Unique Abnormalities in Right Ventricular Longitudinal Strain in Systemic Sclerosis Patients

Monica Mukherjee, MD, MPH; Shang-En Chung, ScM; Von Khue Ton, MD, PhD; Ryan J. Tedford, MD; Laura K. Hummers MD, ScM; Fredrick M. Wigley, MD; Theodore P. Abraham, MD; Ami A. Shah, MD, MHS

Background—Cardiac involvement in systemic sclerosis (scleroderma [SSc]) adversely affects long-term prognosis, often remaining undetectable despite close clinical examination and 2-dimensional echocardiographic monitoring. Speckle-derived strain of the right ventricle (RV) was utilized to detect occult abnormalities in regional and global contractility in SSc patients.

Methods and Results—A total of 138 SSc patients with technically adequate echocardiograms was studied and compared with 40 age- and sex-matched healthy non-SSc controls. Standard assessment of RV chamber function included tricuspid annular plane systolic excursion and fractional area change. RV longitudinal systolic speckle-derived strain was assessed in the basal, mid, and apical free wall. Tricuspid annular plane systolic excursion was not different between groups (P=0.307). Although fractional area change was lower in SSc patients than in controls (mean, 48.9 versus 55; P=0.002), the mean fractional area change was still within the normal range (>35). In contrast, RV longitudinal systolic speckle-derived strain measures were significantly different between groups, both globally (−20.4% versus −17.7%; P=0.005) and regionally: they were decreased in the apex (−8.5% versus −17.1%; P<0.0001) and mid segments (−12.4% versus −20.9%; P<0.0001), and increased in the base (−32.2% versus −23.3%; P=0.0001) for the SSc group. The regional difference in the base compared with the apex was significantly greater for SSc than for controls (P<0.0001 for interaction). The differences observed in regional strain between SSc and control were unchanged after adjusting for RV systolic pressure.

Conclusions—Speckle-derived strain reveals a heterogenous pattern of regional heart strain in SSc that is not detected by conventional measures of function, suggestive of occult RV myocardial disease. (Circ Cardiovasc Imaging. 2016;9:e003792. DOI: 10.1161/CIRCIMAGING.115.003792.)

Key Words: cardiomyopathies • heart ventricles • hypertension, pulmonary • scleroderma, systemic • ventricular function, right

Systemic sclerosis (scleroderma [SSc]) is a complex disease that is characterized by a prominent vasculopathy, dysregulation of the immune system, and fibrosis of multiple organ systems, including the skin, heart, lungs, kidneys, gastrointestinal tract, and blood vessels.1 Cardiac involvement is common in SSc and includes conduction abnormalities, arrhythmias, and myocardial and pericardial involvement. In addition to intrinsic heart disease, there is unique vascular insult of the systemic and pulmonary vascular beds, each of which adversely affects long-term prognosis.1-3 Development of pulmonary arterial hypertension (PAH), in particular, has a strong correlation with reduced mortality, with 50% 3-year survival rates in patients with New York Heart Association class II at the time of diagnosis.4,7

Despite frequent echocardiographic monitoring, significant right ventricular (RV) dysfunction and PAH are commonly undetected until the patient is symptomatic late in the course of the disease process. The lack of detection of right heart dysfunction by standard 2-dimensional (2D) echocardiographic analysis is, in part, because of the complex geometric configuration of the RV chamber and misalignment of the Doppler beam for accurate noninvasive assessment of cardiac hemodynamics.8

Speckle-tracking echocardiography (STE) is a novel imaging modality used in conjunction with conventional 2D echocardiogram that involves a fairly precise software-based algorithm and is not limited by Doppler beam angulation.8 Pixels, or speckles, are generated within the myocardium from random reflection, refraction, and scattering of the ultrasound beam. Tracking of the speckles within a particular myocardial segment over time allows for specific quantification of how
each segment deforms, or shortens, during systole and lengthens during diastole. This result in an estimate of the relative velocity of motion of a particular segment within the myocardium in space as a function of time, defined as strain-derived deformation parameter.\(^6\) Strain is defined as the magnitude of myocardial contraction and relaxation, whereas strain rate is the change in strain over unit time and is a measure of myocardial contractility.\(^8\)\(^,\)\(^9\) STE provides a precise estimate of regional and global systolic function that is not user dependent or angle dependent unlike other Doppler-derived techniques.

