Additional value of T1 and T2 mapping techniques for early detection of myocardial involvement in scleroderma

Antonella Meloni [a], Luna Gargani [b], Cosimo Bruni [c,d], Camilla Cavallaro [e], Marco Gobbo [f], Andreina D'Agostino [b], Gennaro D'Angelo [g], Nicola Martini [a], Francesco Grigioni [e], Gianfranco Sinagra [f], Raffaele De Caterina [b], Emilio Quaia [h], Sophie Mavrogeni [i], Filippo Cademartiri [a], Marco Matucci-Cerinic [c,j], Alessia Pepe [h,*]

[a] *Department of Radiology, Fondazione G. Monasterio CNR-Regione Toscana, Pisa, Italy*
[b] *Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy*
[c] *Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Florence, Italy*
[d] *Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland*
[e] *Cardiovascular Department, University Campus Bio-Medico, Roma, Italy*
[f] *Cardiovascular Department, Azienda Sanitaria Universitaria di Trieste, Department of Medical Surgical and Health Sciences, University of Trieste, Trieste, Italy*
[g] *Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[h] *Institute of Radiology, Department of Medicine, University of Padua, Padua, Italy*
[i] *Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece*
[j] *Unit of Immunology, Rheumatology, Allergy and Rare diseases (UnIRAR), IRCCS San Raffaele Hospital, Milan, Italy*

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ABSTRACT

Background: We evaluated the prevalence of myocardial involvement by native T1 and T2 mapping, the diagnostic performance of mapping in addition to conventional Lake Louise Criteria (LLC), as well as correlations between mapping findings and clinical or conventional cardiovascular magnetic resonance (CMR) parameters in systemic sclerosis (SSc) patients.

Methods: Fifty-five SSc patients (52.31 ± 13.24 years, 81.8% female) and 55 age- and sex-matched healthy subjects underwent clinical, bio-humoral assessment, and CMR. The imaging protocol included: T2-weighted, early post-contrast cine sequences, native T1 and T2 mapping by a segmental approach, and late gadolinium enhancement (LGE) technique.

Results: Global myocardial T1 and T2 values were significantly higher in SSc patients than in healthy subjects. An increase in native T1 and/or T2 was present in the 62.1% of patients with normal conventional CMR techniques (negative LGE and T2-weighted images). Respectively, 13.5% and 59.6% of patients fulfilled original and updated LLC (overall agreement = 53.9%).

Compared with patients with normal native T1, patients with increased T1 (40.0%) featured significantly higher left ventricular end-diastolic volume index and cardiac index, biventricular stroke volume indexes, and global heart T2 values, and more frequently had a history of digital ulcers. Biochemical and functional CMR parameters were comparable between patients with normal and increased T2 (61.8%).

Conclusion: T1 and T2 mapping are sensitive parameters that should be included in the routine clinical assessment of SSc patients for detecting early/subclinical myocardial involvement.

1. Introduction

Systemic sclerosis (SSc) is a complex, clinically heterogeneous disease, characterized by auto-antibodies, inflammation, microvascular dysfunction, and collagen deposition leading to fibrosis [1]. The heart is one of the organs most frequently affected [2], with the myocardium and pericardium damaged separately or concomitantly [3]. Cardiac involvement is one of the major determinants of morbidity and mortality, accounting for a significant number of SSc-related deaths [4]. Therefore, it is essential to detect cardiac involvement early in a

* Corresponding author at: Institute of Radiology, Department of Medicine, University of Padua, Padua, Italy.
E-mail address: alessia.pepe@unipd.it (A. Pepe).

clinically asymptomatic phase for a better management of SSc patients [5]. This would allow the identification of those patients who can benefit from specific treatments, improving their risk stratification and prognosis.

Multiparametric cardiovascular magnetic resonance (CMR) perfectly fits to this purpose, allowing to detect myocardial fibrosis and edema/inflammation, representing the two hallmarks of myocardial involvement [6,7]. The late gadolinium enhancement (LGE) technique is the gold standard for the non-invasive detection of focal/replacement myocardial fibrosis. In SSc replacement myocardial fibrosis predicts ventricular rhythm disturbances, accounting for the majority of cardiac deaths [8], but it represents a relatively late stage of the disease and it is not reversible. Moreover, the LGE technique has strong limitations in the assessment of diffuse myocardial fibrosis, where there may be little unaffected myocardium, as occurs with SSc. Important advantages in this sense have been brought with the introduction of the native T1 and extracellular volume (ECV) mapping techniques by the detection of the interstitial expansion and the diffuse fibrosis, that match more appropriately with the early and subclinical stages of the disease [9,10]. Both elevated native T1 and ECV were demonstrated to predict adverse events in SSc [11]. Although conventional non parametric T2-weighted (T2-w) imaging can identify areas of myocardial inflammation, both T1 and T2 mapping techniques were demonstrated to be more sensitive for this purposes [12–15]. Particularly in SSc, T2 mapping technique is expected to determine a consistent reduction of false negatives. In fact, the non parametric T2-w images rely on the comparison with a reference region such as the skeletal muscle, which is presumed normal, although it may be often inflamed.

Since 2009, the Lake Louise Criteria (LLC) [16] have been extensively used for the CMR-based diagnosis of myocardial inflammation. Recently, the original LLC have been revised with the implementation of T1 and T2 mapping techniques [17]. To the best of our knowledge, only one study has compared the diagnostic performance of the original LLC and the updated LLC for the diagnosis of cardiac inflammation in SSc and it has not detected a significant difference. However, this study involved only patients with diffuse cutaneous systemic sclerosis, which is the most severe subtype, not representative of the whole SSc population [18].

It has been shown that SSc patients have significantly higher myocardial T1, ECV and T2 values compared with controls, despite the absence of differences in left ventricular (LV) volumes and ejection fractions [9,19,20], suggesting that all mapping techniques may serve as an early screening tool, before the occurrence of overt LV dysfunction. However, the correlation of clinical, biological and CMR findings with elevated native T1 values has been little explored in SSc [19,21] and no such data exist for T2 values.

The aims of this study were: 1) to compare CMR findings between SSc patients and healthy controls matched for age and sex, 2) to evaluate the prevalence of cardiac involvement by native T1 and T2 mapping and to assess the diagnostic performance of mapping in addition to the conventional LLC in SSc patients, 3) to determine the correlation of native myocardial T1 and T2 values with classic CMR parameters and clinical findings in SSc patients.

2. Methods

2.1. Study population

Fifty-five consecutive patients fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for SSc [22] were prospectively enrolled between August 2018 and December 2020. Patients were either asymptomatic or paucisymptomatic for symptoms of possible cardiovascular origin (effort dyspnea, fatigue, and palpitations) and none presented renal failure or any contraindication to CMR. All patients underwent biohumoral assessment within three months from the CMR scan and the clinical history was recorded.

