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ORIGINAL PAPER

The effect of hematopoietic stem cell transplantation on cardiac mechanics in systemic sclerosis

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Abstract
Systemic sclerosis (SSc) is an autoimmune disease that causes inflammation and fibrosis. Cardiac involvement in SSc is often subclinical and portends a worse prognosis. Autologous hematopoietic stem cell transplant (HSCT) improves survival in SSc but its effect on cardiac function is unknown. This study aimed to assess HSCT's effect on cardiac mechanics in SSc. Participants with SSc who received HSCT at a single academic center between 2009 and 2018 were identified from a prospective registry. All participants underwent comprehensive conventional and speckle-tracking echocardiography (STE) pre- and post-HSCT, and right heart catheterization before HSCT. Baseline and follow-up clinical and echocardiographic variables were compared. Among 88 HSCT recipients (age 51±11 years, 75% female), there was significant improvement of right ventricular (RV) strain globally (18.1±3.9% versus 20.0±4.5%, $p<0.01$) and within the RV free wall (20.7±5.3% versus 23.2±5.6%, $p<0.01$). Regionally, RV free wall strain improved in the mid (20.4±9.5% versus 23.7±8.0%, $p=0.04$) and apical (15.3±8.6% versus 20.9±9.0%, $p<0.01$) segments, but not the basal segment. While left ventricular (LV) strain did not change, left atrial (LA) reservoir strain improved (35.9±8.7% versus 47.8±11.4%, $p<0.01$) and LA stiffness index (0.24±0.12 versus 0.18±0.08, $p<0.01$) decreased post-HSCT. RV and LA mechanics significantly improve after HSCT among patients with SSc. This suggests a favorable effect of HSCT on the underlying myocardial pathology caused by SSc.

Keywords Speckle-tracking strain echocardiography · Systemic sclerosis · Right ventricle · Left atrium

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Abbreviations

2DE	2D echocardiography
FWS	Free wall strain
GCS	Global circumferential strain
GLS	Global longitudinal strain
HSCT	Autologous hematopoietic stem cell transplant
mRSS	Modified Rodnan skin score
PAH	Pulmonary arterial hypertension
QOL	Quality of life
SSc	Systemic sclerosis
STE	Speckle-tracking echocardiography

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disorder characterized by vascular dysfunction and progressive fibrosis of the skin and internal organs that causes significant morbidity and mortality in affected individuals. SSc can cause a spectrum of cardiac abnormalities starting early in the disease course, including right ventricular (RV) and left ventricular (LV) systolic and diastolic dysfunction, microvascular coronary disease, arrythmias, and pericardial disease [1]. The prevalence of cardiac involvement in SSc is reported to be 20–25% [2], but is challenging to estimate due to myriad possible manifestations and the variability in the modalities used to diagnose them. Autopsy studies in SSc, however, show much greater prevalence of myocardial fibrosis or pericardial disease implying that the majority of cardiac involvement in SSc is subclinical [3]. Since clinically evident cardiac disease in SSc has a poor prognosis [4], the early identification of cardiac disease and its response to therapy is of paramount importance.

Novel imaging methods such as strain-based imaging, which measures myocardial deformation, have enhanced our ability to identify subclinical cardiac dysfunction. Speckle-tracking echocardiography (STE) is the most widely used technique for assessing strain by quantitatively analyzing the displacement of speckles that track with myocardial motion during the cardiac cycle [5]. LV strain is more sensitive than conventional 2D echocardiography (2DE) in measuring abnormal LV mechanics [6, 7]. Left atrial (LA) strain is a more sensitive marker for identifying LV diastolic function [8] and, notably, LA strain parameters are impaired in patients with SSc despite normal diastolic function by 2DE metrics [9, 10]. Similarly, numerous studies show that RV strain is important in detecting subclinical RV abnormalities in SSc patients not detected by conventional measures of RV function [11].