In the present study, we used STE to determine whether there is a distinct pattern of myocardial dysfunction of the RV in SSc patients, suggestive of intrinsic microvascular disease, patchy myocardial fibrosis, or emerging PAH.

**Methods**

**Study Population**

SSc patients were identified through the Institutional Review Board–approved Johns Hopkins Scleroderma Center database. Clinical features of the disease are recorded prospectively at baseline and at return visits, typically occurring at 6-month intervals, in all consenting participants. All participants met 1980 American College of Rheumatology criteria for SSc, or at least 3 of 5 calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia criteria, or had definite Raynaud’s phenomenon, abnormal nailfold capillaries, and SSc-specific autoantibodies. Center standard practice includes annual echocardiograms to screen for the development of PAH, regardless of clinical symptoms. All patients with SSc who had a clinically indicated echocardiogram performed at the Johns Hopkins Bayview Medical Center between January and December 2012 were eligible for inclusion in this cross-sectional analysis. If multiple echocardiograms were performed on the same patient within this specified time frame, the first study performed was analyzed. Of the 162 SSc patients who met these inclusion criteria, 138 (85%) patients had adequate 2D image quality to allow for complete visualization and strain mapping of the RV free wall.

A cohort of age- and sex-matched non-SSc controls, who underwent clinically indicated echocardiograms during the study period, was also evaluated. Control patients were included for this analysis if left ventricular (LV) ejection fraction was normal (≥55%). Exclusion criteria included history of hospitalization for heart failure, hemodynamically significant valvular disease (any stenosis and regurgitation greater than mild in severity), coronary artery disease (segmental wall motion abnormality and history of myocardial infarction), ischemic, dilated, or hypertrophic cardiomyopathy, primary pulmonary disease, and systemic disease associated with secondary pulmonary disease (eg, sarcoidosis, SSc, and connective tissue disease), no evidence of intracardiac shunting, and no evidence of congenital heart disease. Control patients underwent extensive chart review to exclude any cardiovascular and pulmonary disease. Exclusion criteria included hypertension, diabetes mellitus, atherosclerotic cardiovascular disease, atrial fibrillation, and any known history of arrhythmia, stroke, peripheral vascular disease, known history of chronic obstructive pulmonary disease, or sleep apnea. Control patients had to have echocardiographic study quality that was technically adequate to allow for off-line strain analysis.

A cardiologist (M.M.), board certified in echocardiography, was blinded to disease status and analyzed each study including 2D measures and speckle-based strain. To assess for intraobserver and interobserver variability, 20 studies with adequate study quality were randomized for reanalysis 6 months after initial analysis by 2 independent cardiologists (M.M., V.K.T.), again blinded to disease status.

**Clinical Parameters**

Demographic data, disease characteristics, smoking history, medication exposures, history of cardiovascular and pulmonary comorbidities, pulmonary function testing and clinically obtained autoantibody tests results were abstracted for SSc patients from the Scleroderma Center’s database. Hypertension was defined as an average systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg at ≥2 visits, a documented history of hypertension by the patient’s primary care provider, or use of an antihypertensive medication for an indication other than Raynaud’s phenomenon. Atherosclerotic cardiovascular disease was defined as the presence of peripheral arterial disease (history of ankle-brachial index <0.9, history of claudication, history of amputation or ulceration caused by macrovascular disease without other clear indication) or coronary artery disease (history of angina, abnormal stress/ pharmacological stress test, abnormal coronary angiogram, history of myocardial infarction, or history of coronary revascularization). SSc cutaneous subtype was defined by established criteria,\(^11\) and SSc disease duration was calculated as the time interval between the first SSc symptom (either Raynaud or first non-Raynaud symptom) and the echocardiogram date. Measurements of forced vital capacity and diffusing capacity were standardized by age and sex.\(^12\)\(^,\)\(^13\)

For the non-SSc control patients who met our echocardiographic inclusion criteria, extensive chart review was performed to ensure that controls met the exclusion criteria of no known cardiopulmonary disease as outlined above.

**Echocardiographic Acquisition and Measurements**

Echocardiograms were performed at a single clinical site using Philips iE33 ultrasound machine (Philips Healthcare, Andover, MA) with subjects in the left lateral decubitus position. Two-dimensional–directed methods were used to obtain linear measurements of RV chamber size (basal diameter, midventricular diameter, and longitudinal dimension) from the apical 4-chamber view in end-systole in accordance with American Society of Echocardiography guidelines.\(^14\)\(^,\)\(^15\) RV internal dimension at end-diastole was measured from the parasternal long-axis view. Distal measures of the RV outflow tract diameter were measured from the left parasternal short-axis view at the level of the pulmonary valve annulus respectively. Right atrial size was estimated using volumetric area from the apical 4-chamber view. RV function was assessed using tricuspid annular plane systolic excursion (TAPSE) and 2D fractional area change (FAC), with abnormal function defined as <16 mm and <35%, respectively. In the absence of RV outflow tract obstruction and tricuspid or pulmonic stenosis, tricuspid regurgitant velocity was used to estimate RV systolic pressure (RVSP) using the modified Bernoulli equation and adding estimated right atrial pressure based on inferior vena cava dimension and collapsibility with sniff.\(^16\)\(^,\)\(^17\) RVSP of ≥36 mm Hg was identified as abnormal in accordance with American Society of Echocardiography guidelines. Pulmonary vascular resistance (PVR) was noninvasively estimated using the Abbs equation (tricuspid regurgitant velocity/time velocity integral of the RV outflow tract×10+0.16) with an abnormal value defined as ≥2.0 Wood Units (WU).\(^17\) LV diastolic parameters including mitral inflow with early diastolic (E) and late diastolic (A) velocities, and tissue Doppler medial e’ velocities were obtained by convention.\(^18\)

After acquisition of standard 2D echocardiographic images, additional images were acquired at 70 to 90 frames per second at end-expiration and subsequently analyzed using commercially available strain software (Epsilon, Milwaukee, WI).\(^9\) 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.\(^9\)\(^,\)\(^12\)\(^,\)\(^20\) In postprocessing, automated tracking was visually verified and manually adjusted to ensure adequate border delineation. Longitudinal strain is traditionally defined as the percentage shortening of a regional area of interest (ROI) relative to its original length and by convention is expressed as a negative percentage.\(^19\)\(^,\)\(^20\) The extent of myocardial deformation, defined as the peak longitudinal systolic strain, was expressed as percentage of longitudinal shortening in systole compared with diastole for each RV segment of interest.\(^9\)\(^,\)\(^20\) Worsening strain refers to a less negative number (ie, a lower absolute value) than expected for a ROI or to an area of hypokinesis or diminished deformation along the longitudinal axis.
Improved strain, on the contrary, refers to a more negative number (i.e., a higher absolute value) than expected for an ROI or to an area of hypokinesis or enhanced deformation along the longitudinal axis. RV longitudinal systolic strain (RVLSS) was calculated as the average of regional strain from the basal, mid, and apical RV free wall segments and compared with published standard reference values.

Statistical Analysis
Baseline characteristics and echocardiography parameters were compared between patients with SSc and controls. Differences in continuous variables and dichotomous/categorical variables were examined using a Student t test or a χ² test, respectively. Generalized estimating equations analysis was performed to account for clustering of RV strain values across the 3 RV segments within a given individual. First, we examined whether global RVLSS, defined as a repeated strain measure in the basal, midventricular, and apical segments, differed between patients with SSc and controls. We then modeled RVLSS as a function of segment and disease status (SSc versus controls). Segmental differences were examined utilizing RVLSS in the apex as the reference group; therefore, for all multivariable analyses, differences in RVLSS were examined in the midventricular and basal segments compared with the apex, respectively. As we detected regional differences in strain, we performed further analyses to determine whether these regional differences differed by SSc or control status by (1) modeling the interaction between region and disease status and (2) performing stratified analysis by disease status.

