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Native T1 and T2 mapping by CMR in lupus myocarditis: Disease recognition and response to treatment

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ABSTRACT

Background: Lupus myocarditis is likely more common than recognized clinically due to non-specific symptoms and lack of reliable non-invasive diagnostic tests. We investigated the role of native T1 and T2 in recognition of active myocardial inflammatory involvement in patients with systemic lupus erythematous (SLE).
Methods: 76 patients with clinically suspected lupus myocarditis (14 males, age: 44 ± 16 years) underwent quantitative tissue characterization with native T1 and T2 mapping. Normotensive healthy subjects taking no medication served as controls (n = 46). Follow-up CMR studies were performed in a total of 35 subjects of which 14 patients received intensified anti-inflammatory treatment, as guided by SLE disease activity.
Results: Compared to controls SLE patients had higher inflammatory markers, LV mass, native T1 and T2 values, and reduced longitudinal strain ($p < 0.01$). In patients with a positive troponin test (n = 36; 46%), native T1 and T2 were significantly higher ($p < 0.01$) with otherwise similar proportions of diffuse perimyocardial LGE (33%) and pericardial effusion (32%). Sixty-nine patients (83%) had an abnormal native T1, whereas 51 (71%) met diagnostic criteria for acute myocarditis. Follow-up CMRs revealed significantly greater reduction in native T1 and T2 values in patients with intensified anti-inflammatory treatment ($p < 0.001$) with the greatest change observed within the first follow-up period and plateauing thereafter. Native T1 and T2 were significant predictors of treatment response.
Conclusions: Native T1 and T2 mapping support recognition of lupus myocarditis and reflect the response to anti-inflammatory treatment. Native T1 and T2 mapping may support an effective, noninvasive, radiation- and gadolinium contrast-free screening method for lupus myocarditis.

1. Introduction

Lupus myocarditis is thought to be a rare, but serious manifestation most commonly linked with acute cardiac decompensation and HF [1,2]. Yet, there is growing evidence that inflammatory cardiomyopathy in patients with SLE is more prevalent and associated with a high burden of cardiovascular morbidity and mortality in these patients [3–5].

Clinical recognition of lupus myocarditis is challenging due to a paucity of classic cardiac symptoms, which are commonly overshadowed by systemic manifestations. Also, there is a lack of a reliable non-invasive diagnostic test [6]. Inflammatory cardiomyopathy in SLE is characterized by a number of complex systemic and local myocardial autoimmune processes leading to diffuse inflammation, microvascular disease, cardiomyocyte injury and reparative fibrosis [7–11]. Quantifiable myocardial tissue characterization by T1 and T2 mapping now supports direct assessment of diffuse inflammatory myocardial involvement [11–15], also supported with histological correlations in patients with acute and chronic inflammatory cardiomyopathy [16,17]. These advances in non-invasive imaging may allow an important step-change in diagnosis and characterization of lupus myocarditis. We investigated the role of native T1 and T2 mapping by CMR in recognition of lupus myocarditis, as well as in reflecting the evolution of inflammation in response to anti-inflammatory treatment.

Abbreviations: CMR, cardiovascular magnetic resonance; CNS, central nervous system; HF, heart failure; LGE, late gadolinium enhancement; MOLLI, modified Look–Locker Imaging; SAX, short axis; SD, standard deviation; SLE, systemic lupus erythematous; SLEDAI, SLE disease activity index score.

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Table 1
Baseline subjects' characteristics. Comparisons with controls were made using t-test or Chi^2 test, as appropriate for the type of the data. $p < 0.05$ is considered significant.

Variable	Controls (n = 46)	SLE patients (n = 76)	Significance (p-value)
Age	42 ± 15	41 ± 16	0.73
Males, n (%)	9(20)	12 (16)	0.57
Body mass index	25 ± 5	24 ± 4	0.23
Heart rate (beats/min)	65 ± 10	67 ± 13	0.34
BP systolic (mm Hg)	123 ± 13	131 ± 21	**0.02**
BP diastolic (mm Hg)	73 ± 10	79 ± 15	**0.02**
Hypertension, n (%)	0(0)	29(38)	<**0.01**
Diabetes, n (%)	0(0)	8 (11)	**0.02**
Smoker, n (%)	3(7)	8 (11)	0.47
Blood markers			
Haematocrit (%)	44 ± 5	38 ± 9	<**0.001**
eGFR mL/min/m^2	91 ± 21	76 ± 21	<**0.001**
ESR (mm/h)	<7	53 ± 15	<**0.001**
C-reactive protein, mg/mL	2.2 ± 1.8	5.9 ± 4.7	<**0.001**
Troponin test (positive), n (%)	/	36(47)	/
Cardiac symptoms			
Dyspnoea, n(%)	/	49(65)	/
Chest pain, n(%)	/	24(35)	/
Syncope, n(%)	/	2(3)	/
ECG changes, n(%)	/	29(38)	/
Hospitalization for SLE, n(%)	/	6(8)	/
Hospitalization for HF, n(%)	/	3(4)	/
NYHA			
<II	/	60(79)	/
≥III	/	16(21)	/
Cardiac medications			
RAS inhibitors, n (%)	/	53(70)	/
Calcium channel blockers, n (%)	/	18(24)	/
Diuretics, n (%)	/	11(15)	/
Statins n (%)	/	11(15)	/
Characteristics related to SLE			
SLEDAI			
≤2	/	70(92)	/
>3	/	6(8)	/
Time since the diagnosis (years, IQR)	/	8(2–12)	/
Antiphospholipid syndrome, n (%)	/	38(50)	/
History of lupus nephritis, n (%)	/	38(50)	/
History of CNS involvement, n (%)	/	5(6)	/
Systemic symptoms	/		/
Malaise, n(%)	/	36(48)	/
Rash, n(%)	/	14(19)	/
Arthritis, n(%)	/	13(17)	/
Vasculitis, n(%)	/	11(14)	/
Haematological abnormalities, n(%)	/	6(8)	/
DMARDs, n (%)	/		/
Prednisolone, n (%)	/	57(75)	/
Prednisolone (mg/day)	/	24 ± 7	/
Hydroxychloroquine, n (%)	/	59(78)	/
Mycophenolate, n (%)	/	52(69)	/
Anticoagulants, n (%)	/	38(50)	/
Methotrexate, n (%)	/	13(17)	/
Steroids (new or increased dose), n(%)	/	27(36)	/
Immunosuppression (new or increased dose), n(%)	/	13(17)	/
Cardiac structure and function			
LV-EDV index, mL/m^2	67 ± 13	72 ± 16	0.08
LV ejection fraction, %	62 ± 11	56 ± 12	0.007
LV mass index, g/m^2	54 ± 14	66 ± 17	<0.001
LA area, cm^2	16 ± 4	20 ± 4	<0.001
RV ejection fraction, %	56 ± 6	52 ± 9	0.009
Longitudinal strain, %	23 ± 6	17 ± 12	0.002
Radial strain, %	26 ± 6	22 ± 16	0.11
Tissue characterization			
Native T1 (ms)	1057 ± 23	1176 ± 55	<0.001
Abnormal native T1 (native T1 ≥ 2SD), n(%) [32]	0(0)	69 (91)	<0.001
Acute myocarditis (native T1 ≥ 5SD), n(%) [12]	0(0)	54(71)	<0.001
Native T2 (ms)	45 ± 4	65 ± 8	<0.001
Abnormal T2 value (≥2SD), n (%)	0(0)	63(83)	
Oedema ratio	1.9 ± 1.6	2.9 ± 2.8	0.029
Myocardial LGE			
Present, n (%)	/	25(33)	/
Diffuse, n (%)	/	17(22)	/
Intramyocardial, n (%)	/	2(3)	/
Epicardial, n (%)	/	7(9)	/
Pericardial LGE, n (%)	/	9(12)	/
Myocardial extent (% of total LV volume)	/	5.1(0.5–11.1)	/
Lake–Louise criteria, n (%)	/	22(29)	/
Pericardial effusion (>5 mm), n (%)	/	24(32)	/

