




Subclinical Systemic Sclerosis Primary Heart Involvement by Cardiovascular Magnetic Resonance Shows No Significant Interval Change

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Objective. Subclinical systemic sclerosis (SSc) primary heart involvement is commonly described. Whether these findings progress over time is not clear. The study aimed to investigate cardiovascular magnetic resonance (CMR) interval change of subclinical SSc primary heart involvement.

Methods. Patients with SSc with no cardiovascular disease underwent two CMR scans that included T1 mapping and quantitative stress perfusion. The CMR change (mean difference) and association between CMR measures and clinical phenotype were assessed. The study had a prospective design.

Results. Thirty-one patients with SSc participated, with a median (interquartile range) follow-up of 33 (17–37) months (10 [32%] in the diffuse subset, 16 [52%] with interstitial lung disease [ILD], and 11 [29%] who were Scl-70+). Four of thirty-one patients had focal late gadolinium enhancement (LGE) at visit 1; one of four had an increase in LGE scar mass between visits. Two patients showed new focal LGE at visit 2. No change in other CMR indices was noted. The three patients with SSc with increased or new LGE at visit 2 had diffuse cutaneous SSc with ILD, and two were Scl-70+. A reduction in forced vital capacity and total lung capacity was associated with a reduction in left ventricular ejection fraction ($\rho = 0.413$, $P = 0.021$; $\rho = 0.335$, $P = 0.07$) and myocardial perfusion reserve (MPR) ($\rho = 0.543$, $P = 0.007$; $\rho = 0.627$, $P = 0.002$). An increase in the N-terminal pro-brain natriuretic peptide level was associated with a reduction in MPR ($\rho = -0.448$, $P = 0.042$). Patients on disease-modifying antirheumatic drugs (DMARDs) had an increase in native T1 (mean [SD] 1208 [65] vs. 1265 [56] milliseconds, $P = 0.008$). No other clinically meaningful CMR change in patients receiving DMARDs or vasodilators was noted.

Conclusion. Serial CMR detects interval subclinical SSc primary heart involvement progression; however, this study suggests abnormalities remain largely stable with follow-up.

INTRODUCTION

Primary heart involvement in systemic sclerosis (SSc) develops as a direct manifestation of the disease and is a major cause of death (1,2). The reported prevalence of SSc primary heart involvement varies greatly, with more advanced imaging techniques, as well as

pathophysiological studies, describing subclinical findings in a significant proportion of patients with SSc (3,4).

Cardiovascular magnetic resonance (CMR) is one of the most accurate investigative tools for cardiovascular assessment, allowing evaluation of morphology and function, tissue characterization, and myocardial perfusion assessment (5). Late gadolinium

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enhancement (LGE) focal fibrosis, which can be distinguished from that of coronary artery disease is reported commonly in SSc (6,7). T1 mapping with extracellular volume (ECV) quantification is an established technique for detection of diffuse fibrosis, and multiple studies report increased ECV in SSc (8,9). Myocardial perfusion abnormalities and decreased myocardial perfusion reserve (MPR) have also been documented in SSc (10,11).

Preliminary evidence suggests vasodilator treatment in SSc may provide a preventive role for the future development of cardiovascular events as well as short-term improvement in cardiovascular parameters (12–14). The long-term effect of disease-modifying antirheumatic drug (DMARD) and vasodilator treatment on the course of subclinical and clinical progression of SSc primary heart involvement has not yet been investigated.

We have previously reported subclinical CMR features of SSc primary heart involvement, demonstrating CMR findings of diffuse and focal fibrosis and reduced myocardial perfusion in patients with SSc free of other cardiovascular diseases (CVDs) as well as association with SSc disease severity and cardiac serum markers (15). We also reported the potential prognostic value of such subclinical changes and future events (16). It is unclear, however, whether subclinical SSc primary heart involvement findings progress over time and whether CMR is sensitive to such change. The current study aimed to investigate for interval change in CMR detected subclinical SSc primary heart involvement findings, which could inform the value of monitoring with CMR, and to identify blood markers associated with CMR progression.

PATIENTS AND METHODS

Patients. Consecutive patients with SSc were approached for the study. All patients with SSc fulfilled the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for SSc (17) and were classified as having limited cutaneous SSc or diffuse cutaneous SSc (dcSSc) (18). Patients were excluded if they had any prior diagnosis of ischemic heart disease, SSc primary heart involvement and/or other cardiomyopathies, pulmonary arterial hypertension, diabetes, or more than two traditional cardiovascular risk factors, which were defined as current smoker, hypertension, hypercholesterolemia and/or hypertriglyceridemia, and family history of premature CVD. Patients with any other immune-mediated inflammatory diseases were also excluded. The study was conducted according to the Declaration of Helsinki and approved by the Yorkshire and The Humber - Leeds East Research Ethics Committee (REC 12/YH/0298 and RR10/9608). All participants provided written informed consent.