Our models demonstrated significant differences in RVLSS in basal segments compared with apical segments in patients with SSc compared with controls. In light of this, we examined the base–apex difference in RVLSS further. We defined abnormal strain as being present if the base–apex RVLSS difference was >2 SDs from the mean base–apex RVLSS difference for controls. We then examined whether any SSc phenotypic characteristics were different between the 2 groups (P = 0.002), was within normal clinical limits for both SSc and controls (48.9±10.9 versus 55±10.7). The fairly similar distributions of FAC between the 2 groups are illustrated in Figure 1 in the Data Supplement. Similarly, TAPSE was within normal clinical limits between SSc and controls and did not differ between groups (2.16±0.47 versus 2.25±0.40 cm; P = 0.307; Figure II in the Data Supplement). There were no clinically significant differences in LV ejection fraction when comparing patients with SSc with controls. Although there were statistically significant differences in linear dimensions of RV base, length, RV internal dimension at end-diastole, distal RV outflow tract dimension at the level of PV annulus, and right atrial size between SSc and controls, these values were not clinically significant and did not reach pathological values (Table I in the Data Supplement). PVR, as estimated by the Abbas technique, was elevated in SSc patients compared with controls (1.48±0.45 versus 1.24±0.26 WU; P = 0.002), as was RVSP (31.4±13.3 versus 22.6±4.4 mm Hg; P = 0.0001) although values did not reach pathological values.

Regional Abnormalities in RVLSS in SSc Are Primarily Because Of Hypokinesis of the Base and Hypokinesis of the Midventricular and Apical Segments
Our age- and sex-matched control patients had global RV free wall strain of −20.4±2.4% that was less than published reference standards of −26±4 in normal adults without cardiopulmonary disease. Patients with SSc had diminished global RVLS (expected mean difference, 2.71%) compared with controls (P < 0.0001) consistent with RV dysfunction. The distribution of strain in each RV segment is illustrated in Figure 1 for SSc patients and controls. We sought to determine whether these differences were secondary to a global reduction in strain or a regional pattern of RV dysfunction unique to SSc. Although the pattern of strain was similar across RV free wall segments in controls, a heterogeneous pattern was observed across these same segments in SSc. RVLS was decreased in the apex (SSc −8.5% versus control −17.1%; P < 0.0001) and mid (SSc −12.4% versus control −20.9%; P < 0.0001) segments in patients with SSc suggestive of diminished systolic contractility in these regions (Table 2). In contrast, patients with SSc had increased RVLSS in the base (SSc −32.2% versus control −23%; P < 0.0001). The base–apex and midapex difference was significantly greater in SSc patients than in controls (P < 0.0001 and P < 0.0001, respectively, for interaction). Among controls, regional differences in RVLS were detected in the basal and mid segment relative to the apex (−3.8 and −6.2, respectively; P < 0.0001) but not in the midapex comparison (Table 3). In contrast, SSc patients had significant regional differences throughout (base–apex difference −23.6, midapex difference −3.9; both P < 0.0001), especially when comparing the basal with apical segments. Figure 2 demonstrates regional strain curves from the 6 segments of the RV (basal, mid, and apical free wall and apical, mid, and basal interventricular septum) from a representative control (Figure 2A), and a patient with SSc (Figure 2B). In the control patient, there is evidence of synchronous systolic shortening and diastolic lengthening of each of the 6 RV segments throughout the cardiac cycle. In the SSc patient,
there is hyperkinesis of the basal segment (red strain curve), whereas the mid and the apical segments (cyan and yellow strain curves, respectively) are hypokinetic in systole. Although included in the graphical representation, interven- tricular strain was not assessed in this study.

SSc patients had higher mean RVSP than controls (SSc 31.4 versus control 22.6 mm Hg; \( P = 0.0001 \)). There were 38 (27.5%) SSc patients with RVSP >36 mm Hg. When restricting our analysis to those with an RVSP <35 mm Hg, however, we found that the differences observed in regional strain between SSc patients and controls were unchanged (data not shown).

**Examination of SSc-Specific Characteristics That May Associate With Abnormal Regional RV Strain**

We were interested in identifying SSc phenotypic characteristics that may associate with abnormal regional strain. We defined abnormal strain as being present if the base–apex RVLSS difference was >2 SDs from the mean base–apex RVLSS difference for controls. Based on this definition, 81 SSc patients (58.7%) had evidence of abnormal strain. When comparing SSc patients with abnormal strain to those without, there were no statistically significant differences in age, race, smoking status, cutaneous subtype, SSc disease duration, autoantibody status, history of myopathy, vasodilator medication use, extent of dyspnea (examined by MRC, Borg, and UCSD dyspnea scales), forced vital capacity, diffusion lung capacity for CO, RVSP, FAC, or PVR.

