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Essential Hypertension Worsens Left Ventricular Contractility in Systemic Sclerosis

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ABSTRACT. ***Objective.*** Primary cardiac involvement in systemic sclerosis (SSc) is prevalent and morbid; however, the influence of traditional cardiovascular (CV) risk factors, such as essential hypertension (HTN), are unclear. In the present study, we sought to understand the effects of HTN on left ventricular (LV) contractility in patients with SSc using echocardiographic speckle-derived global longitudinal strain (GLS).

Methods. Fifty-six SSc patients with HTN (SSc+HTN+) and 82 SSc patients without HTN (SSc+ HTN–) were compared with 40 non-SSc controls with HTN (SSc–HTN+) and 40 non-SSc controls without HTN (SSc–HTN–), matched by age and sex. All HTN patients were on stable antihypertensive therapies. Echocardiographic measures included LV (LV) ejection fraction (LVEF), left atrial volume index (LAVI), and LV diastolic function. LV contractility was assessed by GLS, averaged across the 18 LV segments.

Results. Patients with SSc had diminished GLS regardless of HTN status when compared to both control groups, despite normal LVEF ($P < 0.001$). SSc+HTN+ had the highest prevalence of diastolic dysfunction, with significantly higher septal E/e′, a marker of LV filling pressures ($P < 0.05$), as well as the largest reduction in GLS compared to SSc+HTN– and both control groups.

Conclusion. Speckle-derived strain revealed diminished LV contractility in patients with SSc, despite normal LVEF. SSc+HTN+ had more prominent reductions in GLS associated with evidence of LV remodeling and worsened diastolic function. Our findings demonstrate the presence of subclinical LV contractile dysfunction in SSc that is further exacerbated by concomitant HTN, thereby identifying HTN as an important modifiable CV risk factor that should be managed aggressively in this at-risk population.

Key Indexing Terms: echocardiography, essential hypertension, global longitudinal strain, systemic sclerosis

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Systemic sclerosis (SSc) is a complex heterogeneous autoimmune disease characterized by widespread fibrosis of multiple organ systems, prominent vasculopathy, and dysregulation of the immune system.[1] Cardiac involvement is highly prevalent in SSc, ranging from 10% to 30%, although it is largely dependent on the diagnostic technique employed.[1,2,3,4] The presence of clinically overt cardiac involvement in SSc is associated with a 2.8-fold increased risk of mortality,[5] underscoring the importance of using clinical suspicion to guide the appropriate application of screening and diagnostic tools before symptoms develop.[4] With increasing utilization of noninvasive imaging techniques, subclinical cardiac involvement has been estimated as high as 70% in SSc.[6]

Although cardiopulmonary complications from pulmonary arterial hypertension (PAH) are the leading cause of mortality in SSc,[7] left ventricular (LV) diastolic dysfunction is common in patients with SSc and may reflect myocardial involvement secondary to microvascular coronary ischemia, myocardial inflammation, and/or myocardial fibrosis.[1,8] In the general population, diastolic dysfunction is estimated at 21% and related to common risk factors of age, essential hypertension (HTN), diabetes, and coronary artery disease.[9] Patients with SSc may also be affected by these traditional cardiovascular (CV) comorbidities in addition to disease-specific risk factors.[10] Diastolic function may appear before clinical symptoms of heart failure, regardless of SSc disease subtype,[11] and is an important and

highly prevalent early manifestation of cardiac involvement in SSc.[12] In SSc, worsening diastolic dysfunction is associated with older age, SSc disease duration, diffuse cutaneous subtype, and presence of CV risk factors such as essential hypertension and ischemic heart disease.[10]

Despite frequent serial clinical examination and echocardiographic monitoring, heart disease in SSc is often underdiagnosed until late in the disease course when clinically symptomatic heart failure develops.[13] Speckle tracking-derived longitudinal systolic strain is a relatively new imaging modality used in conjunction with conventional 2D echocardiography that is not user- or Doppler angle-dependent. Utilizing a software-derived algorithm, speckle-derived strain is able to provide a noninvasive estimation of regional and global myocardial contractile function.[14] The analysis of longitudinal strain provides important additional information on regional and global contractility that is not detectable by standard measures alone.[14] LV global longitudinal strain (GLS) has been extensively studied over the past decade in a wide variety of clinical settings and is thought to be a more sensitive measure of contractile function when compared to LV ejection fraction (LVEF), additionally providing prognostic information.[15] Speckle-derived strain has already shown its relevance in the detection of regional heterogeneity of right ventricular (RV) contractility in SSc,[16] in prediction of mortality in SSc patients with PAH,[17] and in following improvement in RV function after initiation of PAH-directed therapies in SSc.[18] Investigation of heart disease in SSc, however, has largely focused on RV failure, despite the fact that early myocardial disease in SSc may manifest as LV diastolic dysfunction. Further, the effects of traditional CV risk factors such as HTN on the myocardium in SSc have not been well defined. In the present study, we sought to understand the ability of novel speckle-based strain techniques in detecting early myocardial alterations in normotensive patients with SSc, and to explore the additional effects of HTN on LV myocardial contractility in this at-risk population. Preliminary results from this study have been previously reported in abstract form.[19]