BP – blood pressure; eGFR- estimated Glomerular Filtration Rate (eGFR); ESR- erythrocyte sedimentation rate; SLE- Systemic lupus erythematosus; NYHA- New York Heart Association (NYHA) functional classification; SLEDAI- SLE Disease Activity Index; DMARDs- disease-modifying antirheumatic drugs; LV-EDV- Left ventricle end-diastolic volume; LA- left atrium; RV: right ventricle.

2. Methods

A total of 76 consecutive subjects with an established diagnosis of SLE as per the American College of Rheumatology revised classification criteria [18], referred to clinical CMR for a clinically suspected lupus myocarditis, were included in this study. Clinical referral was based on the presence of clinical symptoms, ECG changes, positive troponin, raised inflammatory blood markers, abnormal findings on echocardiography, and absence of significant obstructive coronary artery disease (based on angiographic evidence, negative functional ischemia imaging, and subsequent absence of ischemic-type LGE in the course of the baseline CMR study) [19]. Additional inclusion criteria were an absence of a recent flu-like illness and negative viral serology [20]. Endomyocardial biopsy was not employed routinely for confirmation of disease [21]. The activity of systemic disease was assessed using the SLE disease activity index score, SLEDAI [22]. Normotensive age-gender matched subjects ($n = 46$) with no previous medical history, no clinical or serological evidence of systemic inflammation, taking no regular medication, and with normal findings on CMR study, served as controls [23]. Patient characteristics were recorded for all subjects, including age, sex,