Autologous hematopoietic stem cell transplant (HSCT) significantly improves event-free survival and quality of life in SSc compared to traditional immunosuppressant therapy [12, 13, 14], however, the effects of this treatment on cardiac function have not been studied. This study thus investigated the effect of HSCT on cardiac mechanics in SSc patients using comprehensive echocardiography with 2DE and STE. We hypothesize that HSCT will significantly improve cardiac mechanics in this patient population.

Methods

Study design and patient population

All participants with SSc who underwent HSCT at a single academic institution from 2009 to 2018 as part of a study or on a compassionate basis and enrolled in a prospective registry were considered for this study. Detailed inclusion and exclusion criteria for participants undergoing HSCT and the HSCT protocol have previously been described [15, 16]. Specifically, participants were ineligible for HSCT if they had SSc-associated pulmonary arterial hypertension (PAH), LV ejection fraction < 45%, severe unrevascularized coronary artery disease, untreated severe arrhythmia, constrictive pericarditis or hemodynamically significant pericardial effusion [17]. The participants were included in this study if they received comprehensive 2DE evaluation before and after HSCT. This study was approved by the institutional review board of Northwestern University (Chicago, IL, USA). All study participants provided informed consent prior to enrollment.

Clinical characteristics

Clinical characteristics of each participant in this study were collected from review of medical records. All participants met either 1980 or 2013 American College of Rheumatology classification criteria for SSc [18, 19]. Duration of disease was defined as the time from establishment of SSc diagnosis to initiation of HSCT therapy. Right heart catheterization was performed for each participant prior to HSCT as part of the cardiac evaluation protocol. The modified Rodnan skin score (mRSS) was used to monitor the severity of skin involvement and served as a general marker of disease severity [20]. The mRSS was obtained in the outpatient visit closest to the time of HSCT and at the first outpatient visit following HSCT, within one month when echocardiograms were obtained.

Transthoracic echocardiography

Two echocardiograms were selected for analysis for each participant. Baseline was defined as the most recent echocardiogram prior to HSCT and follow-up as the first

echocardiogram after the hospitalization encounter for HSCT. Transthoracic echocardiography was performed with a standardized protocol using commercially available ultrasound systems (GE Medical Systems, Milwaukee, Wisconsin and IE33 Phillips Medical Systems, Andover, Massachusetts). All echocardiographic parameters and myocardial strain analysis were performed following the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging [21, 22]. Speckle tracking software was utilized to measure LV, RV and LA myocardial strain (TomTec, Unterschleissheim, Germany).

LV, RV and LA myocardial strain were pre-specified primary measure of interest in our study. LV global longitudinal strain (LVGLS) was obtained using a semi-automated algorithm. LV global circumferential strain (LVGCS), RV global (RVGLS), free-wall (RVFWS) longitudinal strain, and LA reservoir strain were measured manually (Fig. 1). The accuracy of endocardial border tracking was optimized manually, and segments were excluded if unable to be satisfactorily tracked. Participants were excluded if there was a foreshortened chamber, suboptimal visualization, and/or inadequate tracking of two or more segments. Image analysis was performed by two assessors who were blinded to the clinical data. Each assessor performed analysis on half of the participants.

For ease of interpretation, all strain values were reported as absolute values (higher absolute strain values indicate better cardiac mechanics). The ratio of E/e' to LA reservoir strain was used to non-invasively estimate LA stiffness [23]. Abnormal cutoffs for LVGLS and RVFWS parameters were both <-20% based on American Society of Echocardiography guidelines [21]. Abnormal cutoff for LA reservoir strain was defined as <39% and LVGCS as <22.3% based on recent studies [24, 25].

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) if normally distributed, or median (interquartile range [IQR]) if not, and categorical variables were expressed as counts and percentages. Pre- and post-HSCT variables were compared using paired Student's *t* test, Wilcoxon signed-rank test, or McNemar's test. Normality was assessed through a combination of visual inspection, skewness and kurtosis assessment, and the Shapiro-Wilk test.