Moreover, 55 healthy subjects matched for age and sex were considered as control population. All healthy subjects had normal electrocardiogram, no history of cardiac diseases or symptoms, no cardiovascular risk factors (CVRF), and no known systemic disease.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the local Ethical Committee (Pisa, Italy). All subjects gave written informed consent.

2.2. CMR

CMR exams were performed on a 1.5 T scanner (Signa Artist; GE Healthcare) using a 30-element cardiac phased-array receiver surface coil with breath-holding and ECG-gating.

Image analysis was performed using MASS® software (Medis, Leiden, The Netherlands).

Three parallel short-axis slices (basal, medial, and apical) of the left ventricle (LV) were acquired in end-diastole by a Modified Look-Locker Inversion recovery (MOLLI) sequence with a 3(3 s)3(3 s)5 scheme for T1 mapping [23] and by a multi-echo fast-spin-echo (MEFSE) sequence for T2 mapping [24]. Pixel-wise T1 and native T2 maps were generated on the scanner and transferred to the workstation for offline post-processing, that involved the manual tracing of endocardial and epicardial borders, avoiding blood pool and epicardial fat, and the definition of the inferior right ventricular (RV) insertion point for the standard myocardial segmentation, according to the AHA/ACC model [25]. Global T1 and T2 values were obtained by averaging the values in all 16 myocardial segments.

Short axis and radial black-blood T2-w short tau inversion recovery (STIR) images were acquired to detect edema. To avoid false negative (inferolateral wall) or false positive (septum) results due to an inhomogeneous sensitivity field of surface coils, a signal intensity (SI) correction algorithm or the body coil were used. The presence of edema was firstly assessed qualitatively by visual analysis and it was considered present when visualised in two different views and confirmed by a semi-quantitative analysis (signal intensity >2 standard deviations above the mean value of skeletal muscle). Moreover, edema was considered present semi-quantitatively when the myocardial T2 ratio, relating the average SI of the LV to that of the skeletal muscle, was >1.9 [16,26].

Short-axis cine steady-state free precession (SSFP) images were acquired immediately after the intravenous administration of a macrocyclic gadolinium-based contrast agent at the standard dose of 0.2 mmol/kg to quantify biventricular function parameters in a standard way [27] and to detect hyperemia [28].

Atrial areas were measured from the 4 chamber view projection in ventricular end-systolic phase.

LGE short-axis, vertical, horizontal, and oblique long-axis images were acquired by a T1-weighted gradient-echo inversion-recovery pulse sequence 8–18 min after the contrast agent administration. Images were evaluated qualitatively by two experienced cardiologists or radiologists for the presence, pattern, and regional distribution of LGE areas.

For 30 patients, post-contrast T1 images were acquired 10 min after contrast medium administration and image analysis was performed by using the same approach employed for pre-contrast T1 images. Segmental ECV values were calculated with input of native and post-contrast myocardial segmental and blood pool T1 values and hematocrit, as described by Arheden et al. [29].

CMR protocol for age- and sex-matched healthy subjects included SSFP, T1 and T2 mapping images.

2.3. Diagnostic criteria

According to data acquired on 80 healthy subjects in our MR center, normal range for global heart T1 values was 928–1060 ms in males and 989–1085 ms in females. For global heart T2 values normal range was 48–56 ms in males and 50–57 ms in females.

The cut-off value previously determined at our MR center for the definition of increased global ECV was 29%.

Myocarditis/myocardial inflammation was defined based on both the original and updated LLC. According to original LLC, a positive diagnosis was established with the presence of at least two out of 3 of the following CMR features: edema, hyperemia, and a positive LGE [16]. The updated LLC do not take myocardial hyperemia into account and include the mapping-based indices [17]. The diagnosis of myocarditis requires the combined presence of a T1 criterion (presence of LGE or increased T1 mapping values or increased ECV value) and a T2 criterion (hyperintensity in T2-w STIR or increased T2 mapping values).

2.4. Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) and categorical variables as frequencies and percentages.

The normality of distribution of the parameters was assessed by using the Kolmogorov-Smirnov test or the Shapiro-Wilk test for a sample size≤50.

The comparison between two groups was made by the independent-samples *t*-test or the Mann-Whitney test for continuous variable while the $\chi 2$ testing was performed for non-continuous variables.

Correlation analysis was performed using Pearson's test or Spearman's test where appropriate.

Logistic regression was used to evaluate the odds ratio (OR) with 95% confidence intervals (CI). The OR was used to compare the odds for two groups.

The agreement between the original and update LLC was assessed with Cohen's kappa test and marginal homogeneity was assessed with McNemar's test. Overall, positive and negative agreement was calculated.

In all tests, a 2-tailed probability value of 0.05 was considered statistically significant.

3. Results

3.1. Comparison between SSc patients and healthy subjects

The main characteristics of SSc patients are summarized in Table 1.

Mean age was 52.31 ± 13.24 years (range: 25–76 years) and 45 (81.8%) patients were women. Twelve (21.8%) patients had disease duration <2 years and 8 (14.5%) patients had diffuse cutaneous SSc (dcSSc).

Table 1 shows the comparison between SSc patients and age- and sex-matched healthy subjects. Per inclusion criteria, healthy subjects had no CVRF and the frequency of systemic arterial hypertension and dyslipidemia was significantly increased in SSc patients. The LV cardiac index was significantly higher in SSc patients than in healthy subjects while no significant difference was found in all other biventricular function parameters. SSc patients showed significantly higher global heart T1 values and T2 values.

3.2. CMR features of SSc patients

A significant correlation was found between global heart T1 and T2 values ($R = 0.695$; $P < 0.0001$).

Compared to females, males showed significantly lower global heart T1 values (1032.64 ± 36.21 ms vs 1078.57 ± 49.68 ms; $P = 0.008$) and T2 values (55.36 ± 4.53 ms vs 58.09 ± 3.66 ms; $P = 0.046$). By using sex specific-thresholds, frequency of females was comparable between patients with normal and increased mapping values (Tables 2–3).

Age was inversely correlated with global heart T1 values (R = -0.333; $P = 0.013$) but not with global heart T2 values (R = -0.131; $P = 0.342$).

Native global heart T1 values, global heart T2 values, and biventricular function parameters were comparable between patients without and with interstitial lung disease.

Table 1
Comparison between SSc patients and healthy subjects matched for age and sex.