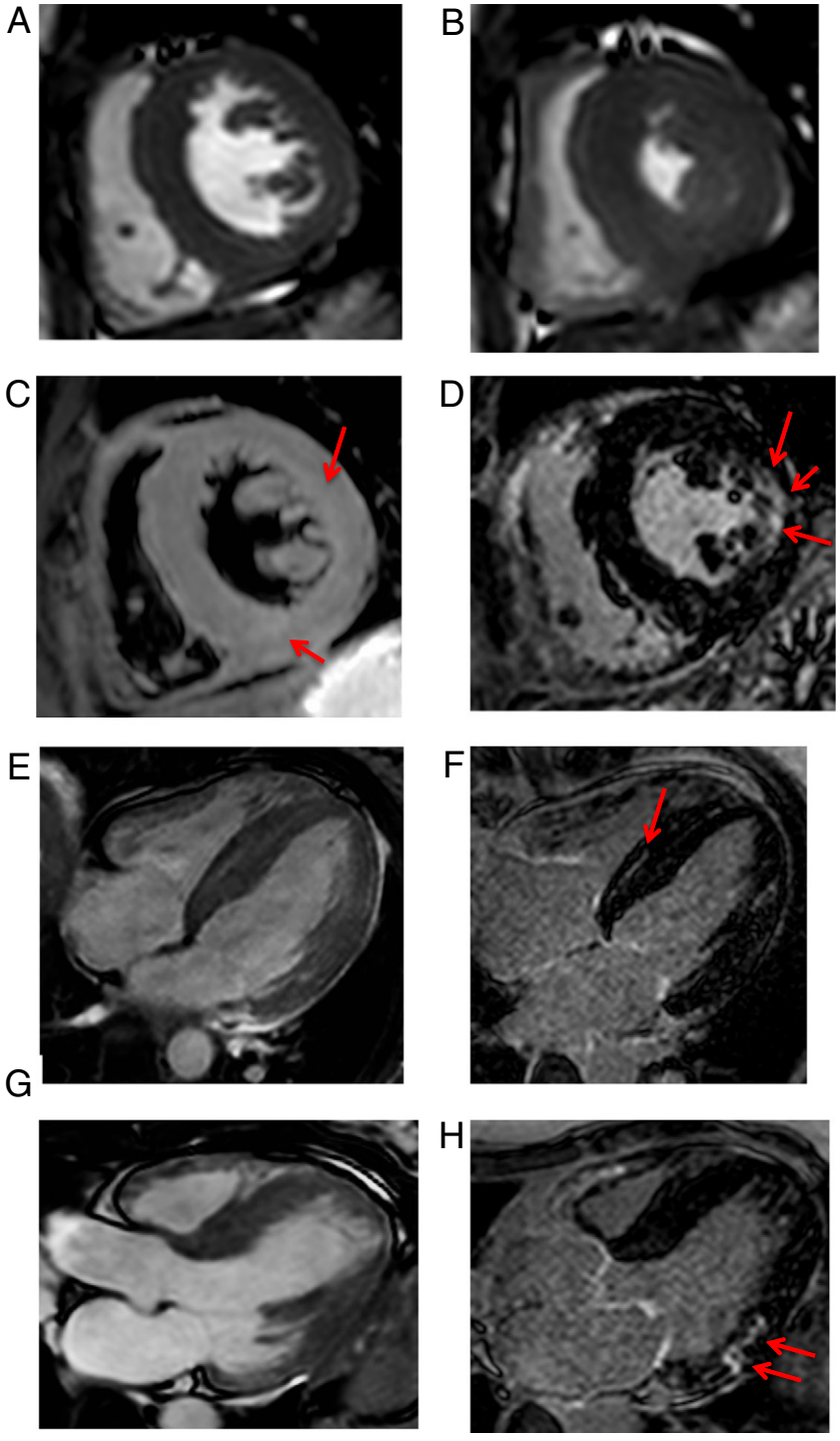

Fig. 1. Representative CMR images of 2 cases with lupus myocarditis. A and B – cine in SAX, in diastole and systole, revealing preserved fractional shortening. 1C – T2 weighted imaging with STIR fat suppression reveals faint patches of intramyocardial hyperenhancement, concordant with LGE (D and F). Long axis cine views revealing thickened inflamed myocardium.

body mass index, blood pressure, presence of cardiovascular risk factors, and medication. Results of routine blood tests including haematocrit, renal function, inflammatory profile, and troponin tests were also recorded.

Exclusion criteria for all subjects were the generally accepted contraindications to CMR (implantable devices, cerebral aneurysm clips, cochlear implants, severe claustrophobia) or a history of renal disease with a current eGFR < 30 mL/min/1.73 m^2. The study protocol was reviewed and approved by the local ethics committee, and written informed consent was obtained from all participants. All procedures were carried out in accordance with the Declaration of Helsinki (2000).

2.1. CMR image acquisition

All subjects underwent a routine clinical protocol for cardiac volumes and mass and tissue characterization with T2 weighted and LGE imaging using 3-Tesla MRI scanner equipped with advanced cardiac package and multi-transmit technology (Achieva, Philips Healthcare, Best, The Netherlands) [24,25]. All routine CMR imaging protocols were reported previously [10–12,26].

Cine imaging was performed using a balanced steady-state free precession sequence in combination with parallel imaging (SENSitivity Encoding, factor 2) and retrospective gating during an expiratory breath-hold (TE/TR/FA: 1.7 ms/3.4 ms/60°, spatial resolution

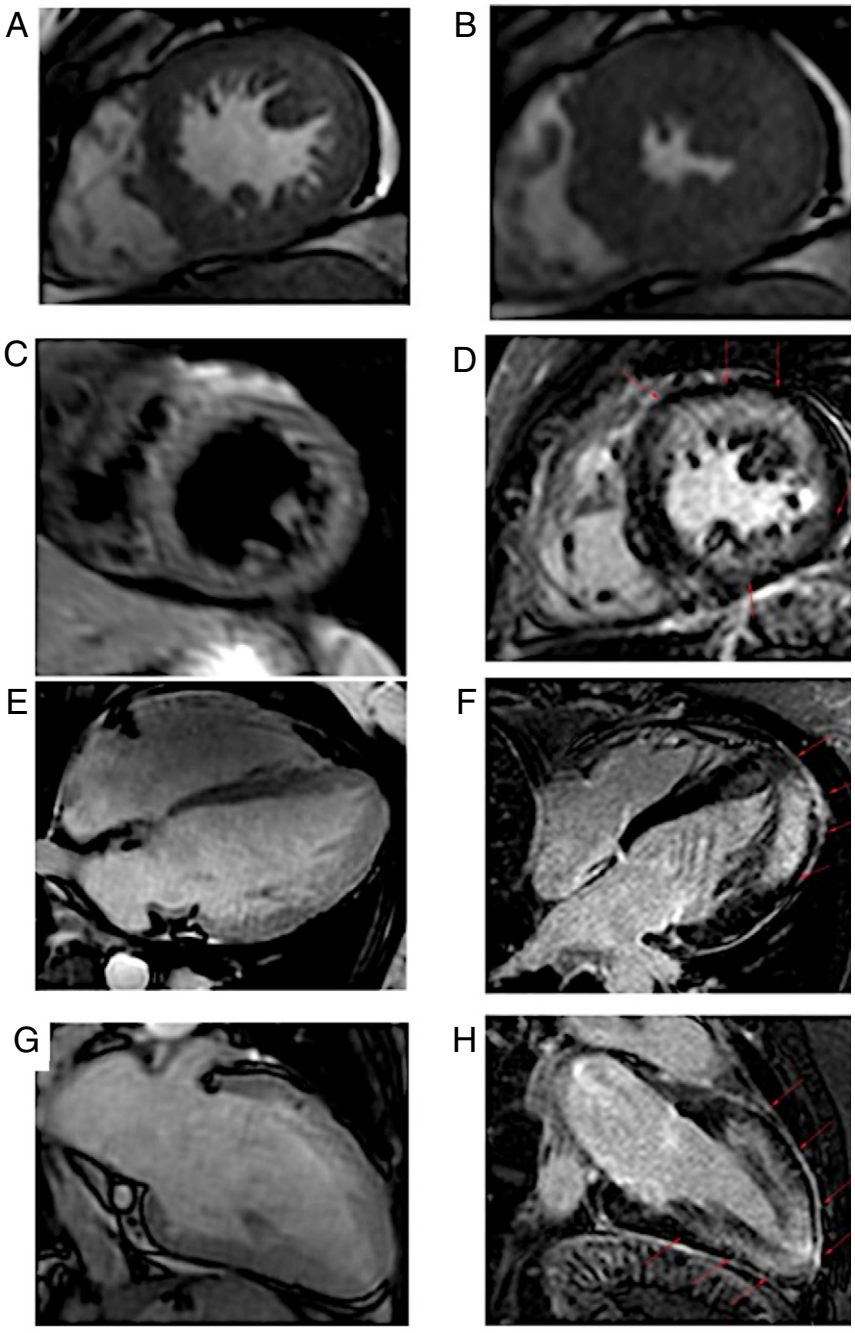

Fig. 2. Representative CMR images of 2 cases with lupus myocarditis. A and B – cine in SAX, in diastole and systole, revealing preserved fractional shortening. 1C – T2 weighted imaging with STIR fat suppression reveals faint patches of intramyocardial hyperenhancement, concordant with LGE (D and F). Long axis cine views revealing thickened inflamed myocardium.