Intra- and inter-observer variability for all strain measures were assessed in 15 randomly selected participants. Intra-observer analysis was performed by having the same observer repeat the analysis 8 months apart. Inter-observer analysis was assessed by having the second observer repeat the analyses originally performed by the other observer. Reproducibility was reported using intraclass correlation coefficient. Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX) and GraphPad Prism 8 (GraphPad Software, CA). Two-sided p values of <0.05 were considered significant.

Results

Baseline clinical characteristics

Ninety of 114 participants in the registry underwent HSCT and were included in the study. Two participants were excluded from the final analysis due to poor image quality for STE analysis. A majority (90%) of participants had diffuse SSc and nearly all (99%) were on immunosuppressant therapy prior to HSCT (Table 1). The median (IQR) time between diagnosis of SSc and HSCT was 2.7 (1.5–6.4) years. The mean pulmonary artery pressure (mPAP) measured prior to HSCT was 18.4±4.4 mmHg, and 27 (31%) participants had a mPAP greater than 20 mmHg (Supplemental Table 1). Four patients had a mPAP greater than 25 mmHg but were deemed to have post-capillary pulmonary hypertension with elevated left-sided filling pressures and normal pulmonary vascular resistance, and thus were considered appropriate for HSCT.

Baseline echocardiographic characteristics

The pre-HSCT echocardiogram was performed a median (IQR) of 2 (1–4) months before HSCT. The median (IQR) time between diagnosis of SSc and baseline echocardiogram was 2.4 (1.3-6) years. At baseline, all mean values of conventional echocardiography measures were within the normal range (Table 2). Abnormal LVGLS was found in 56% of these participants, 22% had abnormal LVGCS, 48% had abnormal RVFWS, and 70% had abnormal LA reservoir strain.

Follow-up echocardiographic findings

The follow-up echocardiographic evaluation was performed a median of 12 (6–14) months after HSCT. At follow-up, significant differences were noted in several conventional echocardiographic measures, including septal e' velocity, lateral e' velocity, mitral E/A ratio and RV end-diastolic area (Table 2). However, the absolute difference was small, and all follow-up measures remained in the normal range.

Both RVGLS and RVFWS significantly improved post-HSCT. Regionally, the improvement was observed in the mid (20.4±9.5% vs. 23.7±8.0%, $p=0.04$) and apical segments (15.3±8.6% vs. 20.9±9.0%, $p<0.01$) of the RV free