	Ssc patients ($N = 55$)	Healthy subjects (N = 55)	P
Demographics, clinical features, and co-morbidity			
Females, N (%)	45 (81.8)	45 (81.8)	1.000
Age (years)	52.31 ± 13.24	51.52 ± 12.09	0.462
NYHA class, N(%)			
I	35 (63.6)		
II	20 (36.4)		
III	0 (0.0)		
IV	0 (0.0)		
Palpitations, N (%)	48 (87.3)	0 (0.0)	<0.0001
Chest pain, N (%)	13 (23.6)	0 (0.0)	<0.0001
Diabetes, N (%)	2 (3.6)	0 (0.0)	0.495
Systemic arterial hypertension, N (%)	11 (20.0)	0 (0.0)	0.001
Dyslipidemia, N (%)	5 (9.1)	0 (0.0)	0.022
Interstitial lung disease, N (%)	17/47 (36.2)		
Disease activity and chronicity indices			
Duration of SSc (years)	7.48 ± 6.31		
VEDOSS, N (%)	37 (67.3)		
dcSSc, N (%)	8 (14.5)		
Seropositivity for anti-topoisomerase I antibody, N (%)	16/52 (29.1)		
Seropositivity for anti-centromere antibody (lcSSc only), N (%)	18/45 (40.0)		
Modified Rodnan skin score	2.49 ± 4.78		
Raynaud phenomenon, N (%)	55 (100.0)		
Biochemical and instrumental parameters			
Hematocrit (%)	40.92 ± 4.08		
Creatinine (mg/dl)	0.76 ± 0.17		
Estimated creatinine clearance (ml/min)	90.41 ± 21.34		
NT-proBNP (ng/l)	164.09 ± 448.85		
High-Sensitivity Troponin (ng/l)	3.73 ± 7.43		
DLCO (%)	71.79 ± 17.53		
Forced vital capacity (%)	107.63 ± 19.28		
Medical therapy			
At least one cardio-active medication, N (%)	24 (43.6)		
Anticoaugulants, N (%)	15 (27.3)		
Beta-blocker, N (%)	4 (7.3)		
ACE inhibitors, N (%)	4 (7.3)		
Angiotensin receptor blockers, N (%)	3 (5.5)		
Calcium antagonists, N (%)	5 (19.1)		
Amiodarone, N (%)	2 (3.6)		
Immunotherapy, N (%)	32 (58.2)		
CMR parameters			
LV EDVI (ml/m2)	71.55 ± 13.68	71.47 ± 12.11	0.952
LV ESVI (ml/m2)	25.18 ± 9.78	25.46 ± 7.76	0.645
LV SVI (ml/m2)	46.33 ± 7.54	46.12 ± 8.14	0.576
LV mass index (ml/m2)	52.56 ± 10.57	51.23 ± 12.69	0.306
LV cardiac index (l/min/m2)	3.29 ± 0.60	2.95 ± 0.67	0.002
LV EF (%)	65.62 ± 7.78	64.68 ± 6.70	0.501
RV EDVI (ml/m2)	69.89 ± 14.51	68.50 ± 12.36	0.590
RV ESVI (ml/m2)	26.25 ± 9.91	25.81 ± 7.86	0.857
RV SVI (ml/m2)	43.75 ± 7.84	43.04 ± 8.10	0.646
RV EF (%)	63.25 ± 6.91	63.24 ± 5.63	0.987
LA area index (cm/m2)	11.67 ± 2.34	10.84 ± 1.76	0.059
RA area index (cm/m2)	11.06 ± 1.92	10.35 ± 1.34	0.184
Positive T2-weighted images for myocardial edema, N (%)	7 (12.7)		

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Table 1 (*continued*)

	Ssc patients ($N = 55$)	Healthy subjects (N = 55)	P
Hyperemia by post-contrast SSFP, N (%)	0 (0.0)		
Presence of LGE, N (%)	26 (47.3)		
Pericardial effusion, N (%)	8 (14.5)	0 (0.0)	0.006
Native global heart T1 values (ms)	1070.22 ± 50.49	1033.56 ± 32.87	<0.0001
Native global heart T2 values (ms)	57.59 ± 3.93	54.66 ± 2.28	<0.0001

Ssc, systemic sclerosis; N, number; NYHA, New York Heart Association; VEDOSS, very early diagnosis of systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; NT-proBNP, N-terminal pro b-type natriuretic peptide; DLCO, carbon monoxide diffusing capacity; ACE, angiotensin converting enzyme; CMR, cardiac magnetic resonance; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; RV, right ventricular; LA, left atrium; RA, right atrium; SSFP, steady-state free precession; LGE, late gadolinium enhancement.

Twenty-two (40.0%) patients had an increased native global heart T1 value (iT1). Thirty-four (61.8%) patients had an increased global myocardial T2 value (iT2).

LGE was detected in 26 (47.3%) patients. One patient showed a transmural LGE in the apical inferior segment. One patient (with previous myocardial infarction) had a mixed LGE. The remaining 24 patients had a non-ischemic LGE pattern: 14 (58.3%) mid-wall, 4 (16.7%) subepicardial, and 6 (25.0%) junctional, with the septum involved in the 87.5% of the cases. Positive LGE patients showed higher global heart T1 values than LGE negative patients but the statistical significance was not reached (1083.08 ± 57.32 ms vs 1058.69 ± 41.12 ms; $P = 0.084$) while a significant difference was detected for global heart T2 values (58.77 ± 4.24 ms vs 56.54 ± 3.36 ms; $P = 0.034$).

Edema by STIR T2-w images was detected in 7 patients (12.7%) and the septum was involved in 5 of them. No patient presented with a T2 ratio > 1.9. All patients with positive STIR T2-w images had an increased global heart T1 and/or T2 value. A significant difference between patients with and without edema detected by non-parametric T2w sequences was detected for both global heart T1 values (1116.29 ± 64.13 ms vs 1063 ± 45.19 ms; $P = 0.009$) and T2 values (60.48 ± 4.57 ms vs 57.17 ± 3.69 ms; $P = 0.036$). Segments with visible edema by STIR T2-w images ($N = 20$) had significantly higher correspondent native T1 values (1120.55 ± 100.56 ms vs 1069.11 ± 78.32 ms; $P = 0.023$) as well as T2 values (63.08 ± 9.61 ms vs 57.42 ± 6.25; $P = 0.004$) than segments without visible edema.

Only 20% of patients had normal conventional CMR (no LGE and no edema by STIR T2-weighted) and normal native mapping indices. An increase in native T1 and/or T2 mapping was present in the 62.1% of the patients (18 out of 29) with normal conventional CMR (Fig. 1).

Fig. 2 displays a patient with normal conventional CMR parameters but increased segmental and global T2 and T1 values.

Disease activity and chronicity indices and biochemical parameters did not differ in patients with versus without normal conventional CMR.