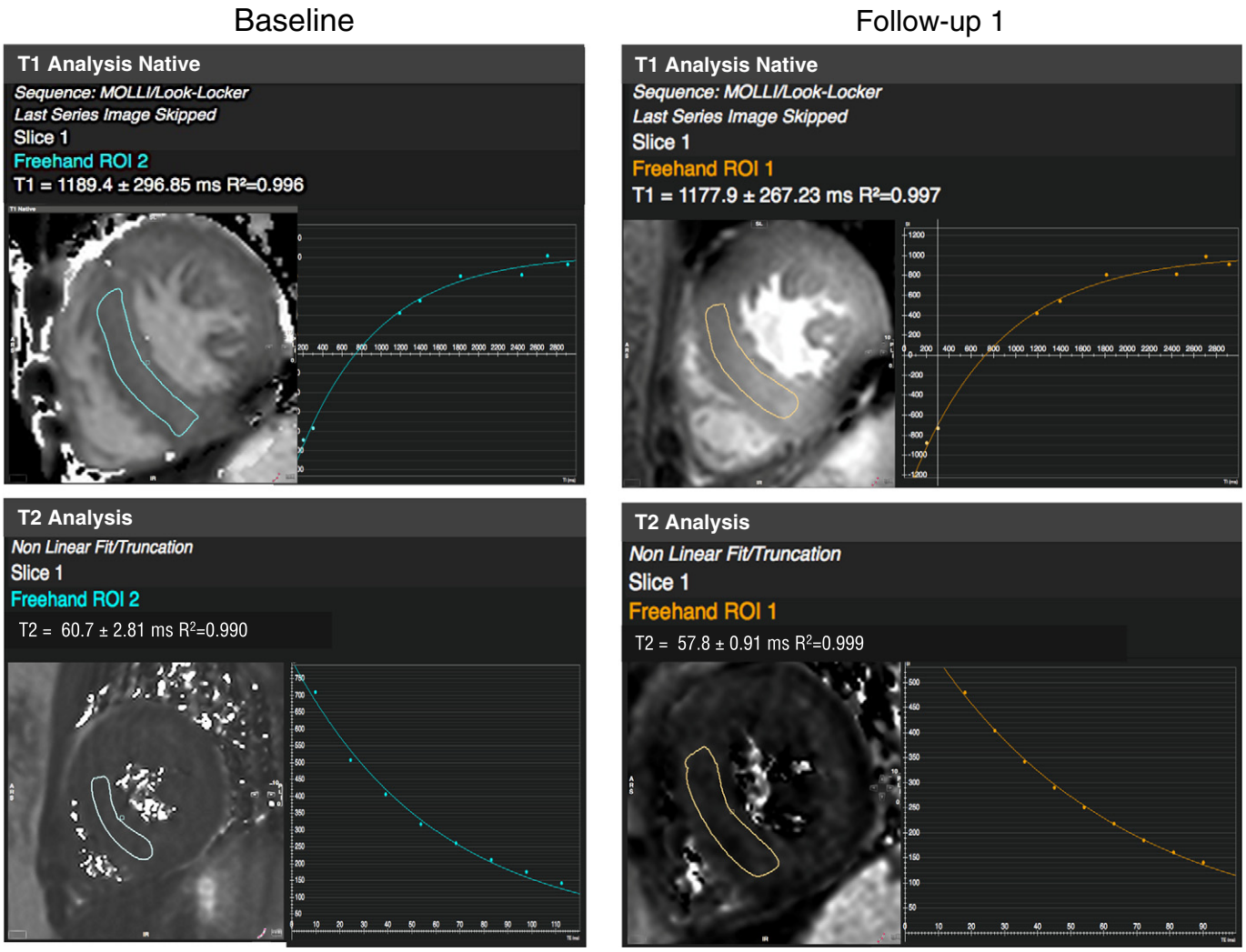

Fig. 3. Measurements of T1 and T2 mapping at baseline and follow-up. Same case as in Fig. 1. ROIs are drawn using conservative septal sampling approach. T1 mapping stands for fitting a curve of evolution of exponential relaxation (recovery) of T1 magnetization, whereas T2 mapping follows the exponential decay of T2 magnetization. T1 and T2 values are obtained when the respective processes are 63% completed.

1.8 × 1.8 × 8 mm). Dark blood T2 imaging for oedema was performed using a STIR sequence with whole heart coverage of short-axis slices (TE/TR/FA: 60 ms/2HB/90°, acquired voxel size 1.4 × 1.4 × 8 mm). LGE imaging was performed with whole heart coverage of SAX slices 20 min after administration of 0.2 mmol/kg body weight gadobutrol (Gadovist®, Bayer, Leverkusen, Germany) using a mid-diastolic

Table 2
Follow-up results of CMR assessment. Thirty-five SLE patients underwent a follow-up CMR scan after 3–6 (Follow-up 1) and subsequent 12 months (Follow-up 2). Change in variables has been assessed against the baseline measurements (expressed as mean differences and standard deviation (MD(SD))). Comparisons were made between the intensified and unchanged treatment. Paired t-tests and repeated measures ANOVA, $p < 0.05$ is considered significant.