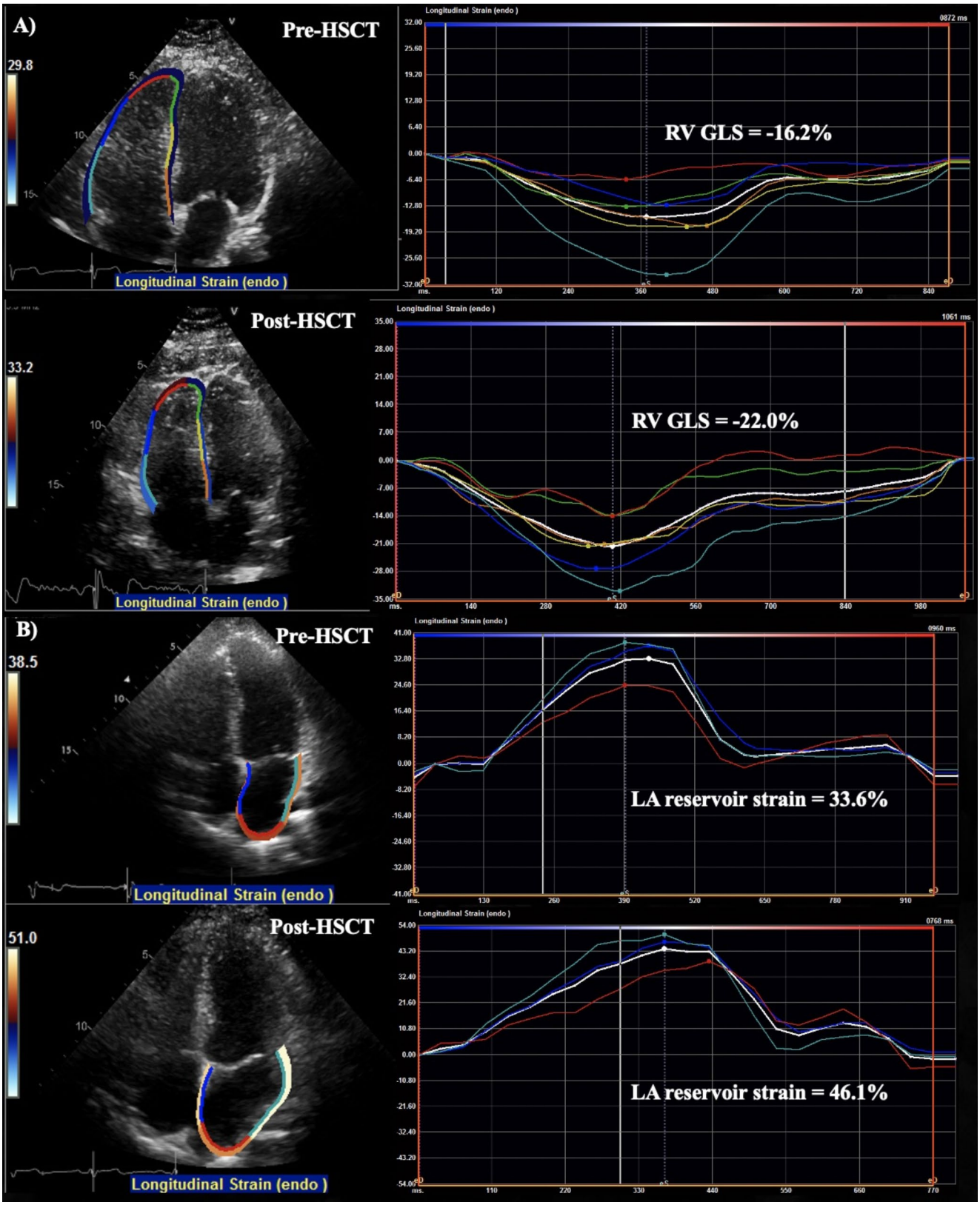

Fig. 1 Representative right ventricular (RV) and left atrial (LA) strain images. X axis is time (ms) and Y axis is strain (%). The white curve represents the average of the systolic segmental strain curves. (**A**) RV global longitudinal strain (GLS) in a patient with systemic sclerosis (SSc) before and after hematopoietic stem cell transplant (HSCT). (**B**) LA reservoir strain in the apical 4-chamber view in a patient with SSc before and after HSCT. The final LA reservoir strain was an average of the maximal longitudinal LA strain from apical 2-, and 4-chamber views

Table 1 Baseline clinical characteristics

Clinical characteristics, No. (%)	
Age, years, mean±SD	51±11
Female gender	66 (75)
Race	
Caucasian	67 (76)
African American	10 (11)
Other	11 (13)
Body mass index, kg/m^2, mean±SD	24±5
Heart rate, beats/min, mean±SD	84±14
Systolic blood pressure, mmHg, mean±SD	110±15
Diastolic blood pressure, mmHg, mean±SD	69±10
Hemoglobin, g/dL, mean±SD	12.0±1.7
BNP, pg/mL, median (IQR)	35 (20–70)
mRSS, median (IQR)	21 (13–34)
Years between diagnosis of SSc and HSCT, median (IQR)	2.7 (1.5–6.4)
SSc characteristics and Seropositivity	
Diffuse cutaneous SSc	79 (90)
Antinuclear antibody	86 (98)
Anti-RNA polymerase III	30 (34)
Anti-topoisomerase I	32 (36)
Anti-centromere	5 (6)
Comorbidities/Cardiovascular risk factors	
Coronary artery disease	2 (2)
Systemic arterial hypertension	9 (10)
Diabetes mellitus	1 (1)
Hyperlipidemia	7 (8)
Smoking history	18 (20)
Medications	
Calcium channel blockers	26 (30)
ACEi/ARB	18 (20)
Diuretics	11 (13)
Beta-blockers	3 (3)
Phosphodiesterase inhibitors	13 (15)
Prostacyclin receptor agonists	1 (1)
Endothelin receptor antagonists	2 (2)
Mycophenolate mofetil	70 (80)
Prednisone	59 (67)
Methotrexate	47 (53)
Cyclophosphamide	25 (28)
Hydroxychloroquine	16 (18)
Biologics or other	16 (18)
Intravenous Immunoglobulin	11 (13)
Azathioprine	11 (13)
Rituximab	14 (16)
D-penicillamine	1 (1)

