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Diffuse Myocardial Fibrosis and Inflammation in Rheumatoid Arthritis

Insights From CMR T1 Mapping

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ABSTRACT

OBJECTIVES The goal of this study was to assess the diffuse myocardial fibrosis and edema in rheumatoid arthritis (RA) using multiparametric cardiac magnetic resonance (CMR) and the association of myocardial T1 and extracellular volume (ECV) with disease activity, duration, and cardiac function.

BACKGROUND RA is a connective tissue disorder, with frequent cardiovascular disease. Myocardial inflammation and diffuse fibrosis can be detected noninvasively by using native T1 mapping and ECV quantification on CMR.

METHODS Thirty-nine RA patients (28 women; mean age 50 ± 12 years) and 39 matched control subjects (28 women; mean age 49 ± 12 years) underwent CMR at 1.5-T, including cine, tagging, T2-weighted, native T1 mapping (shortened modified Look-Locker inversion recovery), late gadolinium enhancement (LGE), and ECV imaging.

RESULTS Focal fibrosis on LGE was found in 46% of RA patients compared with none of the control subjects. Patients with RA had larger areas of focal myocardial edema (10% vs. 0%), higher native T1 values (973 ± 27 ms vs. 961 ± 18 ms; $p = 0.03$), larger areas of involvement as detected by native T1 >990 ms (35% vs. 2%; $p < 0.001$), and expansion of ECV (30.3 ± 3.4% vs. 27.9 ± 2.0%; $p < 0.001$) compared with control subjects. Left ventricular volumes, mass, and ejection fraction were similar between RA patients and control subjects. Peak systolic circumferential strain (-16.9 ± 1.3 vs. -18.7 ± 1.2; $p < 0.001$) and peak diastolic circumferential strain rate (83 ± 21 s^{-1} vs. 112 ± 20 s^{-1}; $p < 0.001$) were impaired in RA patients. Myocardial T1 and ECV were correlated with myocardial strain and RA disease activity.

CONCLUSIONS Subclinical cardiovascular disease is frequent in RA, including focal and diffuse myocardial fibrosis and inflammation, which are associated with impaired strain and RA disease activity. CMR T1 mapping provides potential added value as a biomarker for disease monitoring and study of therapies aimed at reducing diffuse myocardial fibrosis in RA. (J Am Coll Cardiol Img 2015;8:526–36) © 2015 by the American College of Cardiology Foundation.

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Rheumatoid arthritis (RA) is a chronic autoimmune disease of the joints, associated with pain, swelling, limited mobility, disability, and premature death (1). RA is commonly associated with extra-articular features, including cardiovascular complications (2). Cardiovascular involvement in RA predominantly affects young female subjects and accounts for 40% to 80% of the premature mortality and a consequent 10-year reduction in life span (3–5). Myocardial disease in RA results from a combination of processes that includes chronic inflammation, myocardial fibrosis, focal nonspecific diffuse necrotizing or granulomatous myocarditis, microvascular dysfunction, unrecognized myocardial infarction (MI), and the drugs used in the treatment of RA (6).

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Cardiac magnetic resonance (CMR) has been used in the comprehensive noninvasive assessment of myocardial abnormalities in RA (7,8). Late gadolinium enhancement (LGE), representing focal myocardial fibrosis/scarring, reportedly occurs in 39% of RA patients, likely from earlier myocarditis (7). However, LGE relies on the comparison of focal myocardial damage against unaffected normal myocardium and is thus limited in detecting diffuse myocardial fibrosis, which often occurs in RA (6). Results of endomyocardial biopsy may confirm the histologic detection of myocardial fibrosis (9). Extracellular volume (ECV) mapping based on measurement of CMR T1 relaxation times has proved to be a robust tool for the noninvasive assessment of diffuse myocardial fibrosis (10,11). T1 mapping and ECV estimation correlate well with histological evidence of myocardial fibrosis in various clinical contexts (12,13). We therefore hypothesized that CMR T1 mapping would reveal subtle forms of myocardial inflammation and diffuse myocardial fibrosis in asymptomatic RA patients with no known cardiovascular involvement compared with control subjects of similar age and sex. Furthermore, we sought to investigate the relation between CMR parameters of diffuse fibrosis and myocardial inflammation and indexes of RA disease activity and duration. Finally, we examined the relation between diffuse myocardial fibrosis and left ventricular (LV) regional systolic and diastolic function.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CRP = C-reactive protein

DAS28-CRP = disease activity score with 28 tender and swollen joint count, incorporating C-reactive protein