METHODS

Study population. In this prospective single-center study, patients classified with SSc according to the American College of Rheumatology/European League Against Rheumatism criteria,[20] who enrolled in the institutional review board–approved Johns Hopkins Scleroderma Center Research Registry (IRB00226995), were studied. All patients enrolled in the Johns Hopkins Scleroderma Center Research Registry have provided written and informed consent to have their deidentified clinical data utilized for investigation. Center standard practice includes annual echocardiograms to screen for the development of PAH, regardless of clinical symptoms, and therefore patients with SSc who had a clinically indicated echocardiogram performed at the Johns Hopkins Bayview Medical Center were eligible for inclusion in this cross-sectional analysis. If multiple echocardiograms were performed on the same patient, the first study performed with the highest technical quality was chosen for analysis. Of the 162 patients with SSc who met these inclusion criteria, 138 (85%) patients had adequate 2D image quality to allow for complete visualization of the LV chamber and strain mapping.

A cohort of age- and sex-matched non-SSc controls, who underwent clinically indicated echocardiograms during the study period, was also evaluated. 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 (e.g., sarcoidosis, SSc, and connective tissue disease); evidence of intracardiac shunting; and evidence of congenital heart disease.

Control subjects underwent extensive chart review to establish 2 non-SSc control groups: non-SSc patients without HTN (SSc–HTN–) and non-SSc patients with HTN (SSc–HTN+). Additional exclusion criteria for the first control group (SSc–HTN–) included HTN, diabetes mellitus, atherosclerotic CV disease, atrial fibrillation, and any known history of arrhythmia, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, or sleep apnea. The second control group (SSc–HTN+), however, were not excluded based on these additional features. All control patients had to have echocardiographic study quality that was technically adequate to allow for off-line strain analysis.

A cardiologist (MM), 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 (MM, VM), again blinded to disease status.

Clinical assessment. Demographic data, disease characteristics, smoking history, medication exposure, history of CV and pulmonary comorbidities, pulmonary function testing, and clinically obtained autoantibody test results were obtained from the SSc database and clinical records closest to the time of echocardiography. The primary care physician or rheumatologist conducted an extensive chart review and a diagnosis of HTN was based on a documented history of HTN, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or treatment with any antihypertensive medication if not prescribed for the treatment of Raynaud phenomenon (RP). Blood pressure at the time of echocardiogram was also obtained. 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. For the non-SSc control group, individuals with HTN were identified based on a documented history of HTN, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg based on comprehensive chart review.

Echocardiographic analysis. Echocardiographic examinations were performed at a single clinical site using a Philips iE33 ultrasound machine (Philips Healthcare), with subjects in the left lateral decubitus position. Images were obtained with a 3.4-MHz sector transducer. Standard parasternal, apical, and subxiphoid windows were utilized in order to obtain 2D imaging of cardiac chambers, as well as color, pulsed- and continuous-wave Doppler measurements, according to American Society of Echocardiography (ASE) guidelines.[21] 2D-directed methods were used to obtain linear measurements of LV chamber size and wall thickness from the parasternal long-axis view, and then used to calculate LV mass.[21] LVEF was calculated according to the modified Simpson's rule using the apical 2- and 4-chamber views, with normal defined as ≥ 55%. Left atrial volume index (LAVI) was obtained as the average of volumetric measurement of the left atrium from the 2- and 4-chamber views and indexed to body surface area (BSA). Evaluation of LV diastolic function was based on pulsed-wave Doppler imaging of mitral valve inflow, measuring peak early diastolic velocity (E) and peak late diastolic velocity (A) to calculate the E/A ratio and the E-wave deceleration. Using tissue Doppler imaging, the early diastolic velocity (e′) was measured at the level of the interventricular basal segment (septal e′). The septal E/e′ ratio was used to estimate LV filling pressures.[22] In accordance with the ASE guidelines, the diagnosis of diastolic dysfunction was defined by the presence of > 2 of the following abnormal cutoff values for these 4 recommended variables: septal e′ velocity < 7 cm/s, septal E/e′ ratio > 15,