**Inter- and Intraobserver Variability of RV Longitudinal Strain Parameters**

Intraobserver agreement was excellent (interclass correlation coefficient 0.981, 0.984, and 0.970 for RVLSS of the base,
In the present study, we utilized novel echocardiographic techniques to detect global and regional RV systolic dysfunction in a large, well-characterized cohort of SSc patients. Our study demonstrated that standard linear measurements of RV chamber size were not clinically significantly different between SSc patients and controls; however, speckle-derived strain revealed a heterogenous pattern of regional heart strain in SSc. In this study, we defined hyperkinesis as a more negative number than expected for an ROI (higher absolute value), representative of enhanced deformation and contractility along the longitudinal axis. Hypokinesis, on the contrary, was defined as a less negative number than expected for a ROI (lower absolute value) or diminished deformation along the longitudinal axis. The pattern of basal hyperkinesis and hypokinesis of the apical and mid segments in SSc patients suggests occult myocardial dysfunction segmental changes in strain that is not appreciable by standard echocardiographic imaging and was observed in patients with SSc even after restricting our analysis to patients with an RVSP < 35 mm Hg. Our study demonstrates a diminishing gradation in systolic shortening of the RV free wall from base to apex in a large cohort of SSc patients that was observed independent of pulmonary pressures.

Despite well-described limitations, 2D echocardiography is the mainstay of serial monitoring of SSc patients given its high specificity and high positive predictive value in the evaluation for PAH.23,24 Although standard 2D measures of RV size and function are able to identify grossly apparent chamber dilatation, depressed systolic function, and regional wall motion abnormalities, there may be subtle changes in global and regional systolic function not detectable by conventional measures. Our study demonstrates RV dysfunction that is readily detected with a method of strain analysis used in conjunction with conventional 2D imaging that has the potential to provide additional insight into the course of scleroderma heart disease.

There has been extensive investigation correlating standard echocardiographic measures with morbidity and mortality in patients with SSc. Recent studies in small selected cohorts have suggested that global speckle-based strain of both the right and LVs is reduced in patients with SSc and is associated with morbidity, especially in patients with comitant elevation in pulmonary pressures.5,24–29 Our study complements and significantly adds to the body of data that occult changes in RV myocardial contractility occurs in SSc regardless of pulmonary pressures and that these changes occur in a specific regional pattern.

