>
<td>10.5 ± 4.0 (n=122)</td>
<td>8.2 ± 4.2 (n=40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>52 ± 18 (n=108)</td>
<td>34 ± 14 (n=43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Continuous variables shown as mean ± SD

Comparisons by student t-test or Mann-Whitney Rank Sum Test as appropriate
### Online Supplement 2. Chronic Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>IPAH (n=5)</th>
<th>SScPAH (n=7)</th>
<th>P-Value (IPAH vs. SScPAH)</th>
<th>SSc-no-PH (n=7)</th>
<th>P-Value (SScPAH vs. SSc-no-PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5A inhibitor</td>
<td>2 (40)</td>
<td>1 (14)</td>
<td>0.52</td>
<td>1 (14)</td>
<td>1.0</td>
</tr>
<tr>
<td>Endothelin Antagonist</td>
<td>2 (40)</td>
<td>0 (0)</td>
<td>0.15</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Intravenous Prostacyclin</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>0.42</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Inhaled or SQ Prostacyclin</td>
<td>2 (40)</td>
<td>0 (0)</td>
<td>0.15</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>1 (20)</td>
<td>2 (29)</td>
<td>1.0</td>
<td>3 (43)</td>
<td>1.0</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>3 (60)</td>
<td>1 (14)</td>
<td>0.22</td>
<td>2 (29)</td>
<td>1.0</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>3 (60)</td>
<td>1 (14)</td>
<td>0.22</td>
<td>2 (29)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

PAH = Pulmonary Arterial Hypertension; PDE5A = Phosphodiesterase 5A; SQ = Subcutaneous
Comparisons by Fisher Exact Test
30 patients enrolled

- Right IJ obstruction (n=1)
- Unable to place catheter into RV (n=2)

27 with successful placement of conductance catheter into RV

- Inadequate PV loop signals (n=4)
- No imaging for volume calibration (n=1)
- Patients with analyzable PV loop data (n=22)

PAH (n=12)
  - IPAH (n=5)
  - SScPAH (n=7)

No PAH (n=10)
  - No SSc (n=1)
  - Probable SSc-HFpEF (n=2)

No SSc (n=1)
**Online Supplement 3.** Flow chart depicting patient enrollment in pressure-volume loop analysis. HFpEF = Heart failure with preserved ejection fraction.

**Online Supplement 4.** Change in Heart Rate with Valsalva maneuver. 2-4 beats are averaged just prior to initiation of Valsalva (baseline), during onset of initiation (phase 1-2), and after release maneuver (phase 3).