LAVI > 4 mL/m^2, and peak tricuspid regurgitation velocity > 2.8 m/s. LV diastolic function was defined as normal if > 2 of the available variables did not meet the cut-off values for identifying abnormal function. The study was considered inconclusive if 2 of the variables did not meet the cut-off values.[22]

Functional assessment of the RV was performed by analyzing M-mode–derived tricuspid annular systolic plane excursion (TAPSE). In the absence of RV outflow tract obstruction and tricuspid or pulmonic stenosis, the tricuspid regurgitant velocity was used to estimate RV systolic pressure (RVSP), utilizing the modified Bernoulli equation and adding estimated right atrial pressure based on inferior vena cava dimension and collapsibility with sniff.[21,22,23] Echocardiographic analysis was performed using Synapse Cardiovascular software (V4.0.8; Fujifilm Medical Systems) for conventional analysis of 2D images.

For the assessment of peak LV longitudinal systolic strain, standard 2D cine-loops from apical 4-chamber view (inferoseptal and anterolateral walls), 2-chamber view (anterior and inferior walls), and 3-chamber view (inferolateral and anteroseptal walls) were obtained and stored digitally for offline speckle-tracking analysis, using a commercially available vendor-independent strain software (Epsilon, EchoInsight). Each LV wall was divided into 3 segments (basal, midventricular, and apical) to construct an 18-segment model. Peak systolic longitudinal strain of the LV for each segment was obtained by tracing the LV chamber endocardial borders in end-systolic still frames. Frame rates were obtained between 50–70 fps. 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 region of interest (ROI) relative to its original length, and, by convention, is expressed as a negative percentage.[24,25] Worsening strain refers to a less negative number (a lower absolute value) than expected for an ROI or diminished deformation along the longitudinal axis. Improved strain, on the contrary, refers to a more negative number (a higher absolute value) than expected for an ROI or enhanced deformation along the longitudinal axis. Peak GLS was calculated as the average value of longitudinal systolic strain for the 18 LV segments.[25]

Statistical analysis. Data are presented as mean ± SD, median and IQR, absolute numbers, or percentage, as appropriate. The independent unpaired *t* test for parametric data and Wilcoxon-Mann-Whitney test for nonparametric data were used to compare continuous variables between patients with SSc and control subjects, while the chi-square test and Fisher exact test were used to compare categorical data. Multivariable linear regression analysis was performed to evaluate the effect of comorbidities and therapies on GLS. The intra- and interobserver variability was calculated by means of intraclass correlation coefficient. Statistical analysis was performed with the software SPSS for Windows (version 22.0; IBM Corp.). Differences between groups were considered statistically significant if the *P* value was < 0.05.

RESULTS

Clinical characteristics. Our SSc cohort consisted of 138 patients who were mostly female (87.7%), with mean age of 54.3 ± 12.6 years. Among them, 83 patients had limited cutaneous SSc, whereas 55 had diffuse cutaneous SSc. A majority of our SSc cohort was positive for antinuclear antibodies. The median SSc disease duration was 13.5 (IQR 6.7–22.4) years. Control patients were intentionally frequency matched by age and sex, and, by inclusion criteria, control patients either did not have any known CV and/or pulmonary disease (SSc–HTN–) or had HTN with or without other CV risk factors (e.g., diabetes, hypercholesterolemia, or atrial fibrillation; SSc–HTN+).

We further dichotomized our SSc cohort by presence or absence of HTN or other CV risk factors, defined as SSC+HTN– and SSc+HTN+, respectively. There were 82 SSc+HTN– patients and 56 SSc+HTN+ patients. SSc+HTN+ patients were older and more often Black in comparison to SSc+HTN– patients (Table 1). There were no significant differences in terms of disease duration, SSc subtype, and autoantibody status between SSc groups. There were also no significant differences in terms of age and sex, given our frequency-matched study design, or smoking status between both non-HTN groups (SSc+HTN– and SSc–HTN–) and HTN groups (SSc+HTN+ and SSC–HTN+). SSc+HTN– patients tended to have lower BMI and BSA in comparison to SSc–HTN– patients (Table 1).

There was no significant difference in terms of CV comorbidities between HTN groups (SSc–HTN+ and SSc+HTN+). SSc patients with HTN were more frequently treated with calcium channel blockers (as expected, since these drugs are often prescribed in SSc patients also for the treatment of RP). There was a higher prevalence of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) treatment in the SSc patients with HTN (SSc+HTN+) compared to non-SSc controls with HTN (SSc–HTN+), whereas no significant differences were observed in terms of treatment with diuretics and beta blockers.