Table 2. Conventional Two-Dimensional Echocardiographic Parameters and Speckle-Based Strain Parameters for Systemic Sclerosis Patients and Non–Systemic Sclerosis Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scleroderma (n=138)</th>
<th>Controls (n=40)</th>
<th>P Value</th>
<th>Normal Values</th>
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<tbody>
<tr>
<td>Conventional 2D measures</td>
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</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>58.5±6.3</td>
<td>62.9±5.9</td>
<td>0.0001*</td>
<td>≥5514</td>
</tr>
<tr>
<td>Mitral E/A</td>
<td>1.1±0.38</td>
<td>1.4±0.22</td>
<td>0.96</td>
<td>1.28±0.2518</td>
</tr>
<tr>
<td>LV septal E/e′</td>
<td>11.4±4.3</td>
<td>9.4±2.8</td>
<td>0.01</td>
<td>≥1514</td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>48.9±10.9</td>
<td>55±10.7</td>
<td>0.002*</td>
<td>&gt;3515</td>
</tr>
<tr>
<td>TAPSE, cm</td>
<td>2.16±0.47, N=107</td>
<td>2.25±0.40, N=38</td>
<td>0.307</td>
<td>&gt;1.613</td>
</tr>
<tr>
<td>PVR, Wood Units</td>
<td>1.48±0.45</td>
<td>1.24±0.26</td>
<td>0.002*</td>
<td>&gt;315</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>31.4±13.3</td>
<td>22.6±4.4</td>
<td>0.0001*</td>
<td>≤3515</td>
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<tr>
<td>Strain parameters</td>
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<tr>
<td>Basal RVLSS, %</td>
<td>−32.2±13.5</td>
<td>−23.3±4.5</td>
<td>0.0001*</td>
<td>−25±622</td>
</tr>
<tr>
<td>Midventricular RVLSS, %</td>
<td>−12.4±7.6</td>
<td>−20.9±3.2</td>
<td>&lt;0.0001*</td>
<td>−27±522</td>
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<tr>
<td>Apical RVLSS, %</td>
<td>−8.5±6.7</td>
<td>−17.1±4.1</td>
<td>&lt;0.0001*</td>
<td>−26±622</td>
</tr>
<tr>
<td>Global RVLSS, %</td>
<td>−17.7±5.9</td>
<td>−20.4±2.4</td>
<td>0.005*</td>
<td>−26±422</td>
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All parameters presented as mean±SD. Normal values based on American Society of Echocardiography Guidelines14,15 and reference values of RV strain22 are provided to distinguish between statistically significant and clinically significant differences. FAC indicates fractional area change; LV, left ventricle; RV, right ventricle; RVLSS, right ventricular longitudinal systolic strain; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; and PVR, pulmonary vascular resistance.
Right atrial and RV chamber enlargement in SSc is directly related to onset of heart failure symptoms as well as mortality.\textsuperscript{1,6,23} Measures of RV systolic function such as TAPSE, tissue Doppler of the tricuspid annulus S', RV FAC, and Tei Index all correlate with decreased survival.\textsuperscript{5,24,26-29} Noninvasive measures of PVR have been also been shown to predict PAH in SSc and correlate with diminished 6-minute walk test and diffusion lung capacity for CO.\textsuperscript{28}

In fact, volumetric measures of RV chamber size and function may be abnormal in SSc patients even before the elevation in RVSP.\textsuperscript{30,31} Early studies utilizing tissue Doppler index have demonstrated global reduction of RV strain abnormalities in small cohorts of SSc patients with interstitial lung disease and, similar to our study, occur independent of RVSP.\textsuperscript{32-35} Studies utilizing tissue Doppler index–based methods have also demonstrated that abnormalities in RV and LV systolic and diastolic function can be followed prospectively and correlate with disease duration and with elevation in RVSP.\textsuperscript{15}

Given the known association of longitudinal strain and increase in afterload, we also considered the possibility that increases in RV afterload may contribute to our findings of heterogenous RV free wall contractility patterns in SSc patients. It has been well described that the normal ventricular

<table>
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<th>Parameter</th>
<th>β Estimate</th>
<th>95% CI</th>
<th>P Value</th>
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<td>Scleroderma stratum</td>
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<tr>
<td>Intercept</td>
<td>−8.5</td>
<td>−9.6 to −7.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mid vs apex</td>
<td>−3.9</td>
<td>−5.1 to −2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Base vs apex</td>
<td>−23.6</td>
<td>−26.3 to −20.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Control stratum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−17.1</td>
<td>−18.3 to −15.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mid vs apex</td>
<td>−3.8</td>
<td>−4.9 to −2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Base vs apex</td>
<td>−6.2</td>
<td>−8.2 to −4.2</td>
<td>&lt;0.0001</td>
</tr>
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</table>

Figure 2. A, Normal right ventricular longitudinal systolic strain in a non-systemic sclerosis control. B, Abnormal right ventricular longitudinal systolic strain in a patient with systemic sclerosis.
response to increasing RV afterload is a concomitant increase in RV contractility, either by heterometric or homometric adaptation.\textsuperscript{36} In a normal RV, these adaptive responses will occur until the afterload increases beyond a certain pathological threshold, after which, the RV can no longer match its load, and the RV–PA unit becomes uncoupled resulting in decline in systolic function.\textsuperscript{36} Given this hemodynamic rationale, measures of RV contractility such as FAC, TAPSE, and RVLSS should be unchanged or arguably even greater in situations of modestly increased afterload. In our SSc population, there was no pathological increase in afterload, with average PVR 1.48±0.45 WU by noninvasive estimation (Table 2). To further analyze the effect of small increases in RV afterload on our findings, we performed additional analysis in those patients who had PVR>1.5 WU and found that there were no significant differences of conventional 2D measures of RV systolic function (FAC or TAPSE) between groups. Segmental and global RVLSS differences between SSc patients and controls were also unchanged when restricting our analysis to PVR>1.5 WU.

