Assessment of Right Ventricular Reserve Utilizing Exercise Provocation in Systemic Sclerosis

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Abstract

Purpose

Right ventricular (RV) capacity to adapt to increased afterload is the main determinant of outcome in pulmonary hypertension (PH), a common morbidity seen in systemic sclerosis (SSc). We hypothesized that supine bicycle echocardiography (SBE), coupled with RV longitudinal systolic strain (RVLSS), improves detection of limitations in RV reserve in SSc.

Methods

56 SSc patients were prospectively studied during SBE with RV functional parameters compared at rest and peak stress. We further dichotomized patients based on resting RV systolic pressure (RVSP) to determine the effects of load on contractile response.

Results

Our pooled cohort analysis revealed reduced global RVLSS at rest (-16.2 ± 3.9%) with normal basal contractility (-25.6 ± 7.7%) and relative hypokinesis of the midventricular (-14.1 ± 6.0%) and apical (-8.9 ± 5.1%) segments. With exercise, global RVLSS increased significantly (p=0.0005), however despite normal basal contractility at rest, there was no further augmentation with exercise. Mid and apical RVLSS increased with exercise suggestive of RV contractile reserve. In patients with resting RVSP < 35 mmHg, global and segmental RVLSS increased with exercise. In patients with resting RVSP ≥ 35 mmHg, global and segmental RVLSS did not increase with exercise and there was evidence of exertional RV dilation.

Conclusion

Exercise provocation in conjunction with RVLSS identified differential regional contractile response to exercise in SSc patients. We further demonstrate the effect of increased loading conditions on RV contractile response exercise. These findings suggest subclinical impairments in RV reserve in SSc that may be missed by resting noninvasive 2DE-based assessments alone.

1. Introduction

Cardiac involvement in systemic sclerosis (SSc) is associated with increased morbidity and mortality, primarily due to the development of right ventricular (RV) dysfunction and associated pulmonary arterial hypertension (PAH).[1–3] SSc patients with PAH (SSc-PAH) suffer disproportionately poor outcomes, with diminished response to treatment, worsened functional status, and increased rates of mortality in comparison to other PAH etiologies.[3, 4] Although 2-Dimensional Echocardiography (2DE) is a useful screening tool in PAH given its high specificity and high positive predictive value,[5, 6] RV dysfunction and emerging PAH are often undetected or underestimated until late in the disease course.[7] A newer imaging modality, speckle-tracking echocardiography (STE), has several advantages over 2DE alone to allow for optimized RV imaging and assessment of both global and regional contractility.[8, 9] STE can be used in

conjunction with standard 2DE imaging, and by utilization of a software-based algorithm, is not limited by Doppler beam alignment angle or dependent on user technique.[10]

In a prior cross-sectional study of SSc patients with and without PAH, we demonstrated both global and regional abnormalities in resting RV contractility in SSc patients that were independent of pulmonary arterial pressures (PAP) and were not detectable by conventional 2DE measures alone.[11] These findings support the hypothesis that STE can detect occult abnormalities in RV myocardial function, and that abnormalities in RV contractility can develop in SSc patients regardless of PAP. In several recent studies from our group using invasive pressure-volume hemodynamics, we have demonstrated that at similar afterloads, SSc-PAH patients have depressed RV contractility[12] and diminished contractile response[13] to exercise provocation when compared with idiopathic PAH, due to an underlying sarcomeric defect in calcium-handling.[14] Taken together, these findings suggest that the RV is inherently diseased in SSc patients due to underlying sarcomere dysfunction, and is therefore unable to effectively adapt to the increased pressure load that occurs with the development of PAH.[15]

Although there is increased attention on cardiopulmonary screening in SSc,[16] risk prediction of cardiac involvement and PAH in SSc remains poor.[17, 18] Existing screening recommendations may fail to detect early changes in RV contractility that signal impending PAH as standard 2DE metrics fail to identify occult contractile deficits,[11] and the invasive nature of pressure-volume hemodynamics along with its expense and requirement of specialized technical expertise make it unfeasible as a general screening technique. Additionally, current methods to evaluate cardiovascular disease risk in SSc are mostly based on assessments made in the resting state; and as SSc patients frequently complain of dyspnea with exertion, the systemic response of the RV to exercise may carry key prognostic information regarding RV contractility, reserve capacity, and presence of early pulmonary vascular disease.

In the present study, we investigated whether RV longitudinal systolic strain (RVLSS), a novel noninvasive metric of regional and global RV contractile function derived by STE and measured during supine bicycle exercise stress, provides an improved detection method over conventional measures alone to unmask RV contractile defects in at-risk SSc patients. We hypothesized that supine bicycle exercise echocardiography (SBE) coupled with RVLSS is an improved noninvasive tool to detect impaired RV reserve in SSc.