Variables	Anti-inflammatory treatment						Comparisons between treatment groups
	Intensified treatment (n = 14)			Unchanged regime (n = 21)			
	Baseline (Mean ± SD)	Follow-up 1 (MD ± SD)	Follow-up 2 (MD ± SD)	Baseline (Mean ± SD)	Follow-up 1 (MD ± SD)	Follow-up 2 (MD ± SD)	Sig. (p-value)
LV-EDV index, mL/m^2	75 ± 18	−2.6(4.4)	−2.9(3.2)	75 ± 18	−1.8(6.6)	−0.7(4.7)	F = 0.7(0.4)
LV ejection fraction, %	54 ± 12	−2.8(3.8)	−3.3(5.2)	55 ± 13	−1.9(4.1)	2.2(4.9)	F = 0.4(0.52)
LV mass index, g/m^2	64 ± 13	2.1(4.3)	4.1(3.2)	65 ± 13	1.8(4.2)	2.2(4.0)	F = 2.3(0.14)
RV ejection fraction, %	54 ± 7	−1.1(3.5)	−1.3(4.0)	55 ± 6	−0.9(5.2)	−1.1(3.9)	F = 0.02(0.88)
Longitudinal strain, %	17 ± 3	−1.7(2.1)	−1.9(2.0)	18 ± 4	−0.8(2.2)	−0.9(2.2)	F = 1.9(0.18)
Native T1 (ms)	1172 ± 29	29(12)**	34(14)**	1169 ± 36	5(11)	11(14)	F = 22.7(<0.001)
Native T2 (ms)	65 ± 6	6.5(2.6)*	8.5(4.2)*	63 ± 5	1.9(2.7)	3.1(3.0)	F = 19.7(<0.001)
LGE extent (%)	4.7(0.4–5.1)	−0.3(0.4)	−0.3(0.4)	3.9(0.6–9.1)	0.1(0.2)	0.1(0.2)	F = 3.9(0.06)
C-reactive protein, mg/mL	5.7 ± 3.3	2.1(1.2)	1.8 (1.1)	5.4 ± 3.7	0.9(2.1)	0.8(1.7)	F = 3.8(0.063)

* $p < 0.05$.
** $p < 0.01$.

inversion prepared 2-dimensional gradient echo sequence (TE/TR/FA 2.0 ms/2HB/25°, acquired voxel size 1.4 × 1.4 × 8 mm) with an individually adapted prepulse delay to achieve optimally nulled myocardium.

T1 mapping was performed using MOLLI in a single midventricular SAX slice at mid-diastole (TE/TR/FA: 1.64 m/3.3 ms/50°, acquired voxel size 1.8 × 1.8 × 8 mm, 11 images corresponding to different inversion times (3 + 3 + 5 MOLLI scheme), with adiabatic prepulse to achieve complete inversion). The acquisitions were checked for motion and artefacts as well as for goodness of fit immediately after acquisition at the scanner [11,26,27].

T2 mapping was performed in a single midventricular SAX using a hybrid gradient and spin echo (GRASE) sequence combining turbo spin echo and echo-planar imaging methods and using a train of refocusing 180° pulses and an odd number of additional gradient echoes for each spin echo (TE/TR/FA: 60/1HB/90°, echo images (n = 9), acquired voxel size 1.4 × 1.4 × 8 mm, SENSE (acceleration factor of 2), and Cartesian encoding) [14,15].

2.2. CMR image analysis

Analysis was performed using commercially available software (Circle CVI 42®, Calgary, Canada) following standardized post-processing recommendations, as previously reported [26,28]. Quantitative tissue characterization and myocardial deformation analysis was performed blind of the underlying subject group allocation and the time-point of the examination. LGE was quantified by a semiautomatic detection method using a previously validated method of full-width at half maximum and reported as a percentage of total LV mass, as previously described [26,29]. The LGE distribution was characterized as subendocardial, midwall, epicardial or diffuse, based on the predominant pattern [28].

Recovery rate of T1 and T2 relaxation was measured in a midventricular SAX slice conservatively within the septal myocardium, as previously described and validated [27,30,31]. Areas of LGE were excluded from the mapping regions of interests. Cut-off values for abnormal myocardium were defined on the basis of the previously derived normal ranges for native T1 (for 3 T field strength: mean of the normal range 1052 ± 23 ms; i.e. upper limit of normal range: 1098 ms) [32], as well as the definitions of acute myocarditis (≥5SD: ≥1167 ms) [12]. Deformation analysis was performed by tracing the contours within the myocardium in the cine-images, using feature tracking 2-dimensional prototype software (TomTec GmbH, Munich, Germany), as previously described and validated [33]. Longitudinal and radial deformation were obtained in 3 long-axis and SAX views, respectively, and expressed as an absolute global peak systolic strain.

Statistical analysis was performed using SPSS software (version 21.0; SPSS, Chicago, IL, USA). Normality of distributions was tested with the Kolmogorov–Smirnov statistic. Categorical data are expressed as percentages, and continuous variables as mean ± SD or median (interquartile range). Statistical comparisons were performed using paired (within-the group) or unpaired (between the groups) t-tests or one-way ANOVA, or χ^2 and Mann–Whitney tests, as appropriate. Differences between the baseline and follow-up CMRs, as well as the effect of anti-inflammatory treatment were examined using repeated-measures ANOVA. Associations were assessed using linear regressions and non-parametric correlations. Predictors of response to treatment (defined as a change in native T1 at the first follow-up scan which is greater than 1SD to allow a distinction from a chance finding) were examined using binary logistic regression analysis. All tests were two-tailed and p-values <0.05 were considered statistically significant.

3. Results

3.1. Clinical characteristics

SLE patients had higher blood pressure, lower haematocrit and eGFR, and raised levels of inflammatory markers compared to controls (p < 0.05) (Table 1). Dyspnea was the most prevalent cardiac symptom, followed by atypical chest pain. The majority of patients were in NYHA class II or less. Patients were taking a variety of cardiac medications, mainly renin–angiotensin system inhibitors in the context of a known renal disease and blood pressure control. Disease characteristics related to SLE, including previous history, symptoms, and medications are included in Table 1. The majority of patients were in SLEDAI groups ≤2, with 6 subjects in group 3. Thirty-six patients had a positive troponin test. Troponin positive and negative patients were similar in terms of general disease characteristics and the duration of systemic disease (p > 0.05). Compared to troponin negative subjects, these patients were more symptomatic, had higher inflammatory biomarkers (hsCRP: 7.3 ± 3.9, p < 0.01), and were taking more SLE-related anti-inflammatory medication (p < 0.05).