SSc patients without HTN had decreased LV systolic function and GLS relative to age- and sex-matched control patients without HTN.

In our initial analysis, we compared SSc patients without HTN (SSc+HTN–) to age- and sex-matched healthy controls without known cardiopulmonary disease (SSc–HTN–). While LVEF was within the normal range across groups, SSc+HTN– had lower LVEF compared to SSc–HTN– by statistical significance ($P < 0.001$; Table 2). We also found that SSc+HTN– had lower GLS when compared to SSc–HTN– ($P < 0.001$), mostly due to diminished regional strain of the basal and midventricular LV regional segments (Figure 1). Diastolic parameters of mitral inflow such as E/e′, as a measure of LV filling pressures, and LAVI were similar between both SSc+HTN– and SSc–HTN– groups.

SSc patients with HTN have worse parameters of diastolic function and decreased GLS, relative to age- and sex-matched control patients with HTN.

We then compared SSc patients with HTN (SSc+HTN+) to age- and sex-matched non-SSc controls with HTN (SSc–HTN+). Whereas LVEF was similar between HTN groups, SSc+HTN+ patients had lower GLS in comparison to the control group with HTN ($P < 0.01$; Table 2, Figure 1). We also found that diastolic parameters were significantly different. In particular, SSc+HTN+ patients had a lower mitral E/A ratio ($P < 0.05$), mainly because of a lower early diastolic E-wave velocity ($P = 0.06$) in comparison to SSc–HTN+ patients. E′septal wave velocity was significantly reduced in SSc+HTN+ patients as well, when compared to SSc–HTN+ patients ($P = 0.01$), with a borderline significant increase in E/e′ septal ratio ($P = 0.07$). The SSc group with HTN had significantly higher LAVI (35.1 ± 10.9 mL/m^2) when compared to sex-matched control patients with HTN ($P = 0.045$).

Multivariable linear regression analysis revealed that there was

Table 1. Characteristics of SSc vs non-SSc patients with and without HTN.

	SSc–HTN–, n = 40	SSc+HTN–, n = 82	P^a	SSc–HTN+, n = 40	SSc+HTN+, n = 56	P^b	P^c
Age, yrs, mean ± SD	53.5 ± 14.0	51.5 ± 13.1	NS	54.2 ± 16.9	58.5 ± 10.5	NS	0.001
Women, n (%)	35 (87.7)	75 (91.5)	NS	33 (82.5)	46 (82.1)	NS	NS
Race, n (%)							
White	33 (82.5)	66 (81.7)	NS	27 (67.5)	37 (64)	NS	0.007
Black	4 (10)	10 (12.2)		11 (27.5)	16 (32)		
Other	3 (7.5)	6 (7.3)		2 (5)	1 (2)		
Ever smoker, n (%)	15 (37.5)	30 (36.6)	NS	14 (35)	21 (37.5)	NS	NS
Diabetes mellitus, n (%)	0 (0)	0 (0)	–	7 (17.5)	9 (16.1)	NS	0.007
Atrial fibrillation, n (%)	0 (0)	0 (0)	–	2 (5)	3 (5.4)	NS	NS
Hypercholesterolemia, n (%)	0 (0)	0 (0)	–	16 (40)	25 (44.6)	NS	< 0.0001
Anti-HTN medications, n (%)							
Beta blocker	NA	NA	NA	12 (30)	14 (28)	NS	NA
Calcium channel blocker	NA	NA	NA	8 (20)	48 (85.7)	< 0.0001	NA
ACEi/ARB	NA	NA	NA	10 (25)	44 (78.6)	< 0.0001	NA
Diuretics	NA	NA	NA	10 (25)	20 (38)	NS	NA
BMI, kg/m^2, mean ± SD	28.1 ± 7.2	25.0 ± 5.6	< 0.05	27.8 ± 5.7	27.4 ± 5.8	NS	0.02
BSA, m^2, mean ± SD	1.82 ± 0.17	1.73 ± 0.21	< 0.05	1.98 ± 0.47	1.82 ± 0.24	0.05	0.01
SSc disease duration, yrs, mean ± SD	NA	15.7 ± 10.7	NA	NA	16.5 ± 11.9	NA	NS
SSc subtype, n (%)							
Limited cutaneous	NA	50 (61.0)	NA	NA	33 (58.9)	NA	NS
Diffuse cutaneous	NA	32 (39.0)		NA	23 (41.1)		
Autoantibody status, n							
ANA, n = 138	NA	82	NA	NA	53	NA	NA
ACA, n = 137	NA	26	NA	NA	14	NA	NS
Topoisomerase 1, n = 136	NA	26	NA	NA	12	NA	NS
RNAPIII, n = 115	NA	12	NA	NA	7	NA	NS
Pulmonary function data, % predicted ± SD							
FVC% predicted, n = 134	NA	84.1 ± 16.6	NA	NA	80.3 ± 21.0	NA	NS
DLCO% predicted, n = 132	NA	83.6 ± 24.4	NA	NA	78.0 ± 26.7	NA	NS