2. Patients And Methods

2.1 Patient Population.

Our study was approved by the Johns Hopkins Medicine Institutional Review Board. Consenting SSc patients seen at the Johns Hopkins Scleroderma Center for routine clinical care between January 2009 and December 2018 were eligible to participate in this single center observational study. All participants met 1980 or 2013 American College of Rheumatology classification criteria for SSc,[19, 20] or had at least 3 of 5 CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly,

telangiectasia) criteria. Our Center's standard practice is to perform annual pulmonary function and resting echocardiography testing in SSc patients to screen for cardiopulmonary complications.[6]

We included SSc patients deemed at risk for PAH as identified by: resting right ventricular systolic pressure (RVSP) ≥ 40 mmHg on a routine screening echocardiogram with associated dyspnea, an RVSP ≥ 45 mmHg on routine screening echocardiogram regardless of symptoms, an isolated decline in diffusing capacity (DLCO) ≥ 10% predicted from baseline, or new onset unexplained dyspnea. Unexplained dyspnea was defined as dyspnea without significant anemia (hematocrit < 28%), symptomatic interstitial lung disease, significant chronic obstructive pulmonary disease (FEV1/FVC ratio < 0.7 with history of smoking), or a left ventricular (LV) ejection fraction < 50%. SSc patients were enrolled if deemed able to exercise by their referring provider.

Classification of SSc cutaneous subtype was defined by established criteria,[21] and SSc disease duration was calculated as the time interval between the first scleroderma symptom (either Raynaud's or non-Raynaud's) and the exercise echocardiogram date. Measurements of forced vital capacity and diffusing capacity were standardized by age and gender.[22, 23]

2.2 Exercise Stress Protocol.

Supine bicycle stress echocardiograms were performed utilizing a single supine ergometer (Medical Positioning Inc, Kansas City, MO) at a single clinical site, Johns Hopkins Bayview Medical Center. Patients initiated exercise at 25 Watts and increased by 25 Watts every 3 minutes until achieving 85% of their age-predicted maximum heart rate or until limited by symptoms. Continuous electrocardiographic monitoring was performed throughout study duration. An exercise physiologist, cardiac sonographer, and physician's assistant specialized in Cardiology were present throughout the study duration. 2D echocardiographic images and measurements of right and left ventricular chamber size and function were obtained at baseline and within 1 minute of peak exertion.

2.3 Echocardiographic Acquisition and Measurements.

Echocardiograms were performed using Phillips ie33 or Epiq 7 ultrasound machines (Phillips Healthcare, Andover, MA) with subjects in the left lateral decubitus position during image acquisition at 70–90 frames per second at end-expiration. 2D-directed methods were taken at end-diastole to obtain linear and volumetric measurements of the RV chamber in accordance with American Society of Echocardiography (ASE) guidelines.[24, 25] Right atrial area (RAA) was estimated using volumetric area from the apical 4-chamber view. RV function was assessed using tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC), with abnormal defined as < 16 mm and < 35% respectively. Tricuspid regurgitant (TR) velocity was used to estimate right ventricular systolic pressure (RVSP) using the modified Bernoulli equation and adding estimated RA pressure based on inferior vena cava dimension and collapsibility with sniff.[26, 27] Left ventricular (LV) systolic function was estimated using Simpson's biplane method of discs to calculate ejection fraction (EF). LV diastolic parameters including mitral inflow with early diastolic (E) and late diastolic (A) velocities, and tissue Doppler medial e' velocities were obtained.[28]

STE-based strain analysis was performed of the RV using commercially available strain software (Epsilon EchoInsight Version 3.1.0.3358, Milwaukee, WI). From the 4-chamber apical view, peak systolic longitudinal strain of the RV free wall segments was obtained by tracing the RV chamber endocardial borders in end-systolic still frames.[8, 9, 29] In post-processing, automated tracking was visually verified and manually adjusted to ensure adequate border delineation and segment thickness. Peak longitudinal systolic strain was defined as the difference in shortening from the region of interest relative to original length, and by convention, is expressed as a negative percentage with decreased strain refers to a less negative number (i.e. a lower absolute value) than expected, while increased strain refers to a more negative number (i.e. a higher absolute value.[30] Global RV longitudinal systolic strain (RVLSS) was defined as the average of regional strain from the basal, midventricular, and apical RV free wall segments, and compared to published standard reference values.[30, 31] Two board certified echocardiologists (MM, VM) who were blinded to clinical variables performed conventional and speckle-based strain analysis to determine intra- and inter-observer variability.

2.4 Statistical Analysis.

Echocardiographic and hemodynamic parameters were compared at rest and at peak stress using a paired t test for parametric data, and Wilcoxon–Mann–Whitney test for non-parametric data. Statistical analyses were performed using STATA version 15.0 (College Station, TX, USA). Statistical significance was defined by a two-sided p value < 0.05. Intra-observer and inter-observer variability were assessed by intraclass correlation coefficient.