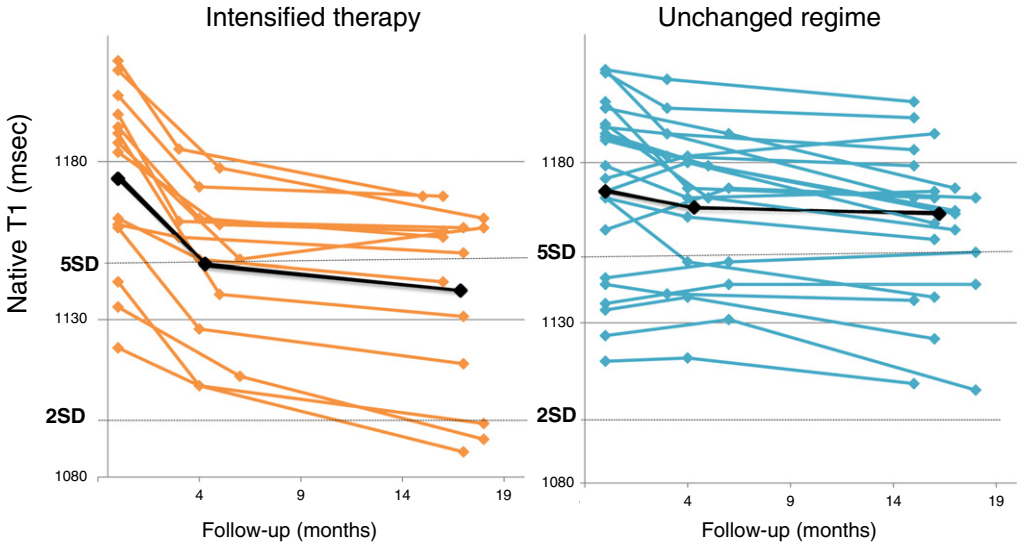

Fig. 4. Native T1 measurements at baseline and follow-up in patients receiving intensified therapy (n = 14) and those with unchanged regime (n = 21). A black line indicates trend line in the respective groups. Cut-off values for abnormal myocardium were defined on the basis of the previously derived normal ranges for native T1 (for 3 T field strength: mean of the normal range 1052 ± 23 ms; i.e. upper limit of normal range: 1098 ms) [32], as well as the definitions of acute myocarditis (≥5SD: ≥1167 ms) [12].

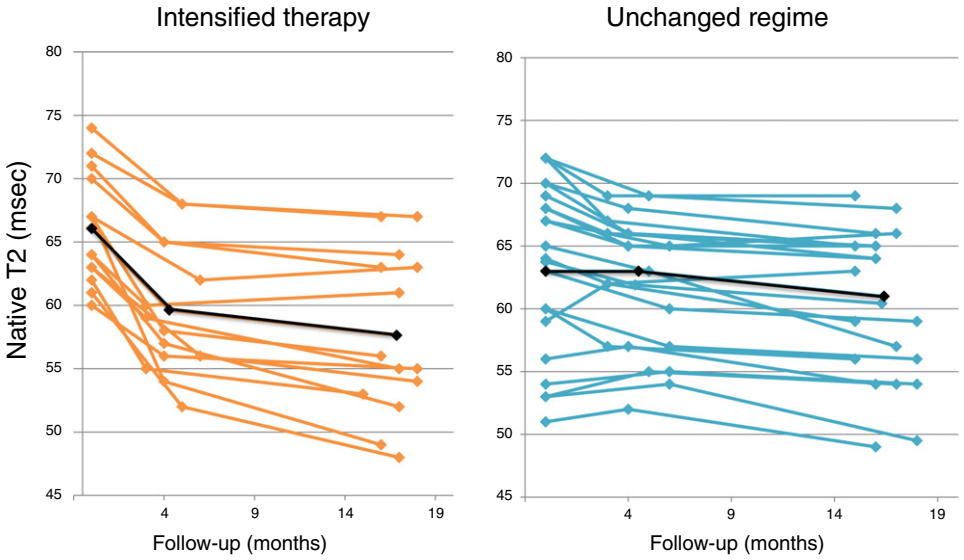

Fig. 5. Native T2 measurements at baseline and follow-up in patients receiving intensified therapy (n = 14) and those with unchanged regime (n = 21). A black line indicates trend line in the respective groups.

3.2. Cardiac function and structure and tissue characterization

Compared to controls, SLE patients had higher LV mass, lower LV and RV ejection fraction (EF), and longitudinal strain ($p < 0.01$) (Table 1, Figs. 1 and 2). There was a trend towards higher LV volumes ($p = 0.08$). Native T1 and T2 values were significantly higher in patients compared to controls ($p < 0.01$). Sixty-nine SLE patients (91%) had native T1 values of ≥2SD above the mean of the normal range [32], and 54 (71%) had native T1 ≥ 5SD above the mean of the normal range (acute myocarditis) [12]. T2 oedema ratio was higher in patients ($p = 0.029$) and LGE was found in 25 (33%) of all patients; a total of 22 (29%) patients have met Lake Louise criteria. In troponin positive subjects, native T1 and T2 were significantly higher than in troponin negative subjects (native T1 (ms): 1186 ± 32 vs. 1154 ± 44, native T2 (ms): 69 ± 6 vs. 58 ± 7, $p < 0.01$) with otherwise similar proportions of perimyocardial LGE.

Table 3
Prediction of treatment response. Univariate and multivariate binary logistic regression. SLEDAI — SLE disease activity index, NYHA — New Yor Heart Association; SD — standard deviation; Lake Louise criteria (LGE and T2 weighted imaging). Prednisolone dose was ranked (mg/kg): none, low (≤0.25), mid (0.26–0.5), high (0.5–1).