Abbreviations: ACEi: angiotensin-converting enzyme inhibitors; ARB: aldosterone receptor antagonists; BNP: brain natriuretic peptide; HSCT: hematopoietic stem cell transplant; mRSS: modified Rodnan skin score; RNA: ribonucleic acid; SSc: systemic sclerosis

Table 2 Echocardiographic and clinical measures before and after HSCT

Echocardiography variables, mean±SD	Baseline	Follow-Up	*P*-value[1]
Left Ventricle			
End-diastolic diameter index, cm/m^2	2.51±0.30	2.47±0.32	0.14
IVS thickness, cm	0.89±0.18	0.90±0.18	0.68
Posterior wall thickness, cm	0.92±0.16	0.93±0.17	0.51
Mass index, g/m^2	74.7±22.0	74.1±21.7	0.82
Ejection Fraction, %	61.7±5.3	61.0±6.9	0.37
GLS, %	18.7±4.4	19.0±3.4	0.61
GCS, %	26.4±7.1	25.7±6.8	0.49
Left Atrium			
Volume index, ml/m^2	24.7±8.3	24.2±7.2	0.64
Septal mitral annular e' velocity, cm/sec	10.1±3.0	9.3±2.8	0.01
Lateral mitral annular e' velocity, cm/sec	12.2±3.4	11.5±3.4	0.03
Transmitral Doppler E/A ratio	1.4±0.5	1.2±0.4	0.01
E/e'	8.0±2.4	8.3±2.6	0.30
Stiffness index	0.24±0.12	0.18±0.08	<0.01
Reservoir strain, %	35.9±8.7	47.8±11.4	<0.01
Right Atrium			
Right atrial area, cm^2	13.3±3.8	13.4±4.5	0.78
Right Ventricle			
Basal diameter, cm	3.6±1.1	3.4±0.6	0.13
End-diastolic area, cm^2	16.7±5.5	17.5±4.9	0.01
End-systolic area, cm^2	9.6±3.9	9.7±3.7	0.21
Fractional area change, %	43.0±11.8	44.8±11.0	0.25
TAPSE, cm	2.2±0.4	2.1±0.4	<0.01
Tricuspid annular S' velocity, cm/sec	12.8±1.9	12.0±2.2	<0.01
TR velocity, cm/sec	2.4±0.4	2.3± 0.6	0.31
Pericardial effusion, No. (%)	12 (14)	10 (11)	0.62
GLS, %	18.1±3.9	20.0±4.5	<0.01
Free Wall Strain, %	20.7±5.3	23.2±5.6	<0.01
Free Wall Strain Segments			
Basal, %	27.9±9.4	28.0±7.9	0.94
Mid, %	20.4±9.5	23.7±8.0	0.04
Apical, %	15.3±8.6	20.9±9.0	<0.01
Clinical outcome measures			
mRSS, median (IQR)	21 (13–34)	9 (4–20)	<0.01

Abbreviations: A: late diastolic mitral inflow velocity; E: early diastolic mitral inflow velocity; e': early diastolic mitral annulus velocity; FWS: free wall strain; GCS: global circumferential strain; GLS: global longitudinal strain; IVS: interventricular septum; mRSS: modified Rodnan skin score; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

[1]Paired t-test, McNemar's test or Wilcoxon sum rank test as appropriate comparing baseline and follow-up measures

wall, but not in the basal segment. LA reservoir strain also improved (35.9±8.7% vs. 47.8±11.4%, $p<0.01$) and LA stiffness index decreased from 0.24 to 0.18 ($p<0.01$). No significant changes were observed in LVGLS or LVGCS after HSCT.