3. Results

3.1 Baseline Patient Characteristics.

The final study population consisted of 56 SSc patients with technically adequate stress bicycle echocardiograms that were predominantly female (87.5%) and white (74.1%), with a mean age of 55.9 ± 12.1 years and SSc disease duration of 16.0 ± 10.9 years. The majority of our patients had limited cutaneous disease (39 patients, 69.6%) while 30.4% of SSc patients had diffuse disease. Additional characteristics of participants are detailed in Table 1. Based on our inclusion criteria, 9 patients (16.1%) were referred for RVSP $\geq$ 40 mmHg on a routine screening echocardiogram with associated dyspnea, 4 patients (7.1%) for RVSP $\geq$ 45 mmHg regardless of symptoms, and 12 patients (21.4%) for an isolated decline in DLCO $\geq$ 10% predicted from baseline. The majority of the patients (31 patients, 55.4%) were referred for new onset unexplained dyspnea.

Table 1
Baseline demographics, co-morbidities, and specific characteristics for systemic sclerosis patients.

Parameter	Systemic Sclerosis (n = 56)
Age (years), mean ± SD	55.9 ± 12.1
Women, no. (%)	49 (87.5)
Race, no. (%), n = 54	40 (74.1)
White	12 (22.2)
Black	1 (1.9)
Asian	1 (1.9)
Other	
Ever Smoker, no. (%)	21 (37.5)
Scleroderma disease duration (years), mean ± SD	16.0 ± 10.9
Scleroderma subtype, no. (%)	39 (69.6)
Limited	17 (30.4)
Diffuse	
Autoantibody status, no. (%)	14 (26.4)
Scl-70, n = 53	14 (25.0)
Centromere, n = 56	4 (8.9)
RNA polymerase III, n = 45	
Pulmonary function data, mean ± SD	81.4 ± 24.0
Forced vital capacity, % predicted, n = 55	68.7 ± 24.1
Diffusing capacity, % predicted, n = 54	1.25 ± 0.54
FVC/DLCO ratio	

3.2 Resting 2D Echocardiographic and Speckle-Based Strain Characteristics.

During rest, all SSc patients had normal LV ejection fraction and normal left atrial areas as shown in Table 2. The mean mitral inflow pattern ratio of early (E) and late (A) diastolic velocities was 1.07 ± 0.30 with normal resting LV filling pressures (septal E/e' 10.8 ± 3.7, n = 46). Three SSc patients (6.5%) had septal E/e' ≥ 15 at baseline suggestive of elevated LV end-diastolic filling pressures at rest.[31]

Table 2
Resting 2D echocardiogram and speckle-based strain findings in systemic sclerosis with normative values based on established guidelines.[28, 31, 33, 37]

Echocardiographic Parameter	Systemic Sclerosis (n = 56)	Normal Values
LV Ejection Fraction, %, n = 56	61.9 ± 4.3	≥ 55[25]
Left Atrial Area, cm2, n = 54	14.9 ± 3.6	< 21[25]
Left Atrial Area Indexed to BSA, cm/m2, n = 49	8.6 ± 2.7	
Mitral E/A, n = 52	1.07 ± 0.30	1.28 ± 0.25[38]
LV Septal E/e', n = 46	10.8 ± 3.7	≥ 15[38]
Right Atrial Area, cm2, n = 55	14.2 ± 3.1	< 18[25]
RV Internal Diastolic Dimension, cm	2.6 ± 0.5	
RVOT Level of Pulmonic Valve, cm, n = 29	2.2 ± 0.5	< 2.7[33]
RV Basal Dimension, cm	3.0 ± 0.5	< 4.1[33]
RV Mid Dimension, cm	2.7 ± 0.7	< 3.5[33]
RV Longitudinal Dimension, cm	6.8 ± 0.7	< 8.3[33]
RV End-Systolic Area, cm2	10.0 ± 2.4	< 9[33]
RV End-Diastolic Area, cm2	17.2 ± 3.5	< 18[33]
RV FAC, %	41.8 ± 7.7	> 35[33]
TAPSE, cm, n = 55	2.26 ± 0.40	> 1.7[33]
RVSP, mmHg, n = 53	29.9 ± 9.3	< 35[33]
Basal RVLSS, %	-25.6 ± 7.7	-25 ± 6[31]
Midventricular RVLSS, %	-14.1 ± 6.0	-27 ± 5[31]
Apical RVLSS, %	-8.9 ± 5.1	-24 ± 6[31]
Global RVLSS, %	-16.2 ± 3.9	-26 ± 4[31]

RAA was normal in size as were linear measures of RV chamber size including mid and distal RV outflow tract and basal, mid, and longitudinal dimensions. Resting RV end-diastolic area (RVEDA) and end-systolic areas (RVESA) were top normal. Specifically, 22 SSc patients (39%) had resting dilated RVEDA ≥ 18 cm^2 and 37 SSc patients (66%) had dilated RVESA ≥ 9 cm^2. 2DE-based RV functional measures were normal at baseline, with mean FAC of 41.8 ± 7.7% and TAPSE 2.26 ± 0.40 cm respectively. Nine SSc patients had abnormal FAC of ≤ 35% at baseline, with mean 30.2 ± 3.4%, while two SSc patients had abnormal of TAPSE ≤ 1.6 cm. Resting TR Doppler signal was available for 53 of the 56 subjects to allow

for estimation of RVSP, with mean 29.9 ± 9.3 mmHg. There were 18 SSc patients (34%) with resting RVSP ≥ 35 mmHg.