Groups are defined as non-SSc controls without HTN (SSc–HTN–), SSc patients without HTN (SSc+HTN–), non-SSc controls with HTN (SSc–HTN+), and SSc patients with HTN (SSc+HTN+). Data are expressed as mean ± SD, absolute number, percentage, or median, if specified. Independent unpaired *t* test and Wilcoxon-Mann-Whitney test for nonparametric data were used to compare continuous variables between SSc patients and control subjects, while chi-square test and Fisher exact test were used to compare categorical data. A cut-off *P* value < 0.05 was considered statistically significant. [a] *P* value: comparison between SSc–HTN– and SSc+HTN–. [b] *P* value: comparison between SSc–HTN+ and SSc+HTN+. [c] *P* value: comparison between SSc+HTN– and SSc+HTN+. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor type 1 blocker; ACA: anticentromere antibody; ANA: antinuclear antibody; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; HTN: systemic hypertension; NS: not significant; NA: not available/not applicable; RNAPIII: RNA polymerase III; SSc: systemic sclerosis.

no significant effect of different antihypertensive medications on GLS, and that the presence of HTN was the only significant contributor to alterations in GLS in patients with SSc (Table 3). Differences in GLS among groups were not affected by loading conditions as estimated by systolic blood pressure (β 0.041, 95% CI –0.012 to 0.023, $P = 0.54$).

Intra- and interobserver variability and power calculation. Intra- and interobserver variability for GLS was excellent, with ICC of 0.95 (95% CI 0.86–0.98) and 0.92 (95% CI 0.70–0.98), respectively. Sample size power calculation revealed a power of 0.86 (data not shown).

DISCUSSION

To our knowledge, our study is the first to demonstrate the effects of systemic HTN on LV contractile function in SSc patients utilizing innovative speckle-based strain techniques. Our enriched study design evaluated 4 well-characterized groups, including SSc patients with HTN (SSc+HTN+), SSc patients without HTN (SSc+HTN–), non-SSc patients with HTN (SSc–HTN+), and non-SSc patients without HTN (SSc–HTN–). Despite normal LVEF by conventional echo analysis, we observed the presence of regional and global abnormalities in LV myocardial contractility in SSc patients that were not detected by conventional echocardiographic techniques alone. Specifically, we found a reduction in global LV contractility, mainly due to reduction in regional basal and midventricular strain across both SSc groups. The significant impairment of GLS in SSc patients, even in the absence of HTN, indicates that SSc disease is an important factor in the presence of regional and global myocardial contractility abnormalities. Although the difference between SSc and controls (both with HTN and without HTN) may seem small, this variation represents at least a 10% difference in absolute value of strain, which could be clinically important.[26] Our results are in agreement with

Table 2. Standard and speckle-tracking–derived echocardiographic characteristics for SSc patients and non-SSc controls according to the presence of systemic HTN.