3.3. Agreement between original and updated LLC

The agreement between original and updated LLC was assessed for 52 patients, as 3 patients with a positive T2 criterion (T2 mapping), had negative LGE and T1 mapping, but ECV was not available. Original LLC were fulfilled in 7 (13.5%) patients and all of them had also positive updated LLC. The updated LLC were fulfilled in 31 patients (59.6%). The Cohen's Kappa was 0.19 (95%CI 0.05–0.33). The overall agreement between the two criteria was 53.85%, the positive agreement 36.84%, and the negative agreement 63.64%.

The McNemar's test revealed a significant difference between the two criteria (absolute difference in proportion 46.15%; Chi-square 22.04; $P < 0.0001$).

Table 2
Clinical, biochemical and CMR differences in SSc patients categorized on the basis of the global heart T1 value.

	Normal global heart T1 value ($N = 33$)	Increased global heart T1 value ($N = 22$)	P
Demographics, clinical features, and co-morbidity			
Females, N (%)	25 (75.8)	20 (90.9)	0.284
Age (years)	55.91 ± 12.11	50.08 ± 13.59	0.114
NYHA class, N(%)			
I	21 (63.6)	14 (63.6)	
II	12 (42.9)	8 (36.4)	1.000
III	0 (0.0)	0 (0.0)	
IV	0 (0.0)	0 (0.0)	
Diabetes, N (%)	2 (6.1)	0 (0.0)	0.511
Systemic arterial hyperthension, N (%)	9 (27.3)	2 (9.1)	0.168
Dyslipidemia, N (%)	4 (12.1)	1 (4.5)	0.638
Interstitial lung disease, N(%)	10/28 (35.7)	7/19 (36.8)	0.937
Disease activity and chronicity indices			
Duration of SSc (years)	7.68 ± 6.55	7.16 ± 6.07	0.757
VEDOSS, N (%)	21 (63.6)	16 (72.7)	0.481
dcSSc, N (%)	4 (12.1)	4 (18.2)	0.700
Seropositivity for anti-topoisomerase 1 antibody, N (%)	9/31 (29.0)	7/21 (33.3)	0.742
Seropositivity for anti-centromere antibody (lcSSc only), N (%)	12/27 (44.4)	6/18 (33.3)	0.456
Modified Rodnan skin score	1.89 ± 3.71	3.29 ± 5.92	0.462
Raynaud phenomenon, N (%)	33 (100.0)	22 (100)	–
Biochemical and instrumental parameters			
Hematocrit (%)	41.64 ± 4.01	39.85 ± 4.06	0.164
Creatinine (mg/dl)	0.75 ± 0.14	0.76 ± 0.22	0.943
Estimated creatinine clearance (ml/min)	94.13 ± 24.74	84.53 ± 13.01	0.196
NT-proBNP (ng/l)	85.77 ± 59.35	285.50 ± 706.45	0.885
High-Sensitivity Troponin (ng/l)	4.26 ± 8.73	2.91 ± 4.86	0.463
DLCO (%)	74.13 ± 16.50	68.05 ± 19.89	0.228
Forced vital capacity (%)	109.03 ± 20.99	105.40 ± 16.44	0.514
Medical therapy			
At least one cardio-active medication, N (%)	16 (48.5)	8 (36.4)	0.375
Anticoaugulants, N (%)	10 (30.3)	5 (22.7)	0.758
Beta-blocker, N (%)	3 (9.1)	1 (4.5)	0.642
ACE inhibitors, N (%)	2 (6.1)	2 (9.1)	1.000
Angiotensin receptor blockers, N(%)	2 (6.1)	1 (4.5)	1.000
Calcium antagonists, N (%)	4 (12.1)	1 (4.5)	0.638
Amiodarone, N(%)	2 (6.1)	0 (0.0)	0.511
Immunotherapy, N (%)	18 (54.5)	14 (63.6)	0.503
CMR parameters			
LV EDVI (ml/m2)	67.91 ± 12.66	77.00 ± 13.59	0.014
LV ESVI (ml/m2)	23.85 ± 7.69	27.18 ± 12.19	0.409
LV SVI (ml/m2)	44.03 ± 7.36	49.77 ± 6.56	0.010
LV mass index (ml/m2)	50.61 ± 7.96	55.50 ± 13.26	0.182
LV cardiac index (l/min/m2)	3.07 ± 0.55	3.63 ± 0.52	<0.0001
LV EF (%)	65.45 ± 6.62	65.86 ± 9.43	0.851
RV EDVI (ml/m2)	67.36 ± 14.22	73.68 ± 14.43	0.114
RV ESVI (ml/m2)	25.45 ± 8.36	27.45 ± 11.99	0.576
RV SVI (ml/m2)	42.03 ± 8.24	46.32 ± 6.58	0.046
RV EF (%)	62.82 ± 6.24	63.91 ± 7.93	0.571
LA area index (cm/m2)	11.41 ± 2.45	12.05 ± 2.17	0.629
RA area index (cm/m2)	11.16 ± 2.01	10.91 ± 1.82	0.695
Positive T2-weighted images for myocardial edema, N (%)	2 (6.1)	5 (22.7)	0.103
Presence of LGE, N (%)	13 (39.4)	13 (59.1)	0.152
Pericardial effusion, N (%)	4 (12.1)	4 (18.2)	0.700
Global heart T2 values (ms)	56.03 ± 3.34	59.95 ± 3.63	<0.0001

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Table 2 (*continued*)

	Normal global heart T1 value ($N = 33$)	Increased global heart T1 value ($N = 22$)	P
Increased global heart T2 value, N (%)	15 (45.5)	19 (86.4)	0.004
Global ECV (%)	32.61 ± 5.75 ($N = 17$)	35.23 ± 4.68 ($N = 13$)	0.192
Increased global ECV, N (%)	11 (64.7)	11 (84.6)	0.407
CV history, N (%)			
History of CV disease, N (%)	14 (42.4)	17 (77.3)	0.011
History of digital ulcers, N (%)	11 (33.3)	16 (72.7)	0.004

Ssc, systemic sclerosis; N, number; NYHA, New York Heart Association; VEDOSS, very early diagnosis of systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; NT-proBNP, N-terminal pro b-type natriuretic peptide; DLCO, carbon monoxide diffusing capacity; ACE, angiotensin converting enzyme; CMR, cardiac magnetic resonance; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; RV, right ventricular; LA, left atrium; RA, right atrium; LGE, late gadolinium enhancement; ECV, extracellular volume; CV, cardiovascular.

3.4. Stratification for T1 values

Table 2 shows the comparison between patients with normal and increased global heart T1 values (nT1 vs iT1). No significant difference was detected for age, sex, frequency of cardiovascular risk factors, indices of disease activity and chronicity, biochemical parameters, and cardio-active therapy.