Following HSCT, mRSS decreased, reflecting an improvement in symptom burden (21 [13–34] at baseline to 9 [4–20] follow up, $p<0.01$). There was no significant correlation between change in strain parameters and change in mRSS (Supplemental Table 2). The intra- and inter-observer reproducibility for all strain measures before and after HSCT was excellent (Supplemental Table 3).

Discussion

In this study of SSc participants without SSc-associated PAH, we found a significant improvement in RV and LA reservoir strain post-HSCT among SSc participants who underwent HSCT. This improvement occurred despite no clinically relevant change in conventional echocardiographic measures of RV function or LA size. To our knowledge, this is the first study to investigate the effects of HSCT on cardiac function in patients with SSc.

Myocardial strain characteristics in SSc

Myocardial strain is a more sensitive marker than conventional parameters of cardiac function and is more conducive to study in SSc with its high prevalence of subclinical cardiac disease. This is the reason LV, RV and LA myocardial strain were chosen as the pre-specified primary measures of interest in our study. Previous studies have shown abnormal strain metrics in SSc patients despite normal conventional 2DE measures of LV, RV, and LA size and function. The baseline LVGLS and LA reservoir strain in our study cohort are similar to prior studies, which are lower than in healthy controls [6, 7, 9, 10, 11]. In previous studies, the reported average RVFWS has ranged from 17 to 19% [7, 11], however, our study cohort had an average RVFWS that was more robust (20.7±5.3%). This could potentially be explained by nuanced selection criteria for HSCT, variabilities in vendor platforms for strain analysis and a shorter disease course of our study cohort (a median disease duration of 2.7 years in our study versus an average of 6–15 years in previous studies) [7, 11].

Cardiac mechanics post-HSCT

Our study showed significant improvement in RVGLS and RVFWS among the HSCT recipients despite no clinically significant changes in conventional 2DE parameters of RV function. There is a predominant focus on RV involvement in SSc particularly in the context of SSc-associated PAH [26]. However, global RV systolic function can be impaired in SSc patients even in the absence of PAH. Our results add to the mounting evidence for occult, intrinsic RV myocardial dysfunction in SSc patients with normal pulmonary pressure [1, 11, 26] and offers HSCT as a potentially disease-modifying therapy [27].

There are likely regional differences in ventricular involvement in SSc. Mukherjee et al. identified a heterogenous pattern of RV dysfunction with RVFWS being preserved in the basal segment and diminished in the mid and apical segments and hypothesized that the basal segment of the RV free wall may initially serve as the primary vector of RV contraction [11]. They also found augmentation in the mid and apical segments, but not in the basal segment, with exercise in SSc patients, demonstrating myocardial reserve in these segments [28]. Our study complemented these findings by showing preferential improvement in strain in the mid and apical segments of the RV free wall following HSCT. This might also explain the overall improvement in RV strain despite the decrease in conventional 2DE RV function parameters such as TAPSE and S' which only measure the basal segment of the RV. Strain provided a more nuanced assessment of myocardial activity than conventional 2DE measures. Again, while the significant increase in RVEDA is noted and warrants further investigation, the absolute change was small and is not considered clinically significant.

Our results also showed a significant improvement in LA reservoir strain post-HSCT despite no significant change in LA volumes or echocardiographic estimates of LV filling pressure. This is consistent with previous studies examining echocardiographic changes in patients with SSc where LA reservoir strain was diminished despite normal LA volumes [9]. This, again, reflects the sensitivity of strain imaging to identify subclinical disease and myocardial alterations that might occur with therapeutic interventions.