At baseline, global RVLSS was diminished in SSc patients (-16.2 ± 3.9%) in comparison to established reference values.[31] In terms of regional strain, RVLSS was normal at rest in the basal RV free wall segments (-25.6 ± 7.7%) relative to the midventricular (-14.1 ± 6.0%) and apical (-8.9 ± 5.1%) segments.[11]

3.3 Exercise Stress Hemodynamics and Echocardiographic Findings.

SSc patients were exercised to 85% MPHR, and on average achieved 81 ± 28 Watts consistent with functional class II level of exertion.[32] With stress, LV ejection fraction appropriately increased to 73 ± 6% as shown in Table 3. There was no difference in resting and peak septal E/e' values in the 23 patients for which both values were available, $p = 0.23$. With stress, there were increases in TAPSE ($p < 0.0001$) and FAC ($p = 0.0001$). We noted a statistically significant increase in RVSP with exertion, from resting value of 30.6 ± 8.9 mmHg to peak 49.9 ± 12.7 mmHg ($p < 0.0001$). With exercise, global RVLSS increased significantly from a diminished baseline of -16.2 ± 3.9% to -18.9 ± 4.2% ($p = 0.0005$). Despite the basal RVLSS being normal at rest, there was no significant augmentation of basal contractility with exertion as shown in Fig. 1. On the other hand, RVLSS of the mid and apical RV segments was diminished at baseline and increased with exercise ($p = 0.02$ and $p = 0.001$, respectively).

Table 3
Rest and stress echocardiographic parameters in systemic sclerosis patients. *Minor differences in resting echocardiographic data between Table 2 and Table 3 are due to the use of paired data samples in Table 3.

Parameter	Rest	Stress	p-value
Heart Rate, bpm, n = 54	74 ± 10	128 ± 15	**p < 0.0001**
Systolic blood pressure, mmHg, n = 55	118 ± 16	160 ± 32	**p < 0.0001**
Diastolic blood pressure, mmHg, n = 55	69 ± 16	88 ± 20	**p < 0.0001**
METs, n = 47		4.5 ± 1.5	
Watts, n = 49		81 ± 28	
Oxygen Saturation, %, n = 44	97.5 ± 1.7	95.5 ± 3.4	**p = 0.001**
*Conventional 2D Echocardiographic Parameters**			
LV Ejection Fraction, %, n = 54	62 ± 4	73 ± 6	**p < 0.0001**
Mitral Inflow E/A, n = 24	1.14 ± 0.34	1.19 ± 0.29	NS
Septal E/e', n = 23	10.8 ± 4.1	10.2 ± 4.4	NS
RV End-Systolic Area, cm2, n = 55	10.0 ± 2.4	9.7 ± 2.6	NS
RV End-Diastolic Area, cm2, n = 55	17.2 ± 3.5	18.0 ± 3.1	**p = 0.01**
RV FAC, %, n = 55	41.9 ± 7.7	45.9 ± 9.3	**p = 0.0001**
TAPSE, cm, n = 47	2.25 ± 0.39	2.58 ± 0.43	**p < 0.0001**
RVSP, mmHg, n = 48	30.6 ± 8.9	49.9 ± 12.7	**p < 0.0001**
Strain Parameters			
Basal RVLSS, %	-25.6 ± 7.7	-28.3 ± 9.1	0.06
Midventricular RVLSS, %	-14.1 ± 6.0	-16.5 ± 4.3	**p = 0.02**
Apical RVLSS, %	-8.9 ± 5.1	-12.0 ± 5.6	**p = 0.001**
Global RVLSS, %	-16.2 ± 3.9	-18.9 ± 4.2	**p = 0.0005**

As the majority of our patients were referred for unexplained dyspnea, we sought to understand whether the global and regional changes seen in SSc patients were related to resting load conditions. We dichotomized SSc patients by resting RVSP value based on the ASE definition of abnormal RVSP of ≥ 35 mmHg.[33] There were 35 SSc patients with resting RVSP < 35 mmHg, and 18 patients with RVSP ≥ 35 mmHg (Table 4). The peak exercise RVSP was 47.0 ± 10.4 mmHg in the low resting RVSP group (n = 31) and 55.2 ± 15.1 mmHg in the elevated resting RVSP group (n = 17, p = 0.03). In both groups, conventional

2D measures of RV function increased with exercise however there was an interesting pattern of RV contractile response as detected by RVLSS analysis.

Table 4
Delta between rest and stress echocardiographic parameters according to resting estimated RVSP (< 35 mmHg versus ≥ 35 mmHg). Bold print signifies statistical significance, p value ≤ 0.05.