Compared to patients with nT1, patients with iT1 had significantly higher LV end-diastolic volume index (EDVI), LV stroke volume index (SVI), LV cardiac index, and right RV SVI. Biventricular ejection fractions were comparable between the two groups. The 59.1% of patients with iT1 showed positive LGE. Patients with nT1 and with iT1 showed a comparable frequency of positive LGE and increased global ECV. Global heart T2 values and frequency of patients with an increased global heart T2 value were significantly higher among patients with iT1.

3.5. Stratification for T2 values

Table 3 shows the comparison between patients with normal and increased global heart T2 values (nT2 vs iT2). No significant difference was detected for age, sex, frequency of cardiovascular risk factors, indices of disease activity and chronicity, biochemical parameters, and cardio-active therapy.

No significant difference was found in biventricular volumes and ejection fractions, LV mass index, frequency of positive LGE or STIR T2-w images. Global heart T1 values and frequency of patients with an iT1 were significantly higher among patients with iT2.

3.6. History of cardiac complications and mapping

Thirty-one (56.4%) patients had a positive history of cardiovascular disease (CVD): one ventricular fibrillation and ST-elevation myocardial infarction, one supraventricular tachycardia, one unstable angina, one atrial flutter and digital ulcers, one pulmonary hypertension, and 26 ulcers. Patients with a positive history of CVD were significantly younger than patients free of cardiac complications (49.26 ± 13.87 years vs 56.24 ± 11.48 years; $P = 0.046$).

A positive history of CVD and digital ulcers was significantly more frequent among patients with iT1 versus patients with nT1 (Table 2). Patients with an history of digital ulcers were more likely to have an increased global heart T1 value (OR = 5.33, 95%CI = 1.63–17.44; $P = 0.006$). Two patients had digital ulcers active at the CMR. Both of them had an iT1 and one showed also an iT2.

Out of the 5 patients with a CVD different from digital ulcers, 4

Table 3
Clinical, biochemical and CMR differences in SSc patients categorized on the basis of the global heart T2 value.

	Normal global heart T2 value ($N = 21$)	Increased global heart T2 value ($N = 34$)	P
Demographics, clinical features, and co-morbidity			
Females, N (%)	16 (76.2)	29 (85.3)	0.480
Age (years)	55.91 ± 12.10	50.08 ± 13.59	0.114
NYHA class, N(%)			
I	12 (57.1)	23 (67.6)	
II	9 (42.9)	11 (32.4)	0.565
III	0 (0.0)	0 (0.0)	
IV	0 (0.0)	0 (0.0)	
Diabetes, N (%)	1 (4.8)	1 (2.9)	1.000
Systemic arterial hypertension, N (%)	6 (28.6)	5 (14.7)	0.300
Dyslipidemia, N (%)	3 (14.3)	2 (5.9)	0.359
Interstitial lung disease, N(%)	6/17 (35.3)	11/30 (36.7)	0.925
Disease activity and chronicity indices			
Duration of SSc (years)	8.09 ± 6.91	7.09 ± 5.99	0.652
VEDOSS, N (%)	14 (66.7)	23 (67.6)	0.940
dcSSc, N (%)	3 (14.3)	5 (14.7)	1.000
Seropositivity for anti-topoisomerase 1 antibody, N (%)	5/19 (26.3)	11/33 (33.3)	0.598
Seropositivity for anti-centromere antibody (lcSSc only), N (%)	6/16 (37.5)	12/29 (41.4)	0.799
Modified Rodnan skin score	1.12 ± 2.29	3.22 ± 5.57	0.330
Raynaud phenomenon, N (%)	21 (100.0)	34 (100)	–
Biochemical and instrumental parameters			
Hematocrit (%)	42.15 ± 2.87	40.23 ± 4.52	0.145
Creatinine (mg/dl)	0.73 ± 0.14	0.77 ± 0.19	0.303
Estimated creatinine clearance (ml/min)	91.89 ± 19.47	89.47 ± 22.72	0.645
NT-proBNP (ng/l)	73.71 ± 61.64	227.37 ± 578.51	0.121
High-Sensitivity Troponin (ng/l)	4.59 ± 10.18	3.07 ± 4.41	0.498
DLCO (%)	72.21 ± 16.52	71.55 ± 18.34	0.897
Forced vital capacity (%)	101.53 ± 19.79	111.15 ± 18.36	0.092
Medical therapy			
At least one cardio-active medication, N (%)	7 (33.3)	17 (50.0)	0.226
Anticoaugulants, N (%)	4 (19.0)	11 (32.4)	0.359
Beta-blocker, N (%)	1 (4.8)	3 (8.8)	0.655
ACE inhibitors, N (%)	1 (4.8)	3 (8.8)	0.655
Angiotensin receptor blockers, N(%)	1 (4.8)	2 (5.9)	1.000
Calcium antagonists, N (%)	2 (9.5)	3 (8.8)	1.000
Amiodarone, N(%)	0 (0.0)	2 (5.9)	0.519
Immunotherapy, N (%)	10 (47.6)	22 (64.7)	0.212
CMR parameters			
LV EDVI (ml/m2)	70.10 ± 9.44	72.44 ± 15.81	0.494
LV ESVI (ml/m2)	24.14 ± 4.78	25.82 ± 11.89	0.876
LV SVI (ml/m2)	45.90 ± 6.54	46.59 ± 8.18	0.993
LV mass index (ml/m2)	50.24 ± 8.16	54.00 ± 11.69	0.263
LV cardiac index (l/min/m2)	3.17 ± 0.58	3.37 ± 0.61	0.187
LV EF (%)	65.71 ± 4.67	65.56 ± 9.26	0.935
RV EDVI (ml/m2)	67.90 ± 11.19	71.12 ± 6.24	0.430
RV ESVI (ml/m2)	24.48 ± 5.31	27.35 ± 11.85	0.487
RV SVI (ml/m2)	43.67 ± 8.06	43.79 ± 7.83	0.954
RV EF (%)	64.10 ± 5.21	62.74 ± 7.81	0.484
LA area index (cm/m2)	11.38 ± 2.38	11.85 ± 2.33	0.367
RA area index (cm/m2)	10.71 ± 1.42	11.27 ± 2.17	0.424
Positive T2-weighted images for myocardial edema, N (%)	1 (4.8)	6 (17.6)	0.232
Presence of LGE, N (%)	8 (38.1)	18 (52.9)	0.284
Pericardial effusion, N (%)	1 (4.8)	7 (20.6)	0.136
	1038.19 ± 40.86	1090.01 ± 45.85	<0.0001

(*continued on next page*)

Table 3 (*continued*)