There have been no studies to date that demonstrate whether there is a distinct echocardiographic pattern defining the segmental nature of RV dysfunction that accompanies SSc. Although patchy myocardial fibrosis can be seen by cardiac magnetic resonance imaging and is related to disease duration and overt RV dysfunction, current recommended echocardiographic measures may not detect these subtle changes. RV FAC and TAPSE provide global assessment of systolic function but may not detail whether there are regional differences in contractility.\textsuperscript{4,28} Furthermore, image and parameter acquisition by 2D assessment is frequently limited by appropriate beam alignment and tend to be sonographer dependent, with great variability in interobserver interpretation.\textsuperscript{35}

Our study demonstrates RV dysfunction that is readily detected with a method of strain analysis used in conjunction with conventional 2D imaging has the potential to provide additional insight into the course of scleroderma heart disease. Based on our findings, we hypothesize that before the development of overt RV failure and PAH, there are subclinical changes in regional RV strain that are a precursor to impending myocardial dysfunction. Hypokinesis of the RV apex may not be appreciable by 2D visualization, and therefore may also not be captured by TAPSE, which measures the systolic excursion of the tricuspid annulus and basal RV segments toward the apex. Our study detected differences in RV apical function that may have important implications in predicting disease course.

Previous findings from our group utilizing multibeat pressure volume analysis have demonstrated RV contractile dysfunction and RV–pulmonary vascular uncoupling in SSc patients with PAH compared with patients with idiopathic PAH.\textsuperscript{37} Importantly, these differences were not detected by magnetic resonance imaging or standard 2D echocardiographic measures. The techniques used in this study, however, are invasive, require sophisticated equipment, and not practical for routine clinical use. STE, on the contrary, can be utilized in conjunction with conventional 2D echocardiogram and provide reproducible and reliable information in regards to global and regional RV contractility.

Furthermore, there has been limited information in regards to global and regional abnormalities of RV systolic function in regards to phenotypic subsets of SSc (ie, diffuse versus limited cutaneous disease or in unique autoantibody groups) as most studies to date have been performed in small cohorts of all-comers with SSc. Our study, performed in a large well--characterized SSc cohort, suggests that regional abnormalities are present in all subtypes without clear distinction. Prospective studies are required to define whether abnormalities in RVLSS predict development of PAH and mortality and whether early intervention with vasodilator or immunosuppressive therapies can improve outcomes in patients with abnormal strain.

Our study had several limitations. First, the ability to perform speckle-based strain is largely dependent on 2D image quality. As this was a retrospective study, frame rates that were used during original clinically indicated acquisition of 2D images tended to result in artificial strain rates when off-line strain analysis was performed. It is well recognized that, although STE adds incremental clinical value over conventional methods alone, standardization of postprocessing is needed, especially given vendor-specific variability in strain measures. These inherent differences may, therefore, limit the reproducibility of our study results.\textsuperscript{38,39} Because 2D tissue Doppler and tricuspid inflow patterns are not routinely performed as a part of our protocol for clinically indicated echocardiograms, S′ as a surrogate of RV systolic function was not available for analysis. Similarly, pulmonary acceleration time, a noninvasive surrogate of PAH, was also not available for analysis. Diastolic function of the RV was not assessed on the present study. Another potential limitation of our study was that RVLSS was not followed in serial observations to determine whether this observed pattern of RV myocardial dysfunction was of clinical consequence and impacts morbidity and mortality, which we propose as a future study.

In summary, speckle-based strain revealed global and regional differences in RV function in patients with SSc that was not fully detected by conventional 2D measures. We identified a specific heterogenous pattern of RV dysfunction in SSc patients where there is hyperkinesis of the base and hypokinesis of the apical and mid segments, which remained significant after restricting our analysis to patients with RVSP<35 mmHg. These findings suggest occult RV myocardial disease that may precede the development of PAH and may serve as an important target for vasodilator-guided therapies.