	Resting RVSP < 35 mmHg	**Resting RVSP ≥ 35 mmHg**
	n = 35	**n = 18**
RVLSS Base (%)	-25.6 ± 8.5	-25.6 ± 6.7
Rest	-28.7 ± 9.4	-26.3 ± 8.7
Stress	-3.1 ± 9.2	-0.78 ± 13.1
Delta Change	**(p = 0.05)**	(p = 0.80, NS)
RVLSS Mid (%)	-12.7 ± 5.7	-16.9 ± 6.2
Rest	-16.7 ± 4.4	-16.4 ± 4.1
Stress	-4.0 ± 7.0	0.4 ± 7.4
Delta Change	**(p = 0.002)**	(p = 0.80, NS)
RVLSS Apex (%)	-7.7 ± 4.1	-11.8 ± 6.0
Rest	-11.6 ± 5.7	-12.6 ± 5.0
Stress	-3.9 ± 5.8	-0.8 ± 7.9
Delta Change	**(p = 0.0003)**	(p = 0.66, NS)
RVLSS Global (%)	-15.3 ± 3.5	-18.1 ± 4.4
Rest	-19.0 ± 4.5	-18.5 ± 4.0
Stress	-3.7 ± 4.8	-0.4 ± 6.5
Delta Change	**(p = 0.0001)**	(p = 0.80, NS)
TAPSE (cm)	n = 28	n = 17
Rest	2.26 ± 0.39	2.22 ± 0.40
Stress	2.61 ± 0.46	2.48 ± 0.38
Delta Change	0.29 ± 0.62	0.26 ± 0.35
	(p = 0.0002)	**(p = 0.007)**

	Resting RVSP < 35 mmHg	**Resting RVSP ≥ 35 mmHg**
	n = 35	**n = 18**
FAC (%)	43.1 ± 7.7	n = 17
Rest	47.5 ± 9.2	38.7 ± 7.7
Stress	4.3 ± 8.1	41.3 ± 7.9
Delta Change	**(p = 0.003)**	2.5 ± 4.8
		(p = 0.045)
RVEDA (cm2)	17.9 ± 3.4	n = 17
Rest	18.4 ± 3.2	15.5 ± 3.2
Stress	0.6 ± 2.5	16.9 ± 2.9
Delta Change	(p = 0.21, NS)	1.5 ± 1.7
		(p = 0.003)
RVESA (cm2)	10.3 ± 2.8	n = 17
Rest	9.8 ± 2.9	9.3 ± 1.6
Stress	-0.5 ± 1.8	9.9 ± 1.8
Delta Change	(p = 0.11, NS)	0.5 ± 1.4
		(p = 0.15, NS)

In the 38 patients with a resting RVSP < 35 mmHg, 35 patients had paired data available for analysis of both resting and peak strain parameters. Global RVLSS was diminished at rest and increased significantly with exercise (rest − 15.3 ± 3.5% vs. peak − 19.0 ± 4.5%, p = 0.0001) with augmented contractility across all three RV free wall segments: base (p = 0.05), midventricular (p = 0.002), and apical RVLSS (p = 0.0003). RVEDA and RVESA areas did not change significantly from rest to stress. Notable differences were observed among the 18 patients with a resting RVSP ≥ 35 mmHg, however. Both TAPSE and FAC increased with exertion however interestingly, while RVEDA increased significantly (rest 15.5 ± 3.2 cm^2 vs 16.9 ± 2.9 cm^2, p = 0.003), there was no significant increase in RVESA (rest 9.3 ± 1.6 cm^2 vs 9.9 ± 1.8 cm^2, p = 0.15). Similarly, there was a statistically significant increases in TAPSE (rest 2.22 ± 0.40 cm vs. peak 2.48 ± 0.38 cm, p = 0.007). There were no significant changes in global and regional RVLSS with exercise. Global RVLSS did not augment significantly from baseline (rest − 18.1 ± 4.4% vs. peak − 18.5 ± 4.0, p = 0.80). There was also no regional increase in RVLSS of the basal, midventricular, and apical segments.

3.4 Inter- and Intra-Observer Variability

Inter-observer variability was excellent for both resting (ICC base 98.1, mid 97.6, apex 90.8, global 95.9) and exercise RV strain parameters (ICC base 97.3, midventricular 89.9, apex 92.8, global 95.4). Intra-observer variability was also excellent for both resting (ICC base 97.9, mid 99.6, apex 96.9, global 98.5) and exercise RV strain parameters (ICC base 98.3, mid 93.1, apex 98.4, global 99.1).

4. Discussion

In the present study, we sought to investigate whether RVLSS, a novel noninvasive metric of regional and global RV contractile function derived by STE, measured during supine bicycle exercise, provides an improved detection method over conventional 2DE measures alone to identify RV contractile dysfunction in at-risk SSc patients. SSc patients in our study were primarily referred for SBE based on the indication of unexplained dyspnea. At rest, mean RVSP was normal with normal conventional 2DE derived measures of RV contractility (TAPSE, FAC). With exertion, there were increases in these conventional measures suggesting normal RV contractile response to exercise provocation. However, the innovative application of STE-based metrics revealed both resting and exercise abnormalities in RV contractile function. At rest, global RVLSS was diminished with evidence of regional heterogeneity in which there was normal contractility of the basal RV free wall segment with relative hypokinesis of midventricular and apical segments. With exercise, there were significant increases in global RVLSS, largely due to regional increases in midventricular and apical contractility, suggestive of myocardial reserve in these segments. Interestingly, despite normal resting basal contractility, there was no further augmentation of basal segment contractility with exercise. These findings suggest that at rest, the basal segment is already contracting maximally and is unable to augment further with exercise provocation. Overall, these findings demonstrate that SSc patients have a differential RV regional contractile response to exercise, suggesting limitations in RV reserve that are missed by conventional 2DE.