	Normal global heart T2 value ($N = 21$)	Increased global heart T2 value ($N = 34$)	P
Native global heart T1 values (ms)			
Increased native global heart T1 value, N (%)	3 (14.3)	19 (55.9)	0.004
Global ECV (%)	32.86 ± 6.73 ($N = 11$)	34.25 ± 4.57 ($N = 19$)	0.504
Increased global ECV, N (%)	6 (54.5)	16 (84.2)	0.104
CV history, N (%)			
History of CV disease, N (%)	10 (47.6)	21 (61.8)	0.304
History of digital ulcers, N (%)	9 (42.9)	18 (52.9)	0.467

Ssc, systemic sclerosis; N, number; NYHA, New York Heart Association; VEDOSS, very early diagnosis of systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; NT-proBNP, N-terminal pro b-type natriuretic peptide; DLCO, carbon monoxide diffusing capacity; ACE, angiotensin converting enzyme; CMR, cardiac magnetic resonance; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; RV, right ventricular; LA, left atrium; RA, right atrium; LGE, late gadolinium enhancement; ECV, extracellular volume; CV, cardiovascular.

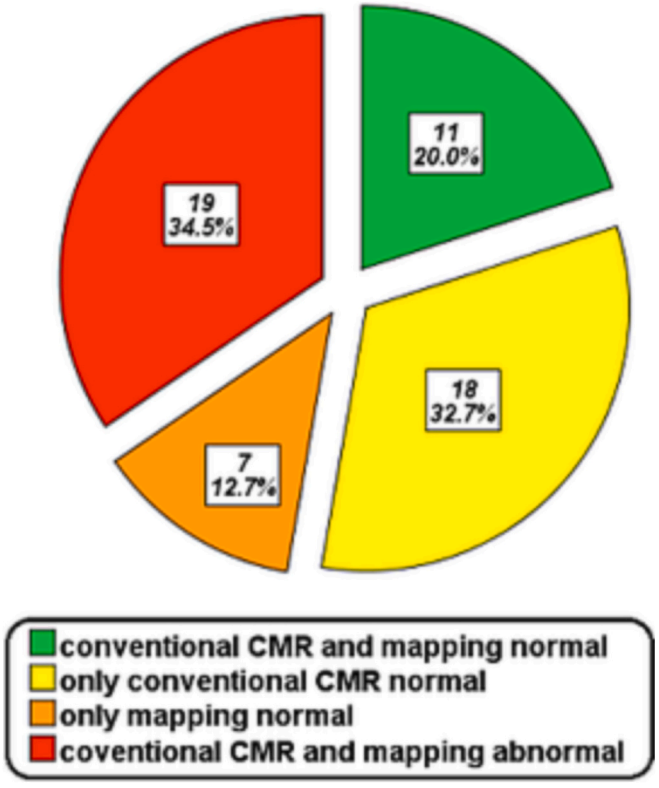

Fig. 1. Distribution of patients with normal and abnormal mapping (native T1 and T2) and conventional CMR for tissue characterization (late gadolinium enhancement and T2-weighted images).

(80%) had an increased global heart T2 value.

4. Discussion

This study assessed diffuse myocardial involvement in SSc patients by parametric T1 and T2 mapping techniques. Most patients were middle-aged and females and were non- or pauci-symptomatic.

In line with previous reports, despite comparable cardiac dimensions

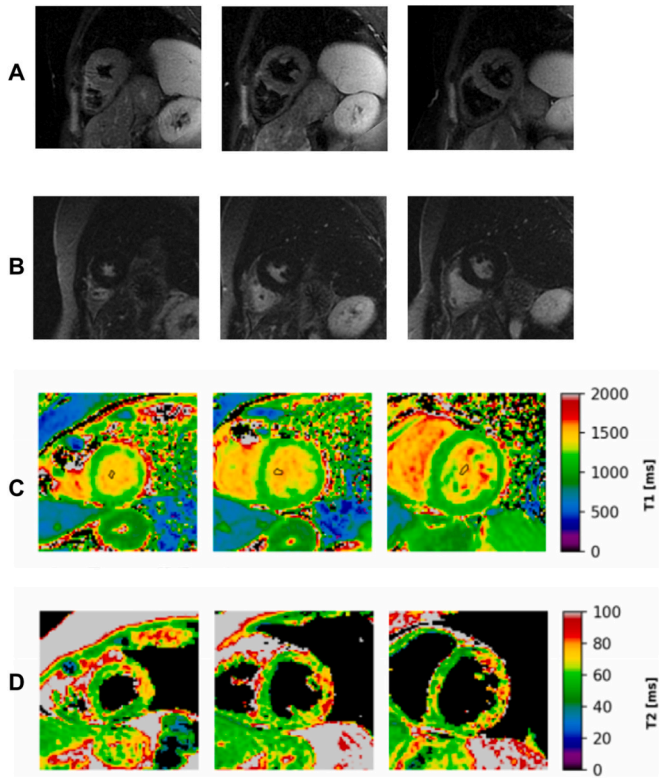

Fig. 2. CMR of a patient with SSc: short axis (from apex to base) STIR-T2-weighted (A) and LGE-images (B) and native T1 (C) and T2 (D) maps. The patient showed no edema in STIR T2-weighted images or LGE but increased segmental and global T1 and T2 values (global T1 = 1182 ms and global T2 = 65.3 ms).

and systolic function, SSc patients had higher native T1 and T2 values than controls [9,19,20], confirming again that subclinical myocardial changes may be common in these population even with apparently normal hearts.

A positive correlation was found between native T1 and T2 values, as both are altered by an increase of extra- and/or intracellular free fluid content. However, the correlation was only moderate (<0.7), likely because a composite information is reflected in native T1 and its increase can be determined by different conditions such as fibrosis [30–32]. In SSc both myocardial inflammation and diffuse fibrosis can coexist, and active myocardial inflammation can develop over existing diffuse fibrosis from previous acute episodes, making it difficult to distinguish how much these two factors contribute to the increase in T1 values.

Frequency of females was comparable between patients with normal and increased mapping values, likely because the use of sex specific-thresholds correct the sex-related differences in T1 and T2 values.