Study design. All participants underwent two CMR scans (visit 1, visit 2) at least 1 year apart. Patients' follow-up ended in August 2018. Clinical data were collected at both visits and

included demographics, disease subtype and duration, organ involvement, and current and any change in DMARD and/or vasodilator treatment, including calcium channel blockers (CCBs), iloprost, sildenafil, bosentan, and angiotensin-converting enzyme inhibitor (ACEI) between the two visits. Iloprost infusion was administered as a 3-day schedule every 3 months at a dosing regimen of 100 µg, as per Leeds Teaching Hospital National Health Service trust protocol. Serum samples were collected for high-sensitivity troponin I (hs-TnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) testing at both visits. hs-TnI was measured on a Siemens Advia XPT system (Advia Chemistry XPT and Advia Centaur XPT Immunoassay) and NT-proBNP was measured on Cobas 6000 (immunochemistry module Cobas e601) at both visits. Patients had annual pulmonary function tests (PFTs) performed as part of routine clinical assessment. The PFT measures approximating to each CMR visit were recorded.

CMR imaging. Patients had the CMR scan performed on a 3T Philips Achieva MR system, using the same protocol, as previously described (19,20). The CMR protocol included left ventricular (LV) function and volume, tissue tagging, LGE, native and postcontrast T1 mapping with ECV quantification, myocardial perfusion with assessment of stress and rest myocardial blood flow (MBF) and MPR estimation, and aortic distensibility.

Image analysis was performed with Circle Cvi42 software (v4.1.3, Circle Cardiovascular Imaging Inc.) by two blinded independent readers (RBD and BE). A second CMR expert reader (AK), with more than 10 years of experience, checked all the LGE and perfusion image analyses as paired scans. LGE and stress and rest perfusion images were assessed and reported according to the 16-segment American Heart Association model (21). The 5-SD method was used for LGE quantification (22). Quantitative myocardial perfusion analysis was undertaken to estimate stress and rest MBF and MPR, the latter being determined by dividing MBF stress by MBF rest (23). Native T1 and ECV were determined from native and postcontrast T1 mapping images. An ECV greater than 29% and native T1 greater than 1240 milliseconds were considered abnormal according to the departmental reference ranges (24,25). For aortic distensibility, aortic cross-sectional measurements were made by manual planimetry of the endovascular blood pool interface at maximal and minimal distension of the aorta (26). For myocardial strain assessment, tissue tagging data were analyzed using a semiautomated method (27).

Statistical analysis. SPSS (IBM SPSS Statistics 22) and GraphPad Prism (V.8) were used for statistical analysis. Descriptive summary statistics are provided for all variables. Continuous variables are reported as mean (SD) or median (interquartile range [IQR]), and categorical data are reported as percentage. The paired sample *t*-test or Fisher's exact test, when indicated, was

used to assess the differences between CMR measures at visit 1 compared to visit 2.

Spearman ρ correlation was used to identify any association between CMR measures and clinical phenotype. When appropriate, further subanalyses, including Student's t -test, the Mann–Whitney U test, and the paired sample t -test, were used to assess for differences between groups.

Because this was a pilot study, P values, if reported, are used to inform strength of findings rather than significance, in line with good practice (28).

RESULTS

Disease characteristics of patients with SSc.

Thirty-one patients with SSc participated in the study and had available baseline and follow-up CMR data. Patients had a median interval of 33 (IQR 17–37) months between the CMR scans. All patients had at least 1 year between visit 1 and visit 2, with the majority (21 [68%] patients) having 3 years between the two CMR visits. Complete LV function and LGE CMR assessment was available in all 31 patients, ECV data were available in 30 patients with SSc, native T1 data were available in 29 patients, aortic distensibility data were available in 26 patients, and MPR and strain analysis data were available in 23 patients.

Participants had a median age of 52 (IQR 47–60) years and disease duration of 9 (IQR 2–16) years; 23 (74%) were female, 10 (32%) had dcSSc, 16 (52%) had a diagnosis of interstitial lung disease (ILD), and 8 (26%) had a history of digital ulceration (DU). Twenty-eight (90%) were antinuclear antibody positive, of whom 11 (36%) were anticentromere antibody positive (ACA) and 9 (29%) were antitopoisomerase antibody (Scl-70+) positive (Table 1).

Baseline treatment and change in treatment between the two visits.

Eighteen patients were receiving DMARD treatment at visit 1 and continued to receive the same DMARD treatment between the two CMR visits (Table 1). Two patients commenced new DMARD treatment during the follow-up period. Of these 20 (65%) patients on DMARDs, 13 (42%) received treatment with mycophenolate mofetil (MMF), five (16%) received treatment with hydroxychloroquine, two (7%) received treatment with methotrexate, one (3%) received treatment with azathioprine, one (3%) received treatment with sulfasalazine, three (10%) received a median of six cyclophosphamide infusions, and one received three cycles of rituximab.

The majority of patients ($n = 27$, 87%) were receiving vasodilator therapy at visit 1, including CCB, of whom 12 patients received more targeted treatment in the form of iloprost, sildenafil, or bosentan (Table 1). Seven patients commenced new targeted vasodilator treatment between visit 1 and visit 2. Thirteen patients (42%) were taking ACEI treatment at visit 1, of whom one patient

Table 1. Disease characteristic of patients with SSc

SSc phenotype	Patients with SSc, n = 31
Demographics and disease history	
Age, median (IQR)	52 (47–60)
Female	23 (74)
LcSSc	21 (68)
DcSSc	10 (32)
ANA	28 (90)
ACA	9 (29)
Scl-70+	11 (36)
Disease duration (years), median (IQR)	9 (2–16)
History of digital ulceration	8 (26)
GORD	27 (87)
ILD	16 (52)
Patients with cardiovascular risk factors	8 (26)
Hypertension	2 (7)
Smoking	3 (10)
Family history of CVD	5 (16)
Clinical profile (visit 1)	
Total modified Rodnan skin score, median (IQR)	2 (1–6)
Digital ulceration	3 (10)
Tendon friction rubs	1 (3)
Calcinosis	3 (10)
Any TJC	14 (45)
Any SJC	3 (10)
Pulmonary function tests (visit 1), mean (SD)	
FVC%	100 (20)
TLC%	90 (15)
DLCO%	63 (11)
DLCO/VA%	81 (14)
Treatment at visit 1	
Any DMARD	18 (58)
Any vasodilator treatment	27 (87)
Targeted vasodilator treatment	12 (39)
Any ACEI	13 (42)

Note: Data are n (%) unless otherwise stated.

Abbreviations: ACA, anticentromere antibody; ACEI, angiotensin-converting enzyme inhibitor; ANA, antinuclear antibodies; CVD, cardiovascular disease; DcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusing capacity of the lungs for carbon monoxide; DLCO/VA, DLCO adjusted for volume; DMARD, disease-modifying anti-rheumatic drug; FVC, forced vital capacity; GORD, gastroesophageal reflux disease; ILD, interstitial lung disease; IQR, interquartile range; LcSSc, limited cutaneous systemic sclerosis; Scl-70+, antitopoisomerase antibody; SD, standard deviation; SJC, swollen joint count; SSc, systemic sclerosis; TJC, tender joint count; TLC, total lung capacity.

discontinued during follow-up and one patient commenced new ACEI treatment between visit 1 and visit 2.

Change in CMR measures from visit 1 to visit 2.

Focal and diffuse fibrosis. Four of thirty-one patients had a nonischemic LGE pattern at visit 1. Two patients had subepicardial distribution, one had midwall distribution, and one had diffuse transmural distribution. There was no change in the pattern and distribution of LGE in these four patients and no notable change in LGE scar mass between the two visits (mean [SD] 3.1 [3.1] vs. 2.4 [1.8], mean difference [95% confidence interval (CI)] 0.71 [−1.5, 2.9]; $P = 0.383$) (Figure 1, Table 2). However, one of the four patients had a clear reduction in LGE scar mass (from 7.59 to 4.99 g), whereas one patient had an increase in LGE scar mass

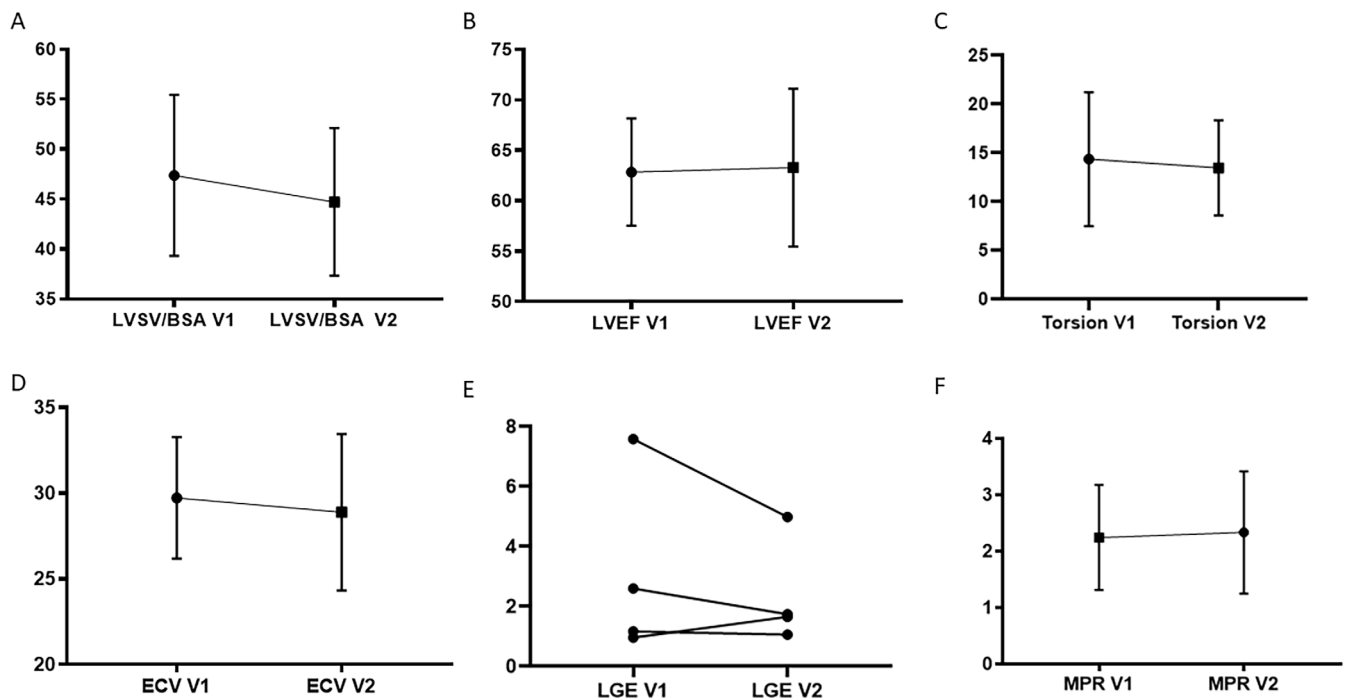


Figure 1. Change in cardiovascular magnetic resonance (CMR) measures between visit 1 (V1) and visit 2 (V2). **A**, Mean (SD) change in left ventricular stroke volume (LVSV). **B**, Mean (SD) change in left ventricular ejection fraction (LVEF). **C**, Mean (SD) change in torsion. **D**, Mean (SD) change in extracellular volume (ECV). **E**, Change in late gadolinium enhancement (LGE) in patients with confirmed LGE at visit 1 ($n = 4$). **F**, Mean (SD) change in myocardial perfusion reserve (MPR). BSA, body surface area.

(from 0.92 to 1.66 g). Two patients with no fibrosis at visit 1 developed new focal fibrosis at visit 2, of whom one presented with new cardiac symptoms that prompted a repeat CMR scan, confirming myocarditis and associated LV systolic dysfunction. The time frame between the CMR visits for the two patients was 22 and 26 months, respectively.

No change in ECV was noted at visit 2 (mean [SD] 29.6 [4] vs. 28.8 [5], mean difference [95% CI] -0.8 [$-2, 0.4$]; $P = 0.192$).

Eleven of the fifteen patients with an ECV above the normal range at visit 1 continued to have an ECV above the normal range at visit 2.

A trend increase in native T1 was noted at visit 2 (mean [SD] 1218 [65] vs. 1248 [60], mean difference [95% CI] 30 [$-5, 65$]; $P = 0.090$) (Table 2). Eight of the twelve patients with a native T1 above the normal reference range (>1240 milliseconds) continued to have increased native T1 at visit 2.

Table 2. Change in CMR measures between visit 1 and visit 2

CMR variable	CMR visit 1	CMR visit 2	Change, mean difference (95% CI)	P
LGE	4/31	6/31		$<0.001^{**}$ (Fisher's exact test)
LGE scar mass (g), $n = 4$	3.1 (3.1)	2.4 (1.8)	0.71 ($-1.5, 2.9$)	0.383
ECV%, $n = 30$	29.6 (4)	28.8 (5)	-0.8 ($-2, 0.4$)	0.192
Native T1 (ms), $n = 29$	1218 (65)	1248 (60)	30 ($-5, 65$)	0.090
MPR, $n = 23$	2.2 (0.9)	2.3 (1.1)	0.18 ($-0.40, 0.76$)	0.523
LVEDV/BSA (ml/m^2)	75 (17)	72 (15)	-3 ($-7, 1$)	0.136
LVESV/BSA (ml/m^2)	29 (9)	27 (11)	-2 ($-5, 1$)	0.158
LVSV/BSA (ml/m^2)	47 (8)	45 (7)	-3 ($-5, 1$)	0.009*
LV mass/BSA (g/m^2)	43 (13)	44 (11)	1 ($-1, 3$)	0.352
LVEF (%)	63 (5)	63 (8)	0.4 ($-2, 3$)	0.701
Torsion, $n = 23$	13 (4)	14 (5)	0.2 ($-2.2, 2.7$)	0.846
Aortic distensibility ($10^{-3}/\text{mm Hg}$), $n = 26$	4.6 (2)	4.5 (2)	-0.1 ($-1, 1$)	0.844

Note: Paired sample t -test; data are mean (SD) unless stated otherwise.

Abbreviations: BSA, body surface area; CMR, cardiovascular magnetic resonance; ECV, extracellular volume fraction; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MBF, myocardial blood flow; MPR, myocardial perfusion reserve.

* $P < 0.05$;

** $P < 0.001$.

Measures of function, perfusion, and aortic distensibility.

A mild decrease in LV stroke volume (LVSV) per body surface area (BSA) was noted at visit 2, although the means remained within normal limits, with little clinical relevance (mean [SD] 47 [8] vs. 45 [7], $P = 0.009$). No abnormality or other change in LV function or volume parameters was noted (Figure 1, Table 2). Only one patient developed moderate systolic dysfunction in the context of myocarditis.

There was no change in LV torsion (mean [SD] 13 [4] vs. 14 [5], $P = 0.846$), MPR (mean [SD] 2.2 [0.9] vs. 2.3 [1.1], $P = 0.523$), or aortic distensibility (mean [SD] 4.6 [2] vs. 4.5 [2], $P = 0.844$) between the two visits (Figure 1, Table 2).

Except for the patient with SSc with myocarditis, no other patients had CMR findings that were associated with clinically overt SSc primary heart involvement.

Change in CMR measures and disease phenotype.

Of the four patients with SSc with evidence of LGE at visit 1, one had dcSSc, three had ILD, one was ACA+, one had anti-Sm/RNP, one was Ro-52+, and one was rheumatoid factor positive. The patient with a more significant decrease in LGE scar mass at follow-up was an Sm/RNP-positive male patient (receiving treatment with methotrexate) with mild ILD and a history of arthritis. Patients with SSc with an increase in pre-existing LGE scar mass ($n = 1$) or new LGE ($n = 2$, one in the context of

myocarditis) all had dcSSc, with a diagnosis of ILD (two were Scl-70+ and one was anti-RNA+) and a mean (SD) disease duration of 3 (2.6) years. The patient with SSc with new myocarditis also had a diagnosis of myositis and inflammatory arthritis, and the patient with an increase in LGE scar mass also had a meaningful increase in the modified Rodnan skin score (mRSS) at visit 2 (from 6 to 13).

The presence of ILD was associated with a change in LV end-systolic volume (LVESV)/BSA and LV end-diastolic volume (LVEDV)/BSA ($\rho = 0.455$, $P = 0.010$; $\rho = 0.527$, $P = 0.002$) and was negatively associated with the change in MPR ($\rho = -0.457$, $P = 0.029$). Further analysis showed no difference in CMR parameters in patients with SSc with and without ILD at visit 1 or in those with ILD between the two visits (Supplementary Table 1). However, compared to those with ILD, the group without ILD had a greater decrease in LVEDV/BSA (median [IQR] of -8.2 [-11.1 , 2.5] vs. -0.15 [-1.48 , 2.75], $P = 0.003$) and LVESV/BSA (median [IQR] of -4.9 [-8.2 , -2.1] vs. -0.3 [-4.3 , 1.8], $P = 0.012$) as well as a greater increase in MPR (median [IQR] of 0.6 [0.08 , -2.1] vs. -0.4 [-0.85 , 0.37], $P = 0.033$). A reduction in percentage forced vital capacity (FVC%) and total lung capacity (TLC%) over the follow-up period was associated with a reduction in LV ejection fraction (LVEF) ($\rho = 0.441$, $P = 0.013$; $\rho = 0.367$, $P = 0.046$) and MPR ($\rho = 0.458$, $P = 0.028$; $\rho = 0.542$, $P = 0.009$) (Figure 2).

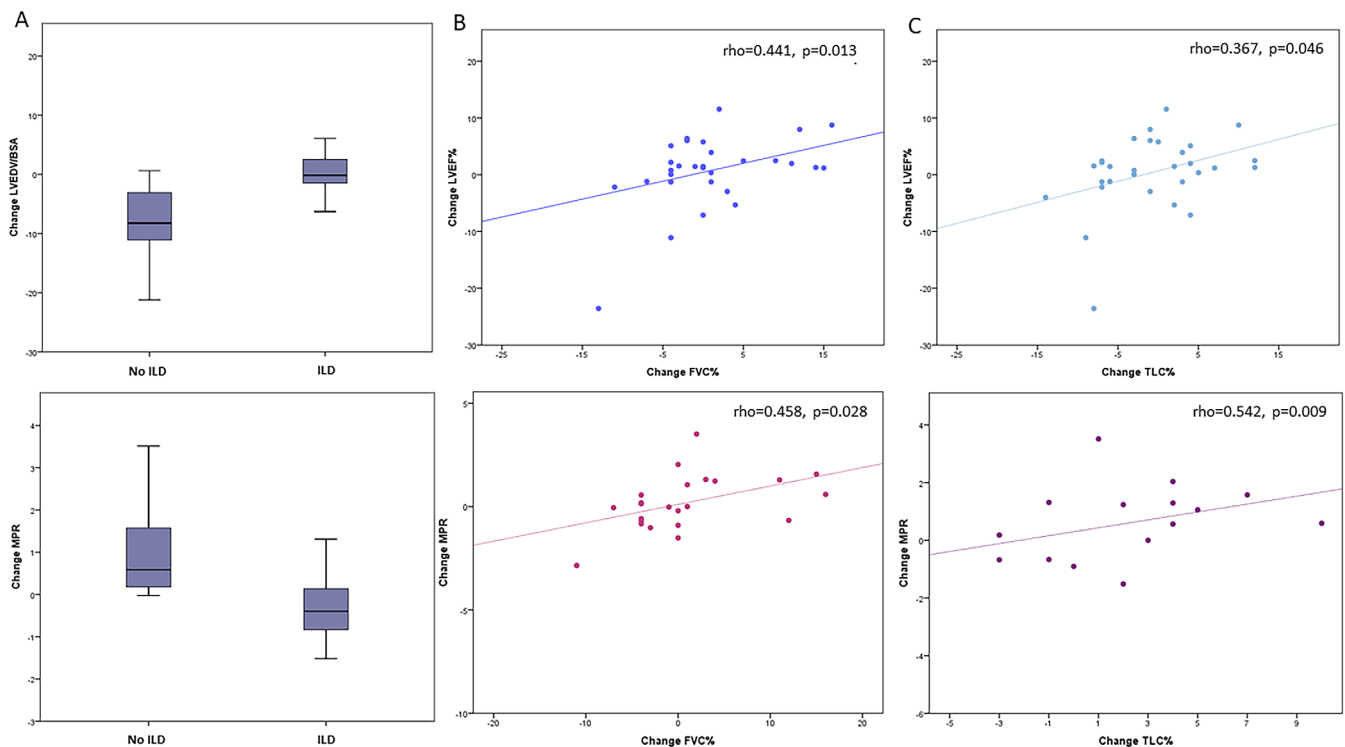


Figure 2. Interstitial lung disease (ILD) and change in cardiovascular magnetic resonance (CMR) indices. **A**, Change in left ventricular end-diastolic volume (LVEDV)/body surface area (BSA) and myocardial perfusion reserve (MPR) in those with and without ILD. **B**, Correlation between the change in forced vital capacity (FVC) and change in left ventricular ejection fraction (LVEF%) and MPR. **C**, Correlation between the change in total lung capacity (TLC) and change in LVEF% and MPR.

There was also a trend association between a history of DU and change in ECV and aortic distensibility ($\rho = 0.348$, $P = 0.059$; $\rho = 0.377$, $P = 0.057$). Further analysis showed no clear difference in CMR parameters in patients with SSc with and without a history of DU at visit 1 or in those with a history of DU between visit 1 and visit 2 (Supplementary Table 1, Table 3). Patients with a history of DU showed a trend increase in ECV and aortic distensibility compared to those with no history of DU between the two visits (median [IQR] 0.8 [−0.2, 1.4] vs. −1.4 [−3.5, 1.1], $P = 0.063$; median [IQR] 1.2 [−0.7, 4.6] vs. −0.5 [−1.8, 0.4], $P = 0.062$).

An increase in the NT-proBNP level was associated with a reduction in MPR ($\rho = -0.448$, $P = 0.042$). No association between the change in hs-TnI and CMR parameters was noted.

No other notable association between CMR change and clinical variables, including disease duration, disease subset, antibodies, mRSS, and mRSS change, was noted.

DMARD treatment and change in CMR measures.

Patients receiving DMARD treatment at visit 1 had higher LVESV/BSA (mean [SD] 32 [10] vs. 24 [5], $P = 0.01$) and LVEDV/BSA (mean [SD] 79 [20] vs. 69 [9], $P = 0.066$) compared to those on no DMARD treatment at visit 1 (Figure 3, Supplementary Table 2).

For those who continued to receive DMARD treatment or commenced a new DMARD treatment during the follow-up period ($n = 20$), an increase in native T1 (mean [SD] 1208 [65] vs. 1265 [56], $P = 0.008$) was noted between the two CMR visits. Although the means remained within normal limits, a decrease in LVSV/BSA (mean [SD] 49 [8] vs. 46 [8], $P = 0.023$) was also noted between the two visits (Supplementary Table 3).

All three patients with either an increase in LGE scar mass or new focal LGE received DMARD treatment between the two visits: two with MMF and one with cyclophosphamide followed by MMF.

Targeted vasodilator and/or ACEI treatment and change in CMR measures. Although the means remained within normal limits, patients with SSc receiving targeted vasodilator treatment had lower LVESV/BSA compared to those with no vasodilator treatment at visit 1 (mean [SD] 25 [4] vs. 32 [11], $P = 0.021$) (Figure 3, Supplementary Table 2). A non-clinically significant decrease in LVSV/BSA between visit 1 and visit 2 in patients receiving targeted vasodilator treatment or commencing new vasodilator therapy during follow-up was noted (mean [SD] 47 [6] vs. 43 [7], $P = 0.013$) (Supplementary Table 3).

There was no significant difference in CMR indices in those with and without ACEI treatment at visit 1 and in those who continued to receive ACEI treatment or commenced new ACEI treatment between visit 1 and visit 2 (Figure 3, Supplementary Tables 2 and 3).

DISCUSSION

The current study is one of the first to assess interval change of CMR-detected SSc primary heart involvement in patients with SSc free of CVD and to explore clinical markers associated with progression. Serial CMR may detect interval subclinical SSc primary heart involvement progression, although this pilot study appears to suggest abnormalities remain largely stable within the follow-up interval. However, when observed, interval CMR change, including increase in LGE focal fibrosis and decline in systolic function and MPR, occurred with the dcSSc subtype, Scl-70+, and ILD progression and in patients receiving DMARD treatment, reflecting a poor prognosis group and perhaps a subgroup in whom follow-up may be justifiable.

Several studies employing echocardiography, including speckle tracking, have investigated interval change in cardiac function of patients with SSc, demonstrating deterioration in systolic or diastolic dysfunction (29–31). However, most of these studies did not clarify the etiology and did not necessarily focus

Table 3. CMR measures at visit 1 and visit 2 in patients with SSc with ILD and history of DUs

CMR parameters	Patients with ILD ($n = 16$), mean (SD)			Patients with a history of DUs ($n = 8$), mean (SD)		
	Visit 1	Visit 2	P	Visit 1	Visit 2	P
LVEDV/BSA (ml/m ²)	76 (20)	77 (17)	0.689	72 (7)	67 (7)	0.087
LVESV/BSA (ml/m ²)	31 (10)	31 (12)	0.714	26 (4)	24 (5)	0.334
LVSV/BSA (ml/m ²)	48 (10)	46 (9)	0.185	46 (7)	43 (4)	0.214
LV mass/BSA (g/m ²)	43 (12)	43 (9)	0.898	41 (11)	44 (6)	0.271
LVEF%	62 (6)	60 (8)	0.427	64 (5)	64 (5)	0.977
ECV%	29 (3), $n = 15$	28 (4)	0.069	30 (4)	31 (4)	0.131
Native T1 (ms)	1222 (79), $n = 14$	1236 (70)	0.659	1208 (22)	1242 (29)	0.488
MPR	2.1 (0.6), $n = 14$	1.9 (0.7)	0.424	2.9 (1.34), $n = 5$	2.03 (0.49)	0.171
Aortic distensibility	5.2 (2.2), $n = 13$	5.1 (2.8)	0.950	4.3 (1.3), $n = 6$	6.2 (3.8)	0.216
Torsion	12.3 (4.6), $n = 13$	12.4 (4.8)	0.924	11.9 (4.6), $n = 5$	12.6 (3.2)	0.648

Note: Paired sample t -test.

BSA, body surface area; CMR, cardiovascular magnetic resonance; DU, digital ulcer; ECV, extracellular volume fraction; ILD, interstitial lung disease; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MPR, myocardial perfusion reserve; SSc, systemic sclerosis.

$P < 0.05$.

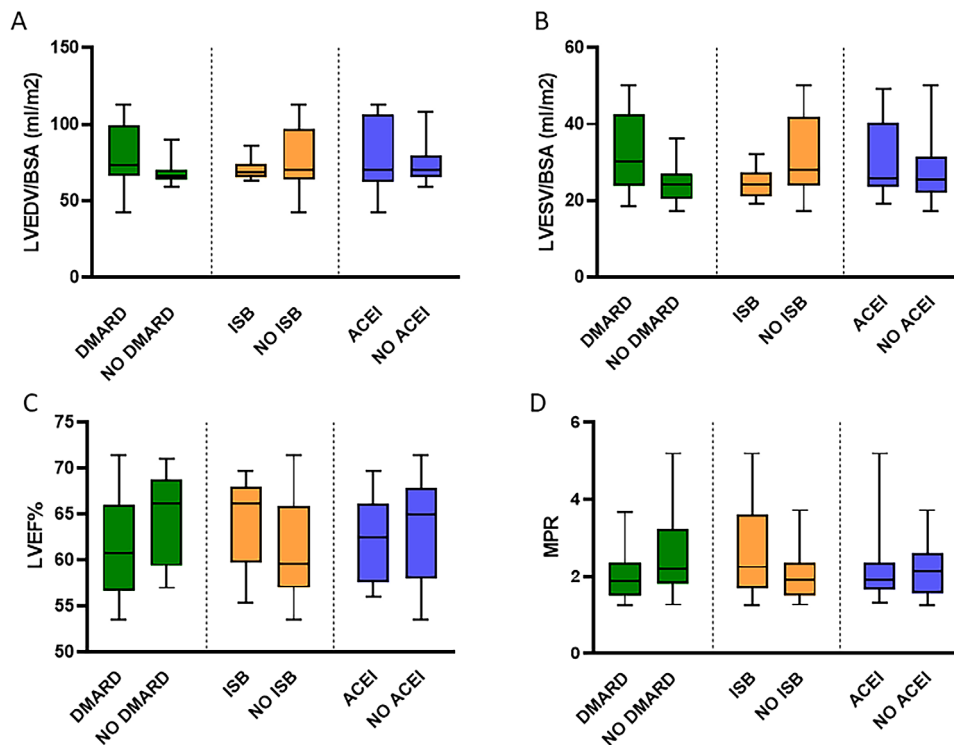


Figure 3. Cardiovascular magnetic resonance (CMR) measures at visit 1 in patients with systemic sclerosis (SSc) with and without disease-modifying antirheumatic drug (DMARD), targeted vasodilator, and angiotensin-converting enzyme inhibitor (ACEI) treatment. **A**, Mean (SD) left ventricular end-diastolic volume (LVEDV)/body surface area (BSA) at visit 1 in those with and without DMARD, targeted vasodilator, and ACEI treatment. **B**, Mean (SD) left ventricular end-systolic volume (LVESV)/BSA at visit 1 in those with and without DMARD, targeted vasodilator, and ACEI treatment. **C**, Mean (SD) left ventricular ejection fraction (LVEF) at visit 1 in those with and without DMARD, targeted vasodilator, and ACEI treatment. **D**, Mean (SD) myocardial perfusion reserve (MPR) at visit 1 in those with and without DMARD, targeted vasodilator, and ACEI treatment. ISB, iloprost and/or sildenafil and/or bosentan.

exclusively on primary cardiac involvement. One small sample study ($n = 11$ of a total of 44) that explored CMR change in patients with SSc, demonstrated new LGE established fibrosis in 8 of 11 patients and overall reduction in MPR (32).

Our study showed that except for one confirmed myocarditis, no other patients with findings on initial CMR showed progression to clinically overt SSc primary heart involvement. Two patients developed new LGE focal fibrosis but with no clinical association, and of those who already presented LGE at visit 1, there was no significant change in the pattern or distribution. Also, no significant change in the CMR measures of diffuse fibrosis was observed. MPR and aortic distensibility showed no sizeable deterioration, and the means of LV function and mass remained within normal limits over the follow-up period.

CMR interval deterioration, when observed, was consistent with a poor prognosis group. All three patients with either an increase in LGE or new LGE at follow-up had dcSSc with ILD (two were Scl-70+, one was anti-RNA+, and one also had myocarditis). Patients without ILD showed marginally improved CMR measures of function and a greater increase in MPR compared to those with ILD, whereas FVC% and TLC% decline was associated with decreased LVEF and MPR. We have previously

demonstrated higher ECV values in patients with SSc with a history of DU (15), and current data showed a trend increase in ECV between the two visits in patients with a history of DU, suggesting a potential correlation between peripheral and myocardial processes. Several studies have also explored the relationship between cardiac functional impairment and disease phenotype in unselected patients with SSc (30,31). By using speckle tracking strain echocardiography, one study showed deterioration of the global longitudinal strain (GLS), LV diastolic function, and right ventricular systolic function in 39 of 234 patients; GLS reduction was associated with higher mRSS, proximal muscle weakness, and lower diffusing capacity of the lungs for carbon monoxide (30).

The results of the current study showed association of hs-TnI measured at visit 1 with systolic function deterioration, whereas there was an inverse correlation between the change in NT-proBNP and MPR. The prognostic implications of hs-TnI and NT-proBNP measurement as well as the dynamic changes of cardiac biomarkers in predicting CVD and CV events have been previously described (33–36). The NT-proBNP level can increase in the setting of myocardial ischemia and has also been associated with decreased MPR in patients with no CVD (37,38), suggesting

a potential relationship between NT-proBNP and myocardial microvascular dysfunction. No association between cardiac biomarkers and CMR measures of fibrosis (focal or diffuse) was found, potentially related to the small sample size. Further research is needed to assess the utility of serial measurement of cardiac biomarkers for identifying patients at risk of SSc primary heart involvement and progression.

The effect of DMARD and vasodilator treatment in CMR-detected SSc primary heart involvement was also explored. The benefit of immunosuppressive treatment has been documented in noninfective myocarditis, and case report as well as more recent small-sample-size studies also report its benefit in SSc myocarditis (39–44). However, there is no evidence on the potential effect of DMARD treatment in sub-clinical SSc primary heart involvement. The current work showed no improvement in CMR measures for those receiving DMARD treatment. Conversely, a greater decline in systolic function and increase in native T1 was observed in the DMARD group at visit 2, and three patients developed new or increased LGE scar mass, reflecting a poor prognostic group that will likely develop CMR deterioration despite receiving immunosuppressive treatment.

The beneficial role of ACEI on LV remodeling in heart failure, LV hypertrophy, and myocardial infarction is well known (45–47). There is also evidence suggesting short-term improvement of myocardial perfusion following vasodilator and/or ACEI treatment (12,13,48) as well as a preventive role of standard vasodilator therapy (CCBs or ACEI) and low-dose aspirin on the occurrence of cardiovascular events in SSc (14). The current study showed no clear benefit of vasodilator and/or ACEI therapy in preclinical SSc primary heart involvement. Appropriately designed studies would be needed to clarify the influence of DMARD and/or vasodilator therapy and the course of sub-clinical SSc primary heart involvement.

One of the main limitations of the study is the small sample size. This was an exploratory study to investigate interval change of CMR-detected SSc primary heart involvement and was not designed to control for confounding. Patients were followed up for a modest period, yet all patients had more than 12 months, with the majority having 36 months, between the two CMR visits, by which time progression would be expected. The study minimized the inclusion of atherosclerotic disease by excluding patients with CVD, diabetes, and more than two cardiovascular risk factors, and none of the patients had evidence of myocardial perfusion defects indicative of ischemic heart disease on CMR.

In summary, this was a first exploratory longitudinal study that used CMR to understand the course of cardiovascular involvement in patients with SSc. CMR was able to detect interval change in parameters of fibrosis and function, and these appeared to be associated with other manifestations of disease. However, aside from one confirmed case of myocarditis,

no other patients with findings on the initial CMR scan showed progression that was associated with clinically meaningful SSc primary heart involvement. Although these data suggest that routine interval monitoring with CMR is of minimal value, a poor prognostic group may benefit from follow-up with CMR as well as cardiac biomarker measurement. Larger prospective studies that are designed to address these unmet needs are needed to advance more tailored use of CMR in patients with SSc.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Dumitru and Buch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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