	Chi^2 (p-value)	HR(95%CI)	Sig. (p-value)
Univariate analysis			
Troponin (positive)	2.6(0.05)	0.64(0.17–2.4)	0.07
SLEDAI (per class)	1.6(0.21)	1.6(0.7–3.4)	0.24
NYHA (per class)	0.63(0.43)	1.3(0.7–2.4)	0.44
Native T1 (10 ms)	9.4(0.002)	1.7(1.2–1.9)	0.010
Native T1 (1SD – 23 ms)	11.7(0.001)	4.6(1.6–11)	0.005
Native T2 (ms)	3.9(0.03)	1.08(1.01–1.12)	0.05
Native T2 (SD – 4 ms)	4.2(0.03)	2.3(1.1–3.2)	0.02
Lake Louise criteria	0.22(0.61)	1.3(0.4–4.9)	0.63
Prednisolone dose (ranked)	2.8(0.06)	1.6(0.7–3.9)	0.08
Multivariate analysis			
Model 1			
Native T1 (10 ms)	9.4(0.002)	1.7(1.2–1.9)	0.010
Other variables: native T2 (0.09); troponin (0.12); SLEDAI (0.24); NYHA(0.64); LGE (0.40); prednisolone (0.13)			
Model 2			
Native T1 (SD – 23 ms)	11.9(0.001)	4.6(1.6–11)	0.005
Other variables: native T2 (0.08); troponin (0.22); SLEDAI (0.27); NYHA(0.51); LGE (0.25); prednisolone (0.24)			

3.3. Analysis of relationships with native T1 and T2

There was a significant association between native T1 and T2 ($r = 0.61$, $p < 0.001$), which was only marginally stronger when controlling for the presence of positive troponin and LGE ($r = 0.69$) (Fig. 3). Native T1 and T2 (SD ranked) showed a weak association with SLEDAI score (Tau = 0.31 and 0.21, $p < 0.02$), and a trend for prednisolone dose (ranked (mg/kg)): none, low (≤0.5), mid (0.5–1), high (>1) (Tau = 0.17, $p = 0.06$ for both). Native T1 and T2 were moderately associated with LVEF, LV mass, longitudinal strain and extent of LGE (native T1, native T2: LVEF: $r = -0.29$, $r = -0.19$; LV mass: $r = 0.51$, $r = 0.42$;

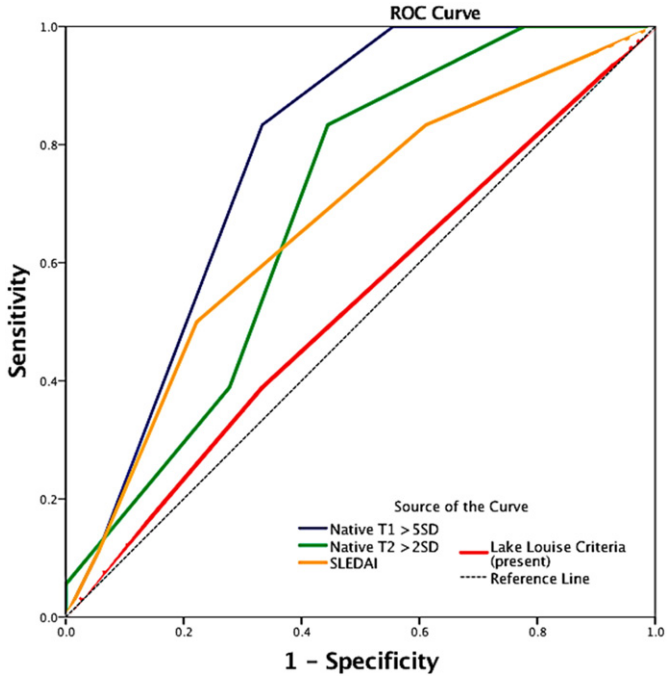

Fig. 6. ROC curve analysis in correctly classifying between patients with treatment response. AUCs for native T1 (>5SD) 0.82 (95%CI: 0.66–0.95; $p = 0.001$); native T2 (>2SD): 0.74 (0.59–88, $p = 0.02$); SLEDAI: 0.64 (0.48–0.82, $p = 0.09$) and Lake Louise criteria: 0.58 (0.35–0.72; $p = 0.77$).

longitudinal strain: $r = -0.39$, $r = -0.32$; extent LGE: $r = 0.30$, $r = 0.29$; $p < 0.05$). There was no association with age ($p = 0.21$) or duration of systemic disease ($p = 0.11$).

3.4. Follow-up CMR and anti-inflammatory treatment

Thirty-five SLE patients underwent two consecutive follow-up CMR studies after 3–6 and 15–18 months. Guided by the change in the SLEDAI score [22], 14 patients received intensified anti-inflammatory treatment including new or increased doses of steroids or immunosuppression, whereas in the other 21 patients, the treatment regime remained unchanged (Table 1). Baseline characteristics of the two subgroups were similar for SLEDAI, inflammatory and imaging markers (Table 2). Patients with intensified treatment showed significantly greater reduction in native T1 and T2 values ($p < 0.001$), and a trend in reduction of LGE extent ($p = 0.06$) with the greatest change observed within the duration of the first follow-up period and a plateau thereafter (Figs. 4 and 5). A detectable reduction of native T1 in a magnitude of 1 SD was observed in 12 (86%) and 6 (27%) subjects in the group with intensified treatment versus the group with unchanged treatment during follow-up ($p = 0.002$). There was no significant change in longitudinal strain or the presence or extent of LGE. In predicting the treatment response, native T1 and T2 were identified as significant univariate predictors, and a trend for positive troponin ($p = 0.07$) and prednisolone dose ($p = 0.09$), whereas the clinical scores and Lake Louise criteria (LGE and T2 weighted imaging) [34] showed no predictive associations (Table 3). ROC curve analysis in correctly classifying patients with response revealed the following AUCs (Fig. 6): native T1 (>5SD) 0.82 (95%CI: 0.66–0.95; $p = 0.001$); native T2 (>2SD): 0.74 (0.59–88, $p = 0.02$); SLEDAI: 0.64 (0.48–0.82, $p = 0.09$) and Lake Louise criteria: 0.58 (0.35–0.72; $p = 0.77$).