In our patient's cohort an increase in global native heart T1 and T2 values were identified in the 40.0% and 61.8% of cases, respectively. An increase in at least one of the two indices was found in the 62.1% of the patients showing no replacement myocardial fibrosis by LGE and no edema by non-parametric T2-w images. Thus, we found out a significant discordance between the original and updated LLC, with a significant higher frequency of patients with myocardial inflammation identified on the basis of the updated LLC. Since no comparison with a diagnostic gold standard was performed, we could not evaluate and compare the specificity and the sensitivity of the two criteria, but we could only assess the agreement [33]. Anyway, taken together our findings suggest that in SSc the mapping techniques can have an additional value in comparison with the conventional non-parametric CMR indices in the detection of myocardial acute/subacute involvement. In the study by

Markousis-Mavrogenis et al. the discordance between the two criteria did not reach the statistical significance [34]. This discrepancy is probably mainly due to the fact that they recruited only patients with diffuse-cutaneous SSc, while the prevalence of this subtype in our study population was only the 13%. In comparison with lcSSc patients, dcSSc patients are characterized by a higher frequency of internal organ damage [18,35]. Indeed, by non-parametric indices the frequency of positive LGE and edema in the study by Markousis-Mavrogenis was 86% and 64% [34], respectively, significantly higher than that one detected in our study (47.3% and 12.7%, respectively).

In agreement with the study by Poindron et al. [21], we did not find any association between the presence of cardiovascular risk factors, indices of disease activity and chronicity, biochemical parameters and the presence of iT1. Conversely, in our study population elevated native T1 values were associated with increased LV dimensions, in line with the data from patients with nonischemic cardiomyopathy [36,37]. The 59.1% of patients with iT1 showed positive LGE. Importantly, as in the study by Ntusi et al. [9], we did not detect a significant association between native T1 and LGE, indicating that the increase in myocardial T1 was not driven by the presence of LGE and that they may result from different underlying pathological processes. We found an association between increased native global heart T1 values and a history of cardiac complications, in particular of digital ulcers. Digital ulcers are considered a biomarker of disease severity [38]. The autoimmune induced vascular injury is considered the main trigger for vasculature abnormalities resulting in fibroblast activation and consequent fibrotic changes characteristic of SSc [39]. So, digital ulcers and myocardial fibrosis share the same pathological substrate of vasculopathy [40].

To our knowledge, this is the first paper comparing patients with and without iT2. There was no statistical association between the presence of cardiovascular risk factors, biochemical parameters, and the presence of iT2. The finding that patients with normal and increased global heart T2 value had comparable biventricular volumes and ejection fractions and LV mass index may be explained by the relatively low number of patients with abnormal values of these parameters. Indeed, conventional systolic functional parameters may be too weak to catch early and/or slight LV involvement. Frequency of positive STIR T2-weighted images was three times higher among patients with iT2 versus patients with nT2, but the statistical significance was probably not reached due to the lower number of cases. Of note, significantly higher T2 values were detected among patients with edema by STIR T2-weighted images. Since we considered the history of cardiovascular complications, it is compatible the lack of an association with increased global heart T2 values, which reflect acute stages of disease.

4.1. Limitations

Our study has some limitations.

This is a single-centre study, involving a relatively small number of patients. However, SSc is a rare disease and our sample size is comparable to other studies using T1 mapping [9,19,20]. Moreover, nowadays, it is challenge to perform multi-centre mapping studies due to the heterogeneity in normal cut-off value among different centers and vendors.

Since myocardial biopsy was not clinically justified, no comparison with histology was performed.

We did not perform right ventricular T1 or T2 mapping since the current clinical consensus is that it is not recommended [32], due to the remaining challenges associated with the morphologic characteristics of the right ventricle.

We did not create two groups on the basis of the ECV values, since post-contrast T1 images were acquired only in 30 patients.

Since all of our patients presented the Raynaud phenomenon, it cannot be inferred that these evidences can be extended to patients without it.

5. Conclusion

T1 and T2 mapping seem to be more sensitive parameters that should be included in the routine clinical assessment of SSc patients for detecting early or subtle LV involvement. Early detection is the key for a better stratification of patients and for the adoption of a tailored specific therapy in order to prevent disease progression. Larger multi-center cross-sectional studies are needed to better explore the diagnostic value of T1 and T2 mapping and to confirm their complementary/additional role in comparison to conventional non-parametric sequences. Moreover, and above all, longitudinal studies are required to determine the utility of both T1 and T2 mapping in prognostication for patients with SSc and other rheumatic disorders.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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References

[1] J. Varga, M. Trojanowska, M. Kuwana, Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities, J. Scleroderma Related Disord. 2 (3) (2017) 137–152.
[2] V.D. Steen, T.A. Medsger Jr., Severe organ involvement in systemic sclerosis with diffuse scleroderma, Arthritis Rheum. 43 (11) (2000) 2437–2444.
[3] G. Habib, C. Bucciarelli-Ducci, A.L.P. Caforio, et al., Multimodality imaging in restrictive cardiomyopathies: an EACVI expert consensus document in collaboration with the "working group on myocardial and pericardial diseases" of the European Society of Cardiology Endorsed by the Indian academy of echocardiography, Eur. Heart J. Cardiovasc. Imaging 18 (10) (2017) 1090–1121.
[4] M. Elhai, C. Meune, M. Boubaya, et al., Mapping and predicting mortality from systemic sclerosis, Ann. Rheum. Dis. 76 (11) (2017) 1897–1905.
[5] C. Bruni, M.H. Buch, D.E. Furst, et al., Primary systemic sclerosis heart involvement: a systematic literature review and preliminary data-driven, consensus-based WSF/HFA definition, J. Scleroderma Related Disord. 7 (1) (2022) 24–32.
[6] S.I. Mavrogeni, J. Schwitter, L. Gargani, et al., Cardiovascular magnetic resonance in systemic sclerosis: "pearls and pitfalls", Semin. Arthritis Rheum. 47 (1) (2017) 79–85.
[7] S. Mavrogeni, G. Karabela, L. Koutsogeorgopoulou, et al., Pseudo-infarction pattern in diffuse systemic sclerosis. Evaluation using cardiovascular magnetic resonance, Int. J. Cardiol. 214 (2016) 465–468.
[8] S. Mavrogeni, L. Gargani, A. Pepe, et al., Cardiac magnetic resonance predicts ventricular arrhythmias in scleroderma: the scleroderma arrhythmia clinical utility study (SAnCtUS), Rheumatology (Oxford) 59 (8) (2020) 1938–1948.
[9] N.A. Ntusi, S.K. Piechnik, J.M. Francis, et al., Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis—a clinical study using myocardial T1-mapping and extracellular volume quantification, J. Cardiovasc. Magn. Reson. 16 (2014) 21.
[10] A. Barison, L. Gargani, D. De Marchi, et al., Early myocardial and skeletal muscle interstitial remodelling in systemic sclerosis: insights from extracellular volume quantification using cardiovascular magnetic resonance, Eur. Heart J. Cardiovasc. Imaging 16 (1) (2015) 74–80.
[11] V. Bordonaro, D. Bivort, T. Dresselaers, E. De Langhe, J. Bogaert, R. Symons, Myocardial T1 mapping and extracellular volume quantification as novel biomarkers in risk stratification of patients with systemic sclerosis, Clin. Radiol. 76 (2) (2021) (162 e1- e8).
[12] V.M. Ferreira, S.K. Piechnik, E. Dall'Armellina, et al., Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 14 (2012) 42.
[13] P. Thavendiranathan, M. Walls, S. Giri, et al., Improved detection of myocardial involvement in acute inflammatory cardiomyopathies using T2 mapping, Circ. Cardiovasc. Imaging 5 (1) (2012) 102–110.