We also examined the effects of loading conditions on RV contractility and found differential contractile response based on resting loading conditions. In patients with low load, defined as resting RVSP < 35 mmHg, global RVLSS increased with exertion due to augmented contractility across all three RV free wall segments, including the initially hypokinetic midventricular and apical segments. In patients with high load, defined as RVSP ≥ 35 mmHg, global RVLSS did not augment significantly from baseline and there were no regional increases in RVLSS of the basal, midventricular, or apical segments. These findings suggest that the RV in high loading conditions may already contracting at its maximal capacity at rest and is unable to augment further with exercise.

Additionally, we also found significant increases in RV end-diastolic areas with exercise in the high load group. These findings are consistent with several prior studies from our group using invasive pressure-volume assessments showing that SSc-PAH patients have depressed RV contractility compared with patients with idiopathic PAH (IPAH) at similar levels of afterload,[12] and maintain stroke volume and augment cardiac output by dilatation of the RV chamber.[13] We also found that there were minimal differences in peak RVSP between the low and high resting load groups suggesting that contractile differences are not entirely due to a primary load phenomenon at the time of exercise. Rather, these data

suggest that intrinsic contractile abnormalities may be present in SSc that affect the adaptive response to increases in afterload. These changes may be attributable due to differential myofilament contractility and calcium sensitivity[34] as well as changes to the pulmonary vascular bed inherent to the disease process. To our knowledge, our study is the first to demonstrate the utility of novel noninvasive STE-based metrics that establish the failure of the scleroderma RV to augment contractility with high loading conditions, resulting in RV chamber dilatation. STE in conjunction with exercise provocation may provide crucial clinical information by identifying SSc patients with limitations in RV reserve and emerging pulmonary vascular disease.

There were several limitations to our study. First, this was a single-center prospective study with a relatively small sample size as exercise studies were performed based on clinical indications. There was a lack of correlation with simultaneous invasive hemodynamics and absence of a control group. There are currently no accepted reference values for the normal RV strain response to exercise and this is an important priority for future studies. Recently, there has been a notable change in the invasive hemodynamic definition of PAH,[35] with mean PAP $\geq$ 21 to < 25 mmHg representing an intermediate form of disease that is high risk for emerging PAH. However, there has not been a corresponding change to the definition of pulmonary hypertension by echocardiography. While understanding that this is a continuum of disease, we chose to dichotomize our SSc patients based on the current ASE recommendations for the noninvasive cut-off of RVSP $\geq$ 35 mmHg for the purposes of this study.[33] Further longitudinal studies are needed to determine if exertional changes in contractility by exercise echocardiography identify SSc patients at risk for resting PAH, and whether strain metrics can serve as a target for disease-modifying therapies. Lastly, given the well-described vendor-specific variability in strain measures, there may be inherent differences that limit the generalizability of our findings.[36]

In this prospective study of at-risk SSc patients, we demonstrated STE-based abnormalities in RV contractile response to exercise that was not detectable by conventional measures alone and may identify SSc patients with limitations in RV reserve and poor clinical outcomes from emerging. We further demonstrated the effect of resting loading conditions on RV contractile response to exercise in which the RV chamber differentially dilates with no further augmentation in contractility in those with elevated RVSP at rest. These findings suggest a maladaptive contractile response of the RV when resting loading conditions are elevated. The significance of our study lies in the use of exercise provocation in conjunction with STE measures, an important noninvasive tool, in assessing the degree of RV contractile reserve in SSc patients at risk for PAH. Our findings of impairments in RV reserve may have clinical implications for the use of exercise provocation in screening for emerging pulmonary vascular disease in at-risk SSc patients.