3.5. Reproducibility

Reproducibility of the T1 and T2 mapping method has been reported previously [30–32]. Intra- and inter-observer agreement ($n = 15$) for native T1 ($r = 0.98$; $r = 0.97$, $p < 0.001$) and native T2 ($r = 0.97$; mean difference (MD) $\pm$ SD $= -0.05 \pm 1.85$; $r = 0.95$, $p < 0.001$ MD $\pm$ SD $= 0.01 \pm 2.5$) values was high. Similarly, the intra- and inter-observer coefficients of variation for T1 (0.66%; 1.19%) and T2 (1.85%; 2.5%) values were low. For strain analysis, intra- and inter-observer agreements were $r = 0.81$ and $r = 0.74$ ($p < 0.001$ for both), with MD $\pm$ SD of 0.05 ± 1.9 and 0.09 ± 2.8, respectively.

4. Discussion

Results of the present study reveal a role of T1 and T2 mapping by CMR in lupus myocarditis to recognize and measure the response to anti-inflammatory therapy. Firstly, we demonstrate that native T1 and T2 values are considerably higher in patients compared to controls. Secondly, we show that these values relay the change induced by anti-inflammatory treatment. Finally, the treatment response in patients receiving intensified treatment was characterized by the greatest change of T1 and T2 values within the duration of the first follow-up period and a plateau thereafter, suggesting an attenuation of the on-going inflammatory process.

To the best of our knowledge, this is the largest cohort of lupus myocarditis patients. We employed T1 and T2 mapping to characterize inflammatory myocardial involvement. A series of studies using CMR previously reported on findings in SLE patients with cardiovascular symptoms, including LV remodelling and myocardial scar consistent with advanced disease [5,35,36]. Using Lake–Louise Criteria based on visualization of increased signal on T2 weighted imaging and the presence of LGE previous studies reported higher oedema ratio in patients with SLE [20,37]. Our findings concord with these observations and expand on several aspects by employing quantitative tissue characterization by T1 and T2 mapping.

Firstly, we specifically aimed to better understand the mechanism of increased native T1 in this cohort. We and others have previously reported on significantly raised myocardial T1 values in asymptomatic SLE patients [11,38]. It is increasingly recognized that T1 mapping is sensitive to identify abnormal myocardium by reacting to a number of histological substrates including myocardial inflammation, oedema and fibrosis [39]. In contrast, the T2 signal relays specifically to the increased myocardial water content. Therefore, we employed a parallel imaging approach of T1 and T2 mapping in order to decipher the complex – acute-on-chronic – nature of myocardial involvement in lupus myocarditis. We demonstrate that both indices are native T1 and T2 significantly raised. Furthermore, the values were significantly higher in patients with serological evidence of troponin release. Our findings reveal significant association between native T1 and T2 as well as a similar change of these two parameters during therapeutic intervention. These findings impart a marked influence of myocardial water content, myocardial oedema, on the two measures in support their application in assessment of disease activity of inflammatory myocardial involvement.

Secondly, we observed the greatest change in myocardial T1 and T2 values within the first follow-up period with plateauing thereafter, suggesting that inflammation has not ceased, but continues at a lower level of activity. On the contrary, patients with unchanged regime showed no significant change, and also no consistent trend of deterioration, suggesting that the established anti-inflammatory regime was key to maintaining the balance.

Thirdly, the findings of prevalently and significantly raised native T1 and T2 values in most of the patients challenge the assumptions of previous reports, which only relate lupus myocarditis to severe manifestations of an acute heart failure [1,2]. It is more likely that such presentations correspond to clinical decompensation of an acute-on chronic inflammatory cardiomyopathy [15].

Thus, the findings of the present study provide new knowledge with immediate implication for clinical care of patients with SLE. Firstly, cardiac involvement in SLE is prevalent and out of proportion with symptoms or indices of systemic disease. Encompassing the more robust manifestations of systemic disease, detachment between the cardiac involvement and SLEDAI score is comprehensible given the lack of typical cardiac symptoms as well as a lack of reliable non-invasive diagnostic means, similar to the difficulties of early detection of lupus nephritis [40]. The epidemiologically documented high burden of cardiac morbidity and mortality [4,41] and the observations of considerable inflammatory myocardial involvement on autopsy [7] only now begin to translate into signals, which are amenable to recognition in-vivo by non-invasive phenotyping by T1 and T2 mapping. Simple means of screening, such as assessment of LV function and structure with echocardiography, are unlikely to uncover the extent of inflammatory involvement as the thickened inflamed myocardium (Figs. 1 and 2) will prevent the cavities from dilating, thus preserving the volumes and global systolic function [42–44]. Direct and quantifiable myocardial tissue characterization by T1 and T2 mapping may provide a reliable path to disease recognition and assessment of activity of myocardial inflammation, as well as a path to development of targeted therapeutic options. Treatment guided directly by T1 and T2 values may allow the fine-tuning of the type, dose and duration of therapy to the desired effect, subject to a future randomized controlled outcome study. Such study should also clarify the diagnostic and monitoring role of contrast-enhanced myocardial imaging by LGE. The latter is relevant in view of the advantages of a contrast-free CMR study in reducing the risk in a potentially vulnerable patient population, which is already receiving a number of contrast enhanced MR studies for CNS involvement [45].

A few limitations apply. This is a proof-of concept study performed in a single centre patient, and subject to external validation. Although this was a purely observational study and not a clinical trial by design,

clinical management of anti-inflammatory therapy was performed independently, with physicians blinded to results of T1 and T2 mapping. Similar baseline characteristics of follow-up groups indirectly support the randomness in treatment allocation. The results of T1 mapping indices are T1 mapping sequence dependent [21]. T1 mapping sequence employed in this study has undergone a thorough pathway of standardization, from derivation of normal values to outcome data. Sequence parameters and details of its validation have been published and are publicly available [26].

In summary, novel quantitative tissue characterization methods by native T1 and T2 mapping, provide important insight into inflammatory involvement in SLE, with respect to disease recognition, monitoring of activity and response to anti-inflammatory treatment. Native T1 and T2 mapping may support an effective, non-invasive, non-contrast and radiation free screening method for lupus myocarditis.

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Conflict of interest

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

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