[14] Y. Zhang, C.P. Corona-Villalobos, A.N. Kiani, et al., Myocardial T2 mapping by cardiovascular magnetic resonance reveals subclinical myocardial inflammation in patients with systemic lupus erythematosus, Int. J. Card. Imaging 31 (2) (2015) 389–397.
[15] G. Markousis-Mavrogenis, A. Pepe, L. Gargani, et al., Myocardial involvement in rheumatic disorders, Curr. Heart Fail Rep. 17 (5) (2020) 171–180.
[16] M.G. Friedrich, U. Sechtem, J. Schulz-Menger, et al., Cardiovascular magnetic resonance in myocarditis: a JACC White Paper, J. Am. Coll. Cardiol. 53 (17) (2009) 1475–1487.
[17] V.M. Ferreira, J. Schulz-Menger, G. Holmvang, et al., Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations, J. Am. Coll. Cardiol. 72 (24) (2018) 3158–3176.
[18] C. Ferri, G. Valentini, F. Cozzi, et al., Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients, Medicine (Baltimore) 81 (2) (2002) 139–153.
[19] M. Hromadka, J. Seidlerova, D. Suchy, et al., Myocardial fibrosis detected by magnetic resonance in systemic sclerosis patients - relationship with biochemical and echocardiography parameters, Int. J. Cardiol. 249 (2017) 448–453.
[20] N. Galea, E. Rosato, A. Gigante, et al., Early myocardial damage and microvascular dysfunction in asymptomatic patients with systemic sclerosis: a cardiovascular magnetic resonance study with cold pressor test, PLoS One 15 (12) (2020), e0244282.
[21] V. Poindron, E. Chatelus, M. Canuet, et al., T1 mapping cardiac magnetic resonance imaging frequently detects subclinical diffuse myocardial fibrosis in systemic sclerosis patients, Semin. Arthritis Rheum. 50 (1) (2020) 128–134.
[22] F. van den Hoogen, D. Khanna, J. Fransen, et al., 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European league against rheumatism collaborative initiative, Arthritis Rheum. 65 (11) (2013) 2737–2747.
[23] A. Meloni, N. Martini, V. Positano, et al., Myocardial T1 values at 1.5 T: Normal values for General Electric scanners and sex-related differences, J. Magn. Reson. Imaging 54 (5) (2021) 1486–1500.
[24] A. Meloni, M. Nicola, V. Positano, et al., Myocardial T2 values at 1.5 T by a segmental approach with healthy aging and gender, Eur. Radiol. 32 (5) (2022) 2962–2975.
[25] M.D. Cerqueira, N.J. Weissman, V. Dilsizian, et al., Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the cardiac imaging Committee of the Council on clinical cardiology of the American Heart Association, Circulation 105 (4) (2002) 539–542.
[26] G. Pontone, G. Di Bella, S. Castelletti, et al., Clinical recommendations of cardiac magnetic resonance, part II: inflammatory and congenital heart disease, cardiomyopathies and cardiac tumors: a position paper of the working group 'Applicazioni della Risonanza Magnetica' of the Italian Society of Cardiology, J. Cardiovasc. Med. (Hagerstown) 18 (4) (2017) 209–222.
[27] G.D. Aquaro, G. Camastra, L. Monti, et al., Reference values of cardiac volumes, dimensions, and new functional parameters by MR: a multicenter, multivendor study, J. Magn. Reson. Imaging 45 (4) (2017) 1055–1067.
[28] M. Perfetti, G. Malatesta, I. Alvarez, et al., A fast and effective method to assess myocardial hyperemia in acute myocarditis by magnetic resonance, Int. J. Card. Imaging 30 (3) (2014) 629–637.
[29] H. Arheden, M. Saeed, C.B. Higgins, et al., Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats, Radiology 211 (3) (1999) 698–708.
[30] V.O. Puntmann, T. Voigt, Z. Chen, et al., Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy, JACC Cardiovasc. Imaging 6 (4) (2013) 475–484.
[31] A. Baggiano, M. Boldrini, A. Martinez-Naharro, et al., Noncontrast magnetic resonance for the diagnosis of cardiac amyloidosis, JACC Cardiovasc. Imaging 13 (1 Pt 1) (2020) 69–80.
[32] D.R. Messroghli, J.C. Moon, V.M. Ferreira, et al., Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI), J. Cardiovasc. Magn. Reson. 19 (1) (2017) 75.
[33] P.F. Watson, A. Petrie, Method agreement analysis: a review of correct methodology, Theriogenology 73 (9) (2010) 1167–1179.
[34] G. Markousis-Mavrogenis, L. Koutsogeorgopoulou, G. Katsifis, et al., The doubled-edged sword of T1-mapping in systemic sclerosis-a comparison with infectious myocarditis using cardiovascular magnetic resonance, Diagnostics (Basel) 10 (5) (2021).
[35] T.S. Rodriguez-Reyna, M. Morelos-Guzman, P. Hernandez-Reyes, et al., Assessment of myocardial fibrosis and microvascular damage in systemic sclerosis by magnetic resonance imaging and coronary angiotomography, Rheumatology (Oxford) 54 (4) (2015) 647–654.
[36] R.V. Shah, S. Kato, S. Roujol, et al., Native Myocardial T1 as a biomarker of cardiac structure in non-ischemic cardiomyopathy, Am. J. Cardiol. 117 (2) (2016) 282–288.
[37] S. Nakamori, K. Dohi, M. Ishida, et al., Native T1 mapping and extracellular volume mapping for the assessment of diffuse myocardial fibrosis in dilated cardiomyopathy, JACC Cardiovasc. Imaging 11 (1) (2018) 48–59.
[38] M. Hughes, Y. Allanore, L. Chung, J.D. Pauling, C.P. Denton, M. Matucci-Cerinic, Raynaud phenomenon and digital ulcers in systemic sclerosis, Nat. Rev. Rheumatol. 16 (4) (2020) 208–221.
[39] Y. Asano, S. Sato, Vasculopathy in scleroderma, Semin. Immunopathol. 37 (5) (2015) 489–500.
[40] L. Gargani, G. Todiere, S. Guiducci, et al., Early detection of cardiac involvement in systemic sclerosis: the added value of magnetic resonance imaging, JACC Cardiovasc. Imaging 12 (5) (2019) 927–928.