Abbreviations

2DE: 2-Dimensional Echocardiography

ASE: American Society of Echocardiography

FAC: Fractional Area Change

MPHR: Maximum Predicted Heart Rate

PAH: Pulmonary Arterial Hypertension

PAP: Pulmonary Arterial Pressure

RAA: Right Atrial Area

RHC: Right Heart Catheterization

RV: Right Ventricle

RVOT: Right ventricular outflow tract

RVEDA: RV End-Diastolic Area

RVESA: RV End-Systolic Area

RVLSS: Right Ventricular Longitudinal Systolic Strain

RVSP: Right Ventricular Systolic Pressure

SSc: Systemic Sclerosis

STE: Speckle-Tracking Echocardiography

TAPSE: Tricuspid Annular Plane Systolic Excursion

TR: Tricuspid regurgitant

Declarations

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References

1. Parks JL, Taylor MH, Parks LP, Silver RM. Systemic sclerosis and the heart. Rheum Dis Clin North Am. 2014;40(1):87-102. doi: 10.1016/j.rdc.2013.10.007. PubMed PMID: 24268011.
2. Hachulla E, Launay D, Yaici A, Berezne A, de Groote P, Sitbon O, et al. Pulmonary arterial hypertension associated with systemic sclerosis in patients with functional class II dyspnoea: mild symptoms but severe outcome. Rheumatology (Oxford). 2010;49(5):940-4. doi: 10.1093/rheumatology/kep449. PubMed PMID: 20144930.
3. Fisher MR, Mathai SC, Champion HC, Girgis RE, Housten-Harris T, Hummers L, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 2006;54(9):3043-50. doi: 10.1002/art.22069. PubMed PMID: 16947776.
4. Ruiz-Cano MJ, Escribano P, Alonso R, Delgado J, Carreira P, Velazquez T, et al. Comparison of baseline characteristics and survival between patients with idiopathic and connective tissue disease-related pulmonary arterial hypertension. J Heart Lung Transplant. 2009;28(6):621-7. doi: 10.1016/j.healun.2009.02.016. PubMed PMID: 19481024.
5. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. doi: 10.1093/eurheartj/ehv317. PubMed PMID: 26320113.
6. Bissell LA, Anderson M, Burgess M, Chakravarty K, Coghlan G, Dumitru RB, et al. Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis. Rheumatology (Oxford). 2017;56(6):912-21. doi: 10.1093/rheumatology/kew488. PubMed PMID: 28160468.
7. Reynertson SI, Kundur R, Mullen GM, Costanzo MR, McKiernan TL, Louie EK. Asymmetry of right ventricular enlargement in response to tricuspid regurgitation. Circulation. 1999;100(5):465-7. PubMed PMID: 10430758.
8. Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: clinical applications. Heart. 2010;96(24):2032-40. doi: 10.1136/hrt.2010.199885. PubMed PMID: 21088126.
9. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr. 2010;23(4):351-69; quiz 453-5. doi: 10.1016/j.echo.2010.02.015. PubMed PMID: 20362924.
10. Blessberger H, Binder T. NON-invasive imaging: Two dimensional speckle tracking echocardiography: basic principles. Heart. 2010;96(9):716-22. doi: 10.1136/hrt.2007.141002. PubMed PMID: 20424157.
11. Mukherjee M, Chung SE, Ton VK, Tedford RJ, Hummers LK, Wigley FM, et al. Unique Abnormalities in Right Ventricular Longitudinal Strain in Systemic Sclerosis Patients. Circ Cardiovasc Imaging.

2016;9(6). doi: 10.1161/CIRCIMAGING.115.003792. PubMed PMID: 27266598; PubMed Central PMCID: PMCPMC4902176.

12. Tedford RJ, Mudd JO, Girgis RE, Mathai SC, Zaiman AL, Housten-Harris T, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. Circ Heart Fail. 2013;6(5):953-63. doi: 10.1161/CIRCHEARTFAILURE.112.000008. PubMed PMID: 23797369; PubMed Central PMCID: PMCPMC3815697.
13. Hsu S, Houston BA, Tampakakis E, Bacher AC, Rhodes PS, Mathai SC, et al. Right Ventricular Functional Reserve in Pulmonary Arterial Hypertension. Circulation. 2016;133(24):2413-22. doi: 10.1161/CIRCULATIONAHA.116.022082. PubMed PMID: 27169739; PubMed Central PMCID: PMCPMC4907868.
14. Hsu S KJ, Mullin C, Mukherjee M, Kolb TM, Damico RL, Mathai SC, Shah AA, Wigley FM, Margulies KB, Hassoun PM, Tedford RJ, Kass DA. . Human Right Ventricular Myofilaments Exhibit Directionally Opposite Changes in Maximal Force and Calcium Sensitivity in Systemic Sclerosis-associated versus Idiopathic Pulmonary Arterial Hypertension. The Journal of Heart and Lung Transplantation. 2017.
15. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol. 2013;62(25 Suppl):D22-33. doi: 10.1016/j.jacc.2013.10.027. PubMed PMID: 24355638.
16. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis. 2014;73(7):1340-9. doi: 10.1136/annrheumdis-2013-203301. PubMed PMID: 23687283; PubMed Central PMCID: PMCPMC4078756.
17. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum. 2005;52(12):3792-800. doi: 10.1002/art.21433. PubMed PMID: 16320330.
18. Hinchcliff M, Fischer A, Schiopu E, Steen VD, Investigators P. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. J Rheumatol. 2011;38(10):2172-9. doi: 10.3899/jrheum.101243. PubMed PMID: 21844142; PubMed Central PMCID: PMCPMC3230328.
19. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23(5):581-90. PubMed PMID: 7378088.
20. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737-47. doi: 10.1002/art.38098. PubMed PMID: 24122180; PubMed Central PMCID: PMCPMC3930146.
21. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202-5. PubMed PMID: 3361530.

22. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179-87. doi: 10.1164/ajrccm.159.1.9712108. PubMed PMID: 9872837.
23. Knudson RJ, Kaltenborn WT, Knudson DE, Burrows B. The single-breath carbon monoxide diffusing capacity. Reference equations derived from a healthy nonsmoking population and effects of hematocrit. Am Rev Respir Dis. 1987;135(4):805-11. PubMed PMID: 3565929.
24. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713; quiz 86-8. doi: 10.1016/j.echo.2010.05.010. PubMed PMID: 20620859.
25. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63. doi: 10.1016/j.echo.2005.10.005. PubMed PMID: 16376782.
26. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol. 1985;6(2):359-65. PubMed PMID: 4019921.
27. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol. 2003;41(6):1021-7. PubMed PMID: 12651052.
28. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016. doi: 10.1093/ehjci/jew082. PubMed PMID: 27422899.
29. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr. 2004;17(10):1021-9. doi: 10.1016/j.echo.2004.06.019. PubMed PMID: 15452466.
30. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range. JACC Cardiovasc Imaging. 2009;2(1):80-4. doi: 10.1016/j.jcmg.2007.12.007. PubMed PMID: 19356538.

31. Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, et al. Reference Values for Right Ventricular Strain in Patients without Cardiopulmonary Disease: A Prospective Evaluation and Meta-Analysis. Echocardiography. 2015;32(5):787-96. doi: 10.1111/echo.12806. PubMed PMID: 25323591.
32. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990;13(8):555-65. PubMed PMID: 2204507.
33. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713. doi: 10.1016/j.echo.2010.05.010. PubMed PMID: 20620859.
34. Hsu S KK, Kirk JA, Kolb, TM, Damico RL, Mathai SC, Mukherjee M, Shah AA, Wigley FM, Rosen LC, Margulies KB, Hassoun PM, Halushka MK, Tedford RJ, Kass DA. Opposite Right Ventricular Myofilament Functional Changes in Humans with Systemic Sclerosis-associated versus Idiopathic Pulmonary Arterial Hypertension Circulation. 2018.
35. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2018. doi: 10.1183/13993003.01913-2018. PubMed PMID: 30545968.
36. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr. 2015;28(10):1171-81, e2. doi: 10.1016/j.echo.2015.06.011. PubMed PMID: 26209911.
37. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70. doi: 10.1093/ehjci/jev014. PubMed PMID: 25712077.
38. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314. doi: 10.1016/j.echo.2016.01.011. PubMed PMID: 27037982.

Figures

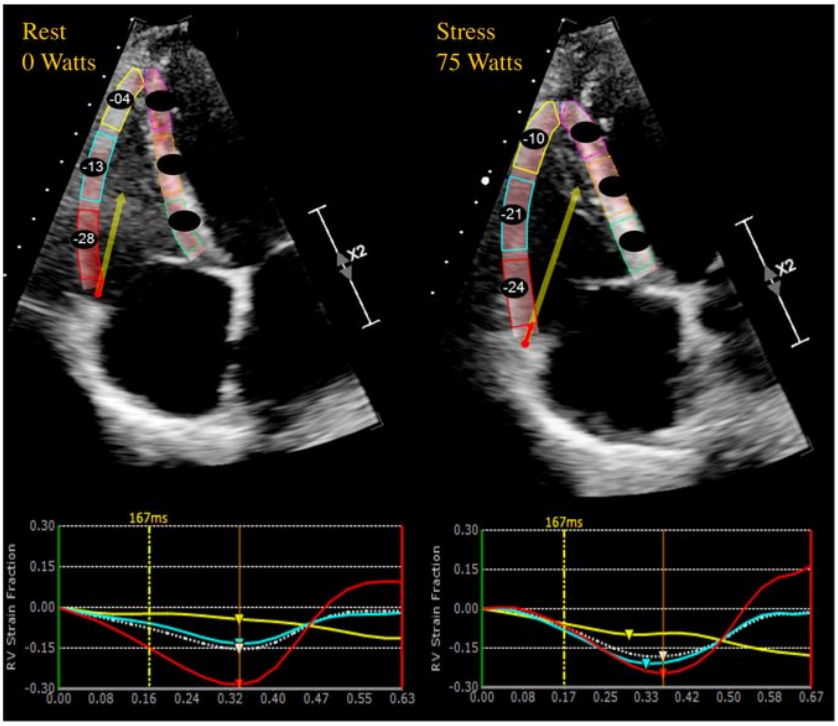

Figure 1

Right ventricular longitudinal systolic strain is shown of the RV free wall in a systemic sclerosis patient at rest and peak stress at 75 Watts. Each of the RV free wall segments corresponds with a color-matched systolic strain curve (lower panels) such that the basal RV segment is red, midventricular cyan, and apical yellow. At rest, there is a heterogeneous pattern of RV free wall contractility such that the basal segment (red) has increased contractility (a more negative strain value) in comparison with the midventricular (cyan) and apical (yellow) segments. With exercise, there is no further augmentation of basal RV contractility while the midventricular and apical segments become more contractile.