Despite the significant improvement in RV and LA strain measures, we did not observe a significant change in LV strain measures after HSCT. While there were significant changes in some conventional measures of LV diastolic function such as septal e' velocity, lateral e' velocity, and E/A ratio, the absolute changes were small and not clinically significant although deserve further study. The absence in improvement in LV systolic function may be explained by minimal LV involvement in this carefully selected cohort as demonstrated by normal left-sided filling pressures, normal LVGLS and LVGCS at baseline, and normal cardiac biomarker profiles. Porpaczy et al. found that LVGLS became impaired only after disease duration approached 7 years [10]. This is also supported by data from MRI studies that

have identified an association between disease duration and degree of late gadolinium enhancement (LGE, a marker of myocardial fibrosis) within the LV myocardium [29]. Our study cohort has a distinctly shorter disease duration and thus may only harbor subclinical LV involvement in its earliest stages that has not reached a threshold for a treatment effect to manifest.

Comparison of echocardiographic measures in SSc patients who did not undergo HSCT

In a hypothesis-generating analysis, we explored the difference in echocardiographic measures between those SSc patients who underwent HSCT (HSCT group) versus those who did not undergo this intervention (non-HSCT group). The non-HSCT group was comprised of SSc participants from the above-mentioned registry who did not undergo HSCT due to patient preference or insurance denial. Supplemental Table 4 details the difference in baseline clinical characteristics between the two groups.

Compared to the HSCT group, patients with SSc in the non-HSCT group did not show any significant change in RV or LA strain in a similar one-year time period (Supplemental Table 5). This offers the possibility that HSCT was associated with improved RV and LA mechanics that were not achieved by immunotherapies alone. It is important to note that this analysis is strictly hypothesis-generating as the non-HSCT group was not a control group and had significant differences in baseline characteristics.

Potential mechanistic explanation for improved myocardial strain post-HSCT

We propose that reduction in the burden of myocardial fibrosis and improvement in myocardial performance as a potential mechanistic explanation for improved RV and LA strain measures post-HSCT. Tedford and colleagues have previously described in- and ex-vivo sarcomeric dysfunction in the RV in SSc-associated PAH and it is possible HSCT may aid in reversing these pathologic processes [26, 30]. In our study, improvement in LA reservoir strain was accompanied by improvement in LA stiffness among HSCT recipients, which was not observed in those who did not receive HSCT. Since myocardial fibrosis is the hallmark for the pathogenesis of SSc [31, 32], we hypothesize that this could represent a direct reduction in LA fibrosis and subclinical reverse atrial remodeling with HSCT. The absence of LV improvement post-HSCT may also represent the subtle changes in fibrosis were more apparent in thin-walled RV and LA than the thicker LV. Further research of myocardial fibrosis post-HSCT, for example, with the use of LGE imaging, may provide further mechanistic insight.

Change in cardiac mechanics are not associated with clinical outcome

There was no significant association between myocardial strain and clinical outcome as measured by the mRSS score. It is not surprising that the improvement in subclinical cardiac abnormalities in these patients is not directly associated with the decrease in skin fibrosis. Further study is needed to examine whether the improvement in cardiac mechanics is associated with improved quality of life and/or a decrease in adverse cardiac events.

Limitation

Our study has several limitations. This is a single-center study. Although HSCT procedures are standard, each center follows a local protocol which can introduce potential inter-center variability. The HSCT group was carefully selected for receiving HSCT. Additionally, there was limited follow-up for clinical outcomes in this study cohort as this was a referral population to our institution and we were thus unable to obtain longitudinal morbidity and mortality data for study participants. As we did not have a comparable control group of SSc patients who did not undergo HSCT, the between-group analysis is limited and must be interpreted with caution. Regression to the mean must also be considered when making inferences with our findings. Finally, our findings are not generalizable to SSc patients who have PAH or overt cardiac dysfunction.

Conclusion

Our study shows significant improvement in RV and LA cardiac mechanics following HSCT in patients with SSc. These results offer insight into processes that are operative in the absence of overt cardiac dysfunction and may serve as a future therapeutic target in this patient population.

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Data availability No datasets were generated or analysed during the current study.

Declarations

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Competing interests The authors declare no competing interests.

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