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Disclosures
None.
1. Mukherjee et al. Right Ventricular Strain in Systemic Sclerosis


CLINICAL PERSPECTIVE

In this study, we utilized novel speckle-tracking echocardiographic techniques for the noninvasive detection of global and regional systolic right ventricular (RV) dysfunction before the development of overt chamber dilatation, dysfunction, and clinical symptoms of right heart failure and pulmonary hypertension in a large cohort of systemic sclerosis patients. We found that standard linear measurements of RV chamber size and function were not clinically different between systemic sclerosis patients and controls; however, novel speckle-derived strain revealed a heterogeneous pattern of regional heart strain in systemic sclerosis in which there was hyperkinesis of the RV base and hypokinesis of the apical and mid segments. This pattern suggested the presence of occult myocardial dysfunction with segmental changes in RV strain that is not appreciable by standard echocardiographic imaging. Despite frequent echocardiographic monitoring, significant RV dysfunction and pulmonary hypertension are commonly undetected until the patient is symptomatic late in the course of the disease process. Early detection of subclinical RV dysfunction utilizing these techniques before the onset of pulmonary hypertension may serve as a future therapeutic goal for earlier initiation of vasodilator and immunomodulating therapies and, therefore, has numerous clinical implications in the morbidity and mortality of systemic sclerosis patients.
Unique Abnormalities in Right Ventricular Longitudinal Strain in Systemic Sclerosis Patients
Monica Mukherjee, Shang-En Chung, Von Khue Ton, Ryan J. Tedford, Laura K. Hummers, Fredrick M. Wigley, Theodore P. Abraham and Ami A. Shah

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SUPPLEMENTAL TABLES AND FIGURES.

SUPPLEMENT TABLE 1. CONVENTIONAL 2D MEASURES OF LINEAR RIGHT VENTRICULAR DIMENSION

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scleroderma N=138</th>
<th>Controls N=40</th>
<th>p-value</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional 2D Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Area (cm²)</td>
<td>14.7 ± 3.7</td>
<td>13.0 ± 2.7</td>
<td>0.01</td>
<td>&gt;18 \textsuperscript{1}</td>
</tr>
<tr>
<td>RV Internal Dimension Diastole (cm)</td>
<td>3.10 ± 0.49</td>
<td>2.75 ± 0.21</td>
<td>&lt;0.0001</td>
<td>&lt;3.5 \textsuperscript{1}</td>
</tr>
<tr>
<td>RV Base (cm)</td>
<td>3.57 ± 0.64</td>
<td>3.26 ± 0.42</td>
<td>0.005</td>
<td>&gt;4.2 \textsuperscript{1}</td>
</tr>
<tr>
<td>RV Length (cm)</td>
<td>7.70 ± 0.93</td>
<td>7.17 ± 0.62</td>
<td>0.0009</td>
<td>&gt;8.6 \textsuperscript{1}</td>
</tr>
<tr>
<td>RV Outflow Tract (cm)</td>
<td>2.44 ± 0.42</td>
<td>2.11 ± 0.34</td>
<td>&lt;0.0001</td>
<td>&gt;2.6 \textsuperscript{1}</td>
</tr>
</tbody>
</table>

**Supplement Table 1**: Conventional 2D echocardiographic measures of linear right ventricular dimension between systemic sclerosis patients and non-SSc controls. Normal values based on ASE Guidelines\textsuperscript{1} are provided to distinguish between statistically significant and clinically significant differences.
SUPPLEMENTAL FIGURE 1. FRACTIONAL AREA CHANGE IN SYSTEMIC SCLEROSIS VERSUS NORMAL CONTROLS.

Supplement Figure 1: Similar distributions of fractional area change (FAC) are shown between SSc patients and controls. While RV FAC (%) was statistically different between the two groups (p=0.002), values were within normal clinical limits for both SSc and controls (48.9 ± 10.9 versus 55 ± 10.7).
Supplemental Figure 2: Similar distributions of tricuspid annular plane systolic excursion (TAPSE) are shown between SSc patients and controls. On average, TAPSE was within normal clinical limits between SSc and controls, and did not differ between groups (2.16 ± 0.47 versus 2.25 ± 0.40, P=0.307).
SUPPLEMENTAL REFERENCES.