ECV = extracellular volume

LA = long atrial

LGE = late gadolinium enhancement

LV = left ventricular

MI = myocardial infarction

SA = short-axis

SI = signal intensity

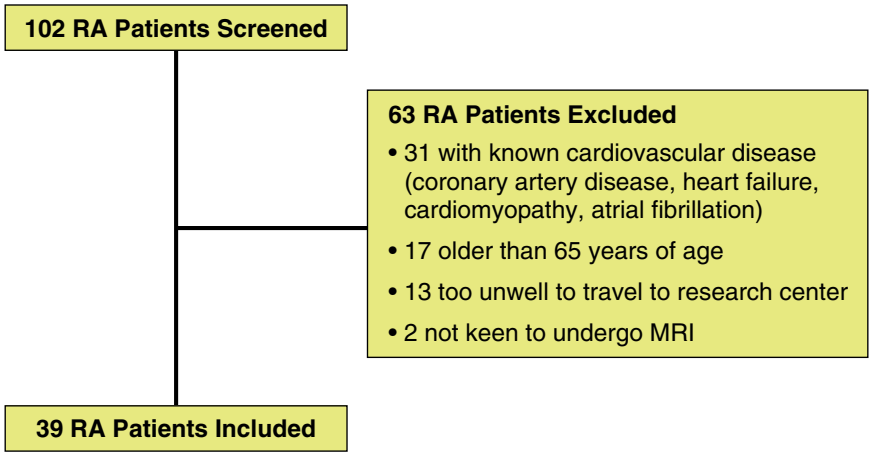
STIR = short-tau inversion recovery

RA = rheumatoid arthritis

METHODS

STUDY POPULATION. This was a prospective study enrolling nonselected patients with RA (N = 39) with no known cardiovascular disease. RA patients were recruited from 4 hospitals in the Thames Valley, United Kingdom. They underwent clinical assessment and CMR scanning between November 2010 and December 2012. Patients with RA included in the study were between 18 and 65 years of age and had a confirmed diagnosis of RA based on the 1987 American College of Rheumatology criteria (modified in 2010) (14), as assessed by clinical consultant

FIGURE 1 Strobe Diagram



Patients with rheumatoid arthritis (RA) screened and included in the study. MRI = magnetic resonance imaging.

rheumatologists. Exclusion criteria included inability to tolerate CMR, contraindications to CMR, nonsinus rhythm, known heart disease (previous MI, previous myocarditis on history, heart failure, arrhythmia on 12-lead electrocardiography, or other chronic cardiac condition), renal impairment (estimated glomerular filtration rate <30 ml/min), impaired liver function (alanine aminotransferase level more than twice the upper limit of normal), and known hypersensitivity to gadolinium (**Figure 1**). Female subjects who were pregnant, lactating, or planning a pregnancy were also excluded. Healthy volunteers were matched for age, sex, and ethnicity (N = 39); they had no cardiac history, were not on cardiovascular medications, and had a normal electrocardiography and underwent CMR as control subjects.

All subjects provided written informed consent to participate in the study. Ethical approval was granted for all study procedures by the Oxford Research Ethics Committee.

TABLE 1 Baseline Characteristics of the Study Population

	Control Subjects (N = 39)	RA Patients (N = 39)	p Value
Demographic and clinical features and comorbidity			
Female	28 (72)	28 (72)	0.99
Age, yrs	49 ± 12	50 ± 12	0.65
Hypertension	2 (5)	5 (13)	0.24
Diabetes	0 (0)	1 (3)	–
Hyperlipidemia	5 (13)	6 (15)	0.75
BMI, kg/m^2	24 ± 4	26 ± 5	0.13
Medical therapy			
Methotrexate	–	34 (87)	–
Chloroquine	–	25 (64)	–
Leflunomide	–	6 (15)	–
Sulfasalazine	–	6 (15)	–
Rituximab	–	2 (5)	–
Prednisolone	–	1 (3)	–
NSAID	–	17 (44)	–
HRT/OCP	7 (18)	9 (23)	0.56
Disease activity and chronicity indexes			
DAS28-CRP	NA	3.3 ± 1.3	–
ESR, mm/h	NA	15 (9–19)	–
CRP, mg/l	1 (1–2)	9 (4–13)	<0.001
Hemoglobin	14.0 ± 1.4	13.0 ± 1.2	0.38
Hematocrit, %	0.42 ± 0.03	0.40 ± 0.05	0.30
Creatinine, μmol/l	NA	74 ± 18	–
Duration of RA, yrs	NA	7 (4–11)	–
Duration of DMARDs, yrs	NA	4 (3–6)	–
RF-positive	NA	31 (79)	–
ACCP-positive	NA	25 (64)	–

Values are n (%), mean ± SD, or median (interquartile range).

ACCP = anti-cyclic citrullinated peptide antibodies; BMI = body mass index; DAS28-CRP = rheumatoid arthritis disease activity score with 28 tender and swollen joint count, incorporating C-reactive protein; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; HRT/OCP = hormone replacement therapy/oral contraceptive pill; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; RF = rheumatoid factor.

CMR IMAGE ACQUISITION. CMