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ORIGINAL RESEARCH

Diffusing capacity of lungs for carbon monoxide associated with subclinical myocardial impairment in systemic sclerosis: A cardiac MR study

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ABSTRACT

Background Systemic sclerosis (SSc) is characterised by microvascular and fibrotic lesions, which are located not only in skin but also in lungs and heart.

Objective This study aimed to investigate the association between lung function and myocardial T1 values using cardiac MR (CMR) imaging in patients with SSc without cardiovascular symptoms.

Methods The SSc patients and age- and sex-matched healthy subjects underwent CMR. The cardiac function and native T1 values of myocardium and lung function were measured. Spearman's rank correlations and linear regression analyses were performed to determine the association between lung function and myocardial T1.

Results Forty-five SSc patients (aged 47.7±13.2 years, 40 females) and 23 (aged 46.0±14.4 years, 20 females) healthy subjects were enrolled. SSc patients exhibited considerably higher native T1 values compared with healthy subjects (1305.9±49.8 ms vs 1272.6±37.6 ms, p=0.006). Linear regression analysis revealed that decrease of diffusing capacity of lungs for carbon monoxide (DLCO) in SSc patients was notably associated with myocardial native T1 value before (β −1.017; 95% CI −1.883 to −0.151; p=0.022) and after adjusting for confounding factors (β −1.108; 95% CI −2.053 to −0.164; p=0.023). Moderate-to-severe decrease of DLCO was found to be significantly associated with myocardial native T1 value (β 48.006; 95% CI 17.822 to 78.190; p=0.003) after adjusting for confounding factors.

Conclusion DLCO inversely correlates with myocardial native T1 values in SSc patients, particularly moderate-to-severely decreased DLCO, suggesting that DLCO might be a potential indicator for subclinical myocardial impairment in SSc patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myocardial involvement (MI) is the primary cause of death in patients with systemic sclerosis (SSc). Cardiac MR (CMR) is the gold-standard method of diagnosis but is not applicable for individuals with contraindications to MR examination, especially for patients with scleroderma renal crisis. Early diagnosis and intervention are important in SSc patients with cardiac complications.

WHAT THIS STUDY ADDS

⇒ First study investigated the association between lung function and myocardial native T1 values using CMR in SSc patients without cardiovascular symptoms.

⇒ A surrogate indicator might be for myocardial impairment in SSc patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ SSc patients with moderate-to-severe decrease of diffusing capacity of lungs for carbon monoxide should be monitored for MI.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease, and microvasculopathy is a major pathophysiological process. Patients with SSc usually exhibit abnormal immune activation, neovascularisation and vascular remodelling. Progressive fibrosis and dysfunction occur in multiple organs with the progression of diseases, such as interstitial lung disease (ILD) and cardiomyopathy.[1] A literature review and meta-analysis on the survival of patients with SSc reported that heart disease is the leading cause of death in SSc patients (19%).[2] Therefore, characterising the myocardial impairment in patients with SSc at in the subclinical stage is important.

Thus, several approaches have been employed for the early detection of myocardial involvement. N-terminal brain natriuretic peptide (NT-proBNP) and cardiac troponin I (CTnI) can be used to diagnose myocardial disorders but their specificity is low.

Echocardiography can detect structural and functional cardiac disorders. However, it is less sensitive in characterising myocardial tissues. Cardiac MR (CMR) imaging has been demonstrated to be an ideal non-invasive modality for assessing myocardial pathology, particularly T1 and T2 mapping.[3] However, CMR is not applicable to individuals with contraindications to MR, especially those patients with scleroderma renal crisis. Therefore, identifying surrogate indicators of myocardial impairment in SSc patients is necessary.

Fibrogenesis is a multistage process that results from impaired tissue repair responses, in which abnormal production of cytokines, growth factors and angiogenic factors turn tissue homeostasis towards the excessive accumulation of extracellular matrix.[4] All organs, including the lungs and heart, can be affected by the same disease process. Limited information is available regarding the association between lungs and heart impairment in patients with SSc.[5] In this study, we aimed to investigate the association between lung function and myocardial native T1 values using CMR in SSc patients without cardiovascular symptoms.

METHODS

Study population

Adult patients with age ranging from 18 to 70 years old were recruited in this study. SSc was diagnosed using the 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for SSc.[6] Patients who met the following criteria were excluded: (1) coexisting with rheumatoid arthritis, systemic lupus erythematosus or polymyositis/dermatomyositis; (2) history of ischaemic or non-ischaemic cardiac diseases; (3) cardiac or respiratory failure; and (4) contraindication to MR examination. All patients underwent examinations for pulmonary function and CMR imaging within 1 week of recruitment. Healthy subjects matched 1:2 with the patient group in terms of age and sex were recruited as normal controls.

Pulmonary function examination

The pulmonary function parameters of all the recruited patients were measured using the Jaeger Masterscreen system (Jaeger Co. Hchberg, Germany): (1) forced expiratory volume in the 1 s (FEV1); (2) forced vital capacity (FVC); (3) total lung capacity (TLC); and (4) diffusing capacity of lungs for carbon monoxide (DLCO). The severity of the decrease of DLCO was categorised into three degrees: normal, DLCO≥80%; mild decrease, DLCO≥60% but <80%; moderate-to-severe decrease, DLCO<60%.[7]

CMR imaging

CMR was performed for all recruited patients and healthy subjects using a 3.0T MR scanner (Ingenia, Philips Healthcare, Best, The Netherlands) with a 16-channel dStream Torso coil and a 12-channel embedded posterior coil. The cine images were acquired with 30 phases per cardiac cycle in standard angulations: 4-chamber view (CV), 2CV and a stack of short-axis slices covering both entire ventricles from the base to the apex. Native T1 mapping imaging was conducted with 4CV and a stack of short-axis slices. Native T1 mapping was acquired on three short-axis views of the mid-ventricular septum and 10 mm up and down with breath holding. The imaging parameters of the CMR protocol are listed in table 1.

CMR image analysis

CMR images were analysed by two experienced observers (H.H. and Z.N.) with over 3-year experience in cardiovascular imaging blinded to grouping and clinical information and pulmonary function measurements using a professional CMR image analysis software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). The boundaries of the left ventricle (LV) were outlined on the corresponding end-systolic and end-diastolic long-axis cine images. In these boundaries, the papillary muscles were excluded. LV end-diastolic volume (LV-EDV), end-systolic volume (LV-ESV) and LV mass were measured and indexed to body surface area (BSA). The global myocardial native T1 values were also assessed on native maps by averaging the global values obtained from the three maps of the short-axis slices. Figure 1 indicates the methodology describing global and regional measurements of myocardial native T1 values.

Table 1 CMR imaging protocol

	CINE	T1 mapping
Acquisition sequence	Turbo field echo	Modified Look-Locker inversion recovery
TE (ms)	1.43	2.0
TR (ms)	2.9	0.89
FA (deg)	40	35
FOV (mm^2)	334×314	300×300
Slice thickness (mm)	10	10
Resolution (mm^2)	0.99×0.99	1.17×1.17

FA, flip angle; FOV, field of view; TE, echo time; TR, repetition time.

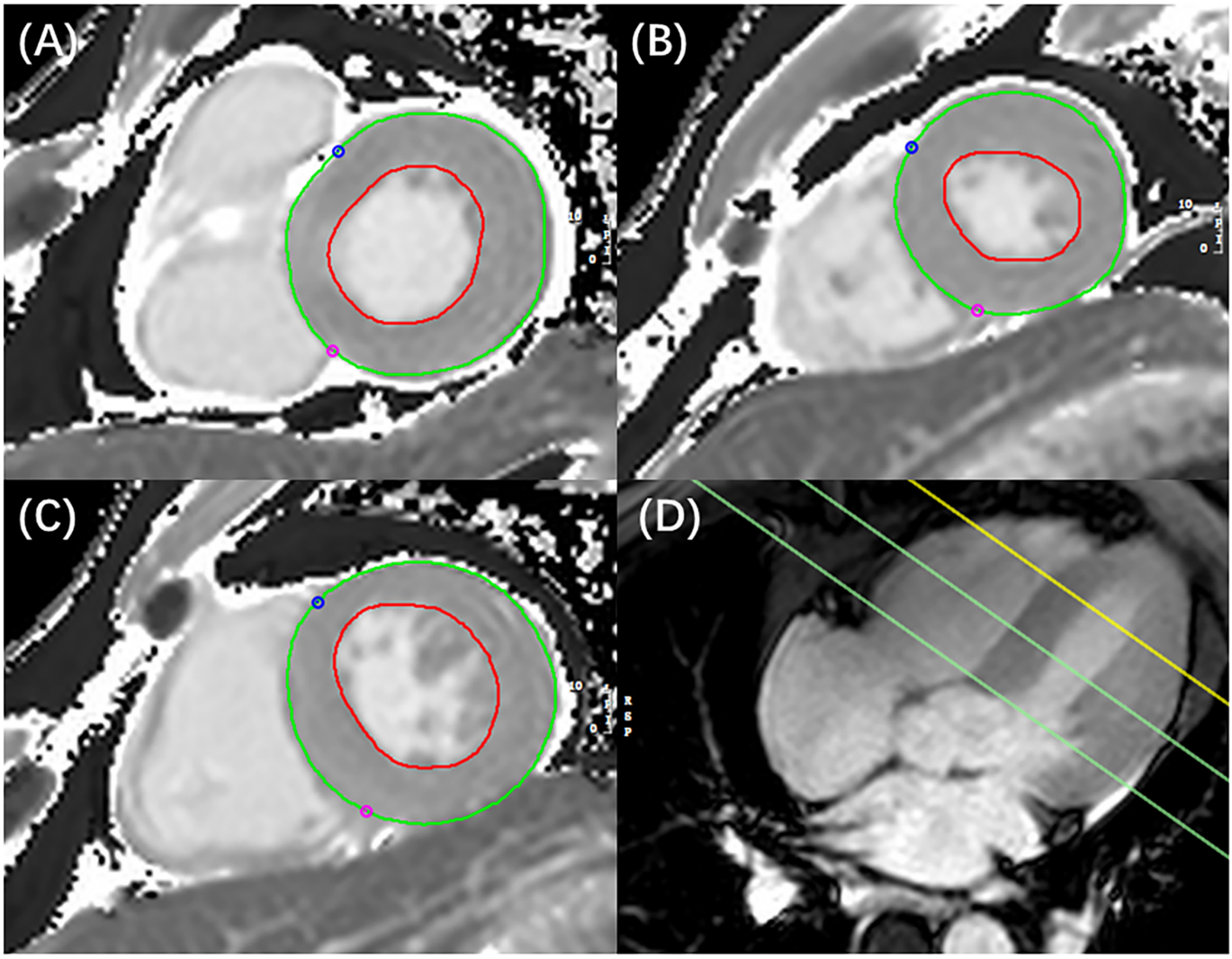

Figure 1 Representative cardiac MR measurements. The image of (A–C) demonstrated measurements of three slices of global native myocardial T1 in a SSc patient using the CVI (CVI42, Calgary, Canada). The image of (D) described the subject's 4 chamber-view (CV) of short-axis slices. The endocardial and epicardial contours were manually drawn, meticulously avoiding potential contamination by blood pool and/or epicardial fat. Global myocardial T1 was then calculated as the mean value of three short-axis slices. CVI, cardiovascular imaging; SSc, systemic sclerosis.

Clinical and laboratory data collection

Clinical characteristics including age, sex, body mass index (BMI), cardiovascular risk factors, age at onset of SSc, SSc subset, Raynaud's phenomenon, digital ulcers, arthralgias, arthritis, myositis, ILD, pulmonary arterial hypertension (PAH), LV diastolic dysfunction, gastrointestinal involvement, renal involvement and haematological involvement were collected. Patients were classified into limited and diffused cutaneous subsets.[8] Age at disease onset was defined as the age at the first non-RP SSc manifestation. ILD was defined as the presence of ground-glass opacification or fibrosis on high-resolution CT (HRCT) imaging. PAH was defined as a mean pulmonary arterial pressure >25 mm Hg at rest, together with pulmonary capillary wedge pressure <15 mm Hg determined via right heart catheterisation or pulmonary artery systolic pressure >40 mm Hg at rest based on an echocardiogram. Leucopenia was defined as a white blood cell count of $<3.5\times10^9$/L whereas thrombocytopenia was defined as a platelet count of $<100\times10^9$/L, excluding other causes, such as drug and infection.

The following laboratory tests were conducted within 1 month after enrolment: BNP or NT-proBNP and CTnI. Anti-topoisomerase I antibodies (anti SCL70) antibodies and anticentromere antibodies within 1 year of enrolment. BNP>100 pg/mL, NT-proBNP>125 pg/mL and cTnI>0.05 ng/mL were considered to be elevated levels.

Statistical analysis

Quantitative variables are presented as the mean±SD or medians (IQR). Qualitative data are presented as count and percentage. Differences between groups were analysed using the independent t, Mann-Whitney U or the χ^2 tests, depending on the normal distribution of the variables. Associations between the clinical and laboratory data and myocardial T1 values were determined using

Spearman's correlation analyses. The correlation coefficient of Spearman's correlation was categorised into the following levels: weak correlation, r=0.2–0.4; moderate correlation, r=0.4–0.6; strong correlation, r=0.6–0.8 and very strong correlation, r>0.8. Univariate and multivariate linear regression analyses were performed to assess the association between the lung function and myocardial native T1 values. For multivariate analysis, the confounding factors for adjustment were defined when the p value was <0.1 in univariate analysis. A p<0.05 was considered to be statistically significant. Data were analysed using SPSS V.26.0 (SPSS, IBM).

RESULTS

A total of 45 SSc patients and 23 healthy subjects were recruited between November 2021 and March 2023. Of the 45 SSc patients, the mean age was 47.7±13.2 years and the mean age for onset was 41.0±14.1 years. Further, 40 (88.9%) were females, 23 (51.1%) were classified as dcSSc, 28 (62.2%) had ILD and 13 (28.9%) had LV diastolic dysfunction. In this study population, the median disease duration was 5.36 (3.0, 9.1) years and the median modified rodnan skin score (mRSS) was 2 (1, 6). Of the 23 healthy subjects, the mean age was 46.0±14.4 years old and 20 (87%) are females. There was no significant difference in age (p=0.639) or sex (p>0.999) between the patient and healthy control groups.

CMR imaging characteristics

In this study population, cardiac cine imaging showed that the LVEDV/BSA, LVESV/BSA, LVED mass/BSA and LVEF were 64.5±10.5 mL/m^2, 23.2±7.4 mL/m^2, 48.1±8.1 g/m^2 and 66.3±4.3%, respectively. Myocardial quantitative imaging showed the mean native T1 value was

Table 2 Clinical characteristics and their correlation with myocardial T1 values

	Mean±SD, median (IQR) or n (%)	r	P value
General information			
Age at onset, years old	41.0±14.3	−0.077	0.616
Years since diagnosis	5.36 (3.0–9.1)	−0.019	0.902
Sex, male	5 (11.1)	−1.74	0.252
BMI, kg/m^2	22.6±3.8	−0.183	0.177
Diabetes	4 (8.9)	0.165	0.278
Hypertension	6 (13.3)	−0.103	0.500
Smoking	2 (4.4)	−0.032	0.832
Subset (dcSSc)	23 (51.1)	−0.161	0.291
Modified Rodnan skin score	2 (1–6)	−0.042	0.783
Manifestations			
Raynaud's phenomenon	42 (93.3)	0.165	0.280
Myositis	6 (13.3)	0.199	0.190
Arthritis/arthralgia	10 (22.2)	0.239	0.114
Digital ulcers	12 (26.7)	−0.006	0.970
ILD	28 (62.2)	0.028	0.854
PAH	1 (2.2)	−0.012	0.940
LV diastolic dysfunction	13 (28.9)	0.021	0.892
Scleroderma renal crisis	2 (4.4)	0.199	0.189
Leucopenia	4 (8.9)	−0.120	0.504
Thrombocytopaenia	3 (6.7)	0.130	0.393
Laboratory test			
eGFR (mL/min)	105±27.6	−0.001	0.996
Anti-SCL70 antibody positivity	17 (37.8)	−0.152	0.320
ACA positivity	4 (8.9)	0.084	0.582
Evaluated BNP or NT-proBNP	12 (26.7)	−0.072	0.640
Evaluated CTnI	1 (2.2)	0.197	0.194

anti-Scl 70, anti-topoisomerase I antibodies; ACA, anticentromere antibody; BMI, body mass index; BNP, brain natriuretic peptide; CTnI, cardiac troponin I; dcSSc, diffuse cutaneous SSc; eGFR, estimated glomerular filtration rate; ILD, interstitial lung disease; LV, left ventricle; NT-proBNP, pro-hormone BNP; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

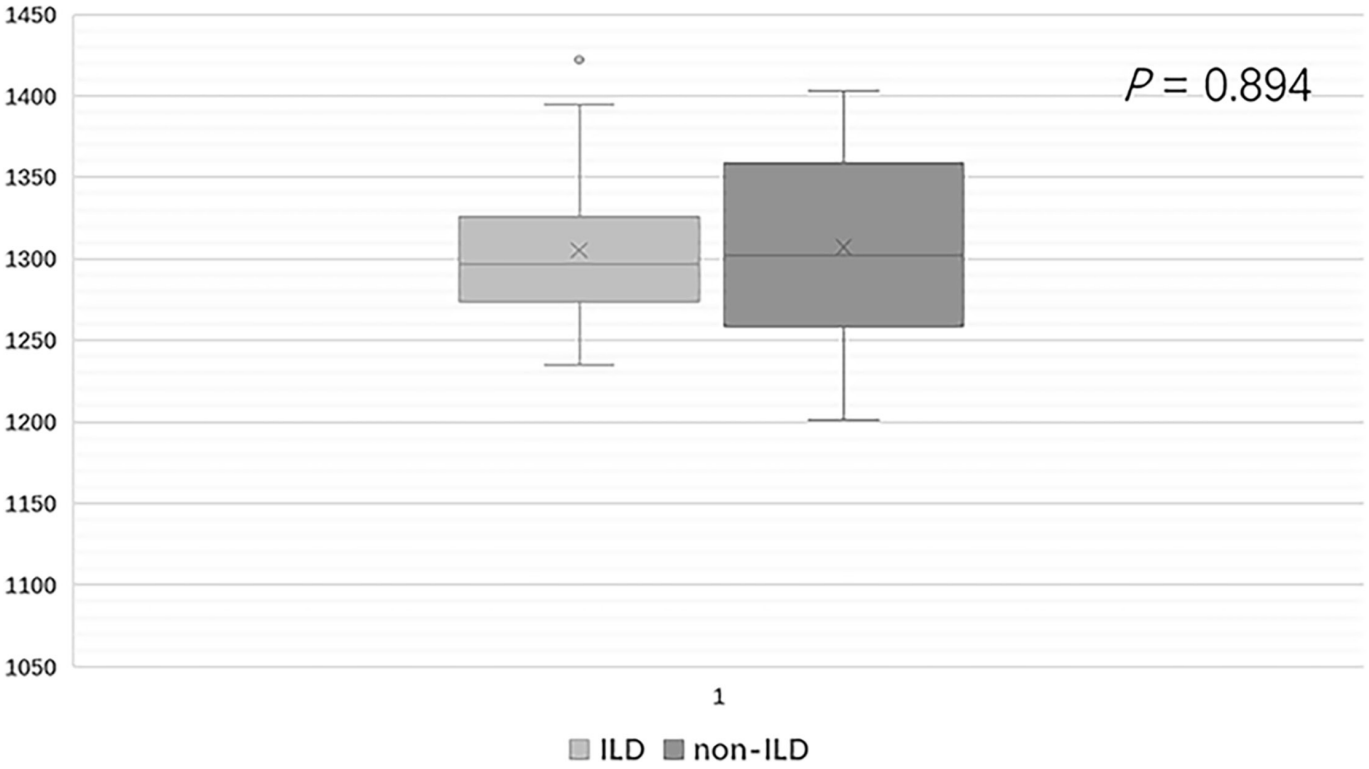

Figure 2 No significant differences were observed between SSc patients with and without ILD in native T1 values. ILD, interstitial lung disease; SSc, systemic sclerosis.

significantly higher in SSc patients than that in healthy subjects (1305.9±49.8 ms vs 1272.6±37.6 ms, p=0.006). LV walls of all subjects were manually segmented according to the AHA 16-segment model. Compared with healthy controls, there were higher native T1 values within most of the LV segments in SSc patients, such as the septal and lateral LV (segments1, 2, 3, 4, 13, 14 and 16) and the mid-region of the LV (segments 7, 8, 9, 10, 11 and 12) (all p<0.05). No significant differences were observed between the patients and healthy subjects in terms of cardiac function (all p>0.05).

Table 3 Lung function and its correlation with myocardial T1 value

	Mean±SD, median (IQR) or n (%)	R	P value
DLCO (%)	65.6±16.6	−0.342	0.022
<80	34 (75.6)	0.195	0.199
<60	16 (36.4)	0.427	0.003
FVC (%)	85.3±19.	−0.170	0.265
<80	13 (28.9)	0.060	0.693
<60	3 (6.7)	0.213	0.161
FEV1 (%)	84.3±16.4	−0.242	0.109
<80	11 (24.4)	0.175	0.250
<60	4 (8.9)	0.226	0.136
TLC (%)	85.2±19.0	−0.158	0.300
<80	16 (35.6)	0.168	0.279
<60	2 (4.4)	0.116	0.447

P value was compared between different subjects or groups of patient lung function and its correlation with myocardial T1 value. DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TCL, total lung capacity; TLC, total lung capacity.

Correlation between clinical and laboratory characteristics and myocardial native T1

Table 2 summarises the results of the correlations between clinical and laboratory characteristics and myocardial native T1 values in the patient group. There was no difference in myocardial native T1 values between SSc patients with and without diastolic dysfunction (n=13, 1307.5±49.0 ms vs n=32, 1305.3±50.9 ms, p=0.894). No significant correlations were found between clinical and laboratory characteristics and myocardial native T1 values in SSc patients (all p>0.05). We also assessed the association of myocardial native T1 values in SSc patients with and without ILD, as shown in figure 2 (p>0.05).

Association between lung function and myocardial native T1 in SSc patients

Lung functional test revealed that the mean FVC, FEV1, TLC and DLCO were 85.3%±19.0%, 84.3%±16.4%, 85.2%±19.0% and 65.6%±16.6%, respectively (table 3). There was a weak negative correlation between DLCO (%) and myocardial native T1 values (r=−0.3427, p=0.022), and a moderate correlation between DLCO<60% and myocardial native T1 values (r=0.427, p=0.003).

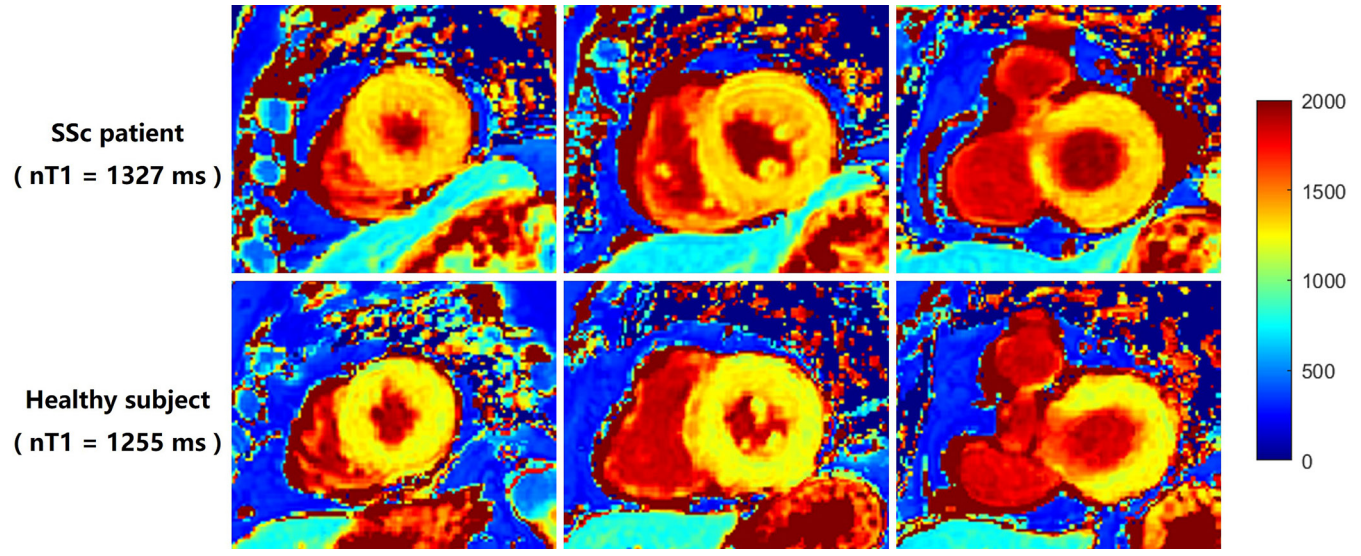

Figure 3 An SSc patient in their 50s with declined DLCO (54%) and elevated myocardial native T1 (1327 ms). Images showed the native T1 maps of myocardium of a healthy subject in their 50s with the mean T1 value of 1255 ms. The MRIs of T1 maps of myocardium were acquired from short axis slices of left ventricle. nT1, native T1 value. DLCO, diffusing capacity of lungs for carbon monoxide; SSc, systemic sclerosis.

Myocardial native T1 values in SSc patients with DLCO (%) <60% were significantly higher than those with DLCO≥60% to <80% (1334.5±44.5 ms vs 1289.9±46.4 ms, p=0.007) and ≥80% (1334.5±44.5 ms vs 1290.5±47.5 ms, p=0.019). Figure 3 presents a typical case of myocardial native T1 value in a SSc patient (DLCO<60%) and an age-matched and sex-matched healthy subject. Correlations between other lung function measurements and myocardial native T1 values were not statistically significant (all p>0.05, table 3).

Univariate linear regression analysis revealed that DLCO was significantly associated with myocardial native T1 value (β −1.017; 95% CI −1.883 to −0.151; p=0.022). This association remained significant after adjustment in multivariate regression analysis (β −0.887; 95% CI −1.810 to −0.037; p=0.059) in model 1 including confounding factors of age, sex and BMI and in model 2 (β −1.108; 95% CI −2.053 to −0.164; p=0.023) including confounding factors of age, sex, BMI and ILD. When normal DLCO was considered as reference, moderate-to-severe decrease in DLCO was found to be significantly associated with myocardial native T1 before (β 44.397; 95% CI 15.845 to 72.948; p=0.003) and after adjusting for confounding factors of age, sex and BMI (model 1: β 42.867; 95% CI 13.696 to 72.039; p=0.005) and confounding factors of age, sex, BMI and ILD (model 2: β 48.006; 95% CI 17.822 to 78.190; p=0.003). However, the association between mild decreases in DLCO and myocardial native T1 was not statistically significant (all p>0.05) (table 4).

DISCUSSION

This study investigated the association between lung function and myocardial native T1 values using quantitative MRI. We observed that DLCO inversely correlated with myocardial native T1 values, particularly for

Table 4 Linear regression analysis between lung function and myocardial native T1 value

			Multivariate regression			
	Univariate regression		Model 1		Model 2	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
DLCO	−1.017 (−1.883 to −0.151)	0.022	−0.971 (−1.889 to 0.053)	0.039	−1.108 (−2.053 to 0.164)	0.023
Severity of DLCO						
Normal	Reference		Reference		Reference	
Mild decrease	−20.548 (−55.228 to 14.132)	0.239	−16.039 (−53.084 to 21.006)	0.387	−17.974 (−55.313 to 19.364)	0.336
Moderate-to-severe decrease	44.397 (15.845 to 72.948)	0.003	42.867 (13.696 to 72.039)	0.005	48.006 (17.822 to 78.190)	0.003

Model 1: adjusted for age, sex, BMI; model 2: adjusted for age, sex, BMI, progression of skin fibrosis and ILD.
BMI, body mass index; DLCO, diffusing capacity of lungs for carbon monoxide; ILD, interstitial lung disease.

moderate-to-severe decrease of DLCO. Our findings indicate that lung function may be a surrogate indicator for myocardial impairment in SSc patients.

In the present study, we found that the myocardial native T1 value of SSc patients was higher than that of healthy subjects. In our study population, the mean value of myocardial T1 was 1305.9±49.8 ms. A previous study of SSc patients demonstrated that the cut-off point of native T1 of abnormal myocardium was >1240 ms (with 3T Philips Achieva TX system equipped with a 32-channel coil, mid-LV native T1 maps were using an MOLLI sequence).[9] An increase in T1 values in the myocardium may indicate myocardial fibrosis pathophysiologically. Gotschy *et al* reported that diffuse myocardial fibrosis may occur with subclinical cardiac involvement in patients with early stages of SSc.[10] Increased T1 values in the myocardium can also be attributed to oedema. However, Gargani *et al* reported that only 2.5% of SSc patients had myocardial oedema, but LGE (with negative T2-weighted images) was detected in 27.9% of SSc patients,[11] suggesting that fibrosis is more common than oedema in the myocardium of SSc patients. Mavrogeni *et al* found that T1 values correlated with decreased cardiac function in SSc patients.[12] There were also evidences between T1 values and diastolic dysfunction (with impaired peak diastolic strain rate, elevated E/E′ and increased left atrial dimensions).[13 14]

In our study population, most patients (75.6%) showed decreased DLCO. However, HRCT demonstrated that only 62.2% of patients had ILD. Meanwhile, no significant differences were observed in native T1 values between patients with and without ILD. The DLCO in SSc may reflect the loss of the alveolar surface or thickening of the blood–gas barrier. SSc patients with ILD have lower DLCO compared with those without ILD.[15] Microangiopathy in patients with SSc can lead to a decrease in DLCO.[16] A cross-sectional study found a lower DLCO in patients with SSc-PAH than in those with non-connective tissue disease and pulmonary hypertension. A correlation between DLCO and peak RVEF and LVEF exists,[17] but the direction of causation is unclear, and the exact cause is yet to be determined. A cross-sectional study recruiting 136 patients showed that patients with abnormal capillaroscopic findings had slightly worse DLCO (71.43%±21.19% vs 85.9%±19.81%, p<0.01) compared with those without abnormal capillaroscopic findings.[18]

In our study, we found that some lung function measurements, especially moderate-to-severe decreases in DLCO, were significantly associated with the native T1 value of the myocardium in patients with SSc. Chronic inflammation, the major pathophysiological process of SSc in the early stage, persistently activates interstitial fibroblasts in multiple organs, including the lungs and heart, leading to irreversible fibrosis and a subsequent decline in function.[19] McCann *et al* evaluated patients with SSc and PAH and found a significant association between myocardial late enhancement and the right ventricular ejection fraction.[20] Patrick *et al* demonstrated a significant association between the extent of the pulmonary GG (ground glass) subcomponent of pulmonary fibrosis and early-stage myocardial fibrosis on CMR in SSc patients.[21] In our study, we found that a moderate-to-severe decrease in DLCO was significantly associated with myocardial native T1 but this association was not found in a mild decrease in DLCO. We also found that 62.2% (28/45) of the SSc patients had known ILD, but none showed cardiac dysfunction or clinical symptoms. Our findings indicate that in SSc patients, tissue impairment may occur earlier in the lungs than in the heart. The pulmonary diffusion function may decline earlier in subclinical myocardial impairment, suggesting that it may be a potential indicator for myocardial involvement in patients with SSc. In contrast, because DLCO can be affected by many factors, combined with other clinical indicators of myocardial impairment (such as NT-proBNP, CTnI and Echo), it is more helpful for predicting myocardial involvement at an early stage.

This study had some limitations. First, the sample size was small and the ratio of samples in the patient and healthy groups was not 1:1. Therefore, future studies with larger sample sizes are warranted. Second, an isolated decrease in DLCO is a frequent indication for spiroergometry. In addition, cardiopulmonary exercise testing (CPET) is useful for characterising multifactorial exercise limitations in patients with SSc and for identifying SSc-related complications such as ILD and PAH.[22] In the absence of baseline PAH, CPET indices may predict pulmonary function deterioration and death in SSc patients.[23] However, this was not the case in our study because we did not undertake it. Third, considering the potential side effects of contrast medium administration, postcontrast CMR imaging was not performed in this study. This leads to the unavailability of late enhancement and extracellular volume assessments. Finally, because HRCT images of most patients are unavailable, it was challenging to quantitatively analyse ILD.

CONCLUSION

The decrease in lung function inversely correlates with increased myocardial native T1 values in SSc patients, particularly for moderate-to-severe decreases in DLCO, suggesting that lung function measurements might be a potential indicator for subclinical myocardial impairment in SSc patients.

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Contributors HH, DX and XZ were major contributors to the study design, data interpretation, and writing and revision of the manuscript. XT and ZN performed the data analysis. JZ, YW, Z-XH, QW and XZ performed the patient studies and acquired the data from patient studies. CD technically defines the CMR protocol. All the authors read and version of the approved the final manuscript. DX is responsible for the overall contact as the guarantor.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and the study protocol was approved by institutional review board (The Research Ethics Committee of Peking Union Medical College Hospital, No. ZS-3245). Participants gave informed consent to participate in the study before taking part.

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