	SSc–HTN–, n = 40	SSc+HTN–, n = 82	P^a	SSc–HTN+, n = 40	SSc+HTN+, n = 56	P^b	P^c
Conventional echocardiographic measures							
LV ejection fraction, %	62.9 ± 5.9	58.3 ± 6.3	< 0.001	59.4 ± 4.3	58.7 ± 6.3	NS	NS
E wave, cm/s	79.0 ± 15.8	81.9 ± 18.8	NS	89.1 ± 23.8	79.7 ± 22.9	0.06	NS
A wave, cm/s	70.1 ± 17.3	72.1 ± 19.9	NS	81.1 ± 30.2	80.9 ± 23.8	NS	0.02
E deceleration time, m/s	218.6 ± 53.5	216.1 ± 57.6	NS	213.7 ± 69.6	226.6 ± 56.1	NS	NS
Mitral E/A	1.38 ± 1.39	1.21 ± 0.40	NS	1.2 ± 0.44	1.0 ± 0.32	< 0.05	0.005
E′ septal, cm/s	8.8 ± 2.3	8.6 ± 2.3	NS	8.4 ± 2.7	7.1 ± 2.0	0.01	< 0.0001
E/e′ septal	9.4 ± 2.8	10.2 ± 3.3	NS	10.7 ± 2.8	12.1 ± 5.3	0.07	0.02
LAVI, mL/m^2	31.7 ± 13.6	33.9 ± 8.4	NS	31.0 ± 7.7	35.1 ± 10.9	0.045	NS
RVSP, mmHg	22.6 ± 4.4	29.4 ± 11.7	< 0.001	23.0 ± 4.7	34.5 ± 15.0	< 0.001	0.04
TAPSE, cm	2.25 ± 0.40	2.18 ± 0.42	NS	2.26 ± 0.43	2.14 ± 0.53	NS	NS
Diastolic function, n (%)							
Absent	35 (87.5)	63 (76.8)	NS	28 (70)	32 (57.1)	NS	0.04
Inconclusive	3 (7.5)	9 (11)		6 (15)	9 (16.1)		
Present	2 (5)	10 (12.2)		6 (15)	15 (26.8)		
Echo-based strain measures, %							
Basal inferoseptal	−19.0 ± 2.9	−17.0 ± 4.6	< 0.01	−18.3 ± 4.0	−16.1 ± 4.1	< 0.02	NS
Midinferoseptal	−18.7 ± 3.1	−17.7 ± 5.1	NS	−19.2 ± 3.6	−17.1 ± 3.7	< 0.01	NS
Apical inferoseptal	−22.5 ± 4.9	−24.3 ± 5.5	NS	−23.0 ± 5.4	−22.6 ± 5.1	NS	NS
Basal anterolateral	−21.4 ± 5.3	−19.7 ± 4.9	NS	−19.9 ± 5.5	−18.1 ± 4.6	NS	NS
Midanterolateral	−19.6 ± 3.0	−17.8 ± 4.0	< 0.01	−18.2 ± 3.2	−16.7 ± 3.9	0.06	NS
Apical anterolateral	−21.0 ± 4.4	−20.8 ± 4.9	NS	−19.4 ± 4.7	−19.6 ± 5.1	NS	NS
Basal inferior	−19.5 ± 3.3	−17.6 ± 5.2	< 0.05	−18.5 ± 4.5	−16.8 ± 4.9	NS	NS
Midinferior	−19.2 ± 3.1	−18.1 ± 4.1	NS	−17.7 ± 4.0	−17.6 ± 4.6	NS	NS
Apical inferior	−22.8 ± 3.8	−23.5 ± 5.3	NS	−23.5 ± 6.0	−22.6 ± 7.0	NS	NS
Basal anterior	−21.4 ± 4.6	−19.3 ± 5.4	< 0.05	−18.6 ± 4.9	−18.0 ± 5.4	NS	NS
Midanterior	−20.0 ± 2.9	−18.0 ± 4.2	< 0.005	−17.3 ± 3.5	−16.4 ± 4.5	NS	NS
Apical anterior	−20.2 ± 3.1	−19.7 ± 5.3	NS	−19.2 ± 4.6	−18.8 ± 5.9	NS	NS
Basal inferolateral	−22.5 ± 5.5	−19.6 ± 6.2	< 0.02	−19.6 ± 4.8	−17.3 ± 4.5	< 0.05	0.03
Midinferolateral	−19.7 ± 3.1	−16.3 ± 5.1	< 0.0001	−17.2 ± 3.7	−17.2 ± 4.2	NS	NS
Apical inferolateral	−19.7 ± 4 .3	−18.5 ± 5.1	NS	−20.2 ± 5.0	−19.2 ± 5.2	NS	NS
Basal anteroseptal	−18.4 ± 7.2	−17.0 ± 4.2	NS	−17.1 ± 4.6	−15.8 ± 4.7	NS	NS
Midanteroseptal	−19.9 ± 3.7	−18.3 ± 4.2	< 0.05	−18.0 ± 6.7	−17.7 ± 5.2	NS	NS
Apical anteroseptal	−21.0 ± 4.1	−21.6 ± 7.9	NS	−21.6 ± 4.9	−19.2 ± 5.9	< 0.05	NS
GLS	−20.3 ± 1.2	−19.1 ± 2.2	< 0.001	−19.2 ± 1.3	−18.2 ± 2.3	< 0.01	0.02

Groups are defined as non-SSc controls without HTN (SSc–HTN–), SSc patients without HTN (SSc+HTN–), non-SSc controls with HTN (SSc–HTN+), and SSc patients with HTN (SSc+HTN+). Data are expressed as mean ± standard deviation, absolute number, or percentage. Independent unpaired *t* test and Wilcoxon-Mann-Whitney test for nonparametric data were used to compare continuous variables between SSc patients and control subjects, while chi-square test and Fisher exact test were used to compare categorical data. A cutoff *P* value < 0.05 was considered statistically significant. [a] *P* value: comparison between SSc–HTN– and SSc+HTN–. [b] *P* value: comparison between SSc–HTN+ and SSc+HTN+. [c] *P* value: comparison between SSc+HTN– and SSc+HTN+. GLS: global longitudinal strain; HTN: systemic hypertension; LAVI: left atrial volume indexed for body surface area; LS: longitudinal strain; LV: left ventricular; NA: not available/not applicable; NS: not significant; RVSP: right ventricular systolic pressure; SSc: systemic sclerosis; TAPSE: tricuspid annular plane systolic excursion.

previous studies using speckle-tracking strain analysis, which have shown differences in GLS between SSc subjects and age- and comorbid disease–matched controls.[27,28,29] Similar to Spethmann, *et al*, we found that impairments in LV strain were most notable in the basal segments, whereas the mid- and apical segments were relatively preserved.[27] Impaired GLS have previously been associated with a decrease in exercise functional capacity (measured by 6-minute walk test and peak VO_2 on cardiopulmonary exercise testing),[28,30] autonomic dysfunction,[31] and ventricular tachycardia or ectopic beats on 24-hour Holter monitoring.[28] Additionally, abnormal GLS has been associated with an increase in CV events (symptoms and/or signs of heart failure, coronary artery disease, atrial fibrillation, or CV death) at 20-month follow-up.[29]

SSc patients with concomitant HTN had evidence of abnormal GLS, a marker of LV contractile function, as well as greater evidence of cardiac remodeling when compared to SSc patients without HTN or non-SSc patients with HTN, as evidenced by greater left atrial dimensions and higher elevations in LV end-diastolic pressures by medial E/e′ estimation. Our

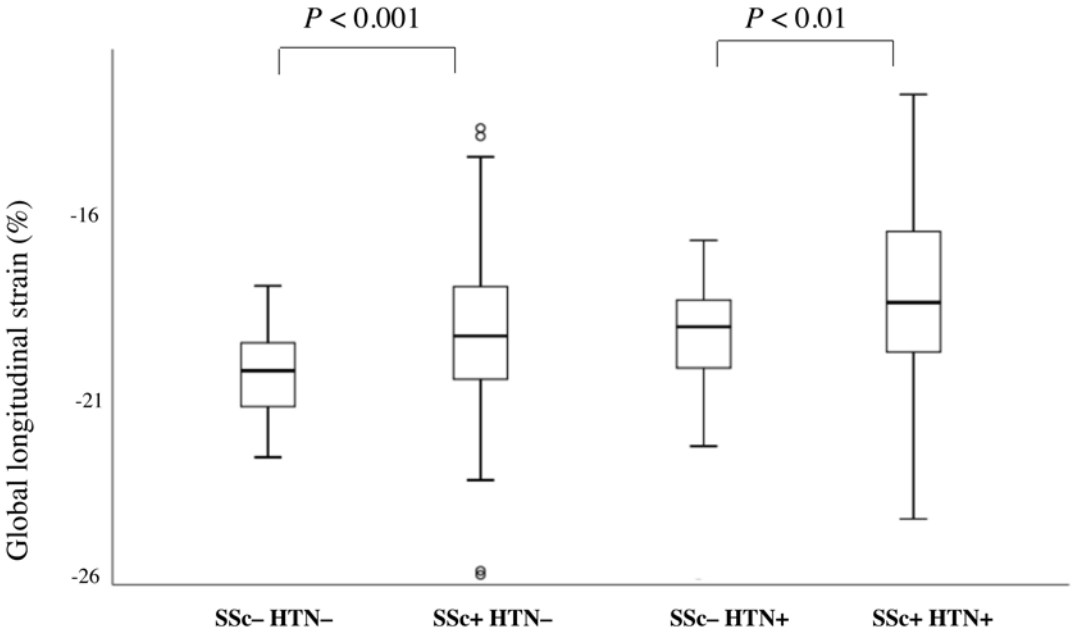

Figure 1. Box-plot graphic presentation of differences in left ventricular global longitudinal strain between SSc patients without systemic HTN (SSc+HTN–) and age- and sex-matched controls (SSc–HTN–), and between SSc patients with systemic HTN (SSc+HTN+) and age- and sex-matched controls with systemic HTN (SSc–HTN+). HTN: hypertension; SSc: systemic sclerosis.

Table 3. Multivariable linear regression analysis to explore the effect of age, comorbidities, and therapies on GLS in patients with SSc.

	β	95% CI	*P*
Age	–0.126	–0.057 to 0.011	0.18
Smoking	–0.075	–0.898 to 0.362	0.40
Dyslipidemia	–0.113	–1.618 to 0.516	0.31
Diabetes	–0.137	–3.057 to 0.514	0.16
Hypertension	0.337	0.488–2.664	**0.005**
Calcium channel blocker	–0.010	–0.874 to 0.781	0.91
Beta blocker	0.041	–1.371 to 2.137	0.67
ACEi	–0.130	–2.020 to 0.450	0.21
Angiotensin receptor antagonist	0.048	–1.233 to 2.080	0.61
Diuretic	–0.008	–1.110 to 1.022	0.94
Statin	0.083	–0.797 to 1.726	0.47

Values in bold are statistically significant. ACEi: angiotensin-converting enzyme inhibitor; GLS: global longitudinal strain; SSc: systemic sclerosis.

findings demonstrate the significant effect of HTN, a common and prevalent CV risk factor, on the SSc myocardium, and suggest that HTN has additional and unfavorable effects on the vulnerable SSc myocardium that results in more pronounced adverse remodeling, and LV diastolic and systolic function, when compared to other groups.

Diastolic dysfunction is an early noninvasive manifestation of cardiac involvement in SSc and suggestive of underlying myocardial fibrosis, occurring early in SSc independent of other cardiac comorbidities, with an estimated prevalence of 20–60%.[10] Echocardiography is an important diagnostic tool for the identification of diastolic dysfunction in SSc, and previous studies utilizing tissue Doppler septal e′ velocities have suggested that diminished e′ velocities are associated with increasing mortality.[10] Impairment of several diastolic echocardiographic variables have all been shown to correlate with disease duration and can occur as early as RP onset.[11] HTN is known to accelerate adverse remodeling in the general population and results in diastolic dysfunction, underlining the clinical syndrome of heart failure with preserved ejection fraction (HFpEF).[13,32] HFpEF is highly prevalent in SSc and thought to be due to fibrotic processes inherent to the SSc disease process. HFpEF in SSc is a highly morbid condition and when associated with pulmonary hypertension, has a 2-fold increase in mortality.[33] Given the increased morbidity and mortality of HFpEF in SSc, we sought to understand the effect of traditional risk factors such as HTN on the SSc myocardium, as the early management of HTN in patients with SSc may have significant clinical implications.

We importantly demonstrated that SSc patients with HTN have a greater degree of diastolic dysfunction and LV remodeling when compared to age- and sex-matched non-SSc patients with HTN. In addition to diastolic abnormalities, SSc+HTN+ patients had speckle-based strain abnormalities in global LV contractility not appreciable by conventional echocardiographic measures alone. While there are no guideline-based therapies for the management of HFpEF in the general population or in SSc, the presence of conventional cardiac risk factors such as HTN in SSc signifies an important clinical finding that should be managed aggressively due to the increased risk of adverse cardiac remodeling in these patients. Systolic blood pressure should be managed in accordance with guidelines utilizing beta blockers, ACEis, and ARBs.[34] Dihydropyridine calcium

channel blockers may have additional vasodilatory benefits in SSc patients with active RP. In the general population, there continues to be considerable controversy on the use of mineralocorticoid-receptor antagonists, such as spironolactone, and its utility in HFpEF.[35] Antifibrotic agents are not currently indicated for management of diastolic dysfunction and HFpEF in SSc; however, the role of HTN management in the prevention of HFpEF in the SSc population with abnormal LV GLS needs to be evaluated in prospective longitudinal studies.

There were several limitations to our study. First, the ability to perform speckle-tracking strain analysis is largely dependent on 2D image quality. Nevertheless, the strain analysis in our cohort was feasible in most of the cases, and patients were excluded if image quality precluded endocardial border delineation. Additionally, there is well-described vendor-specific variability in strain measures[36,37]; to limit this, all analyses were performed using a single software by 2 experienced readers. In addition, while important associations can be made between the effect of HTN on the heart in SSc as detected by innovative echocardiographic methods, our findings cannot be extrapolated as cause and effect.

In summary, speckle-tracking–derived longitudinal systolic strain analysis revealed regional and global abnormalities in left ventricular myocardial contractility in patients with SSc compared with age- and sex-matched controls that were not detected by standard echocardiography alone. Further, SSc patients with HTN showed greater abnormalities in diastolic function, LV remodeling, and LV myocardial contractility in comparison to non-SSc subjects with HTN. These findings highlight that subclinical cardiac involvement in SSc is common and that the presence of HTN may have an additional clinically important effect on the vulnerable SSc myocardium. Our findings therefore underscore the need for early screening and aggressive management of CV risk factors such as HTN in this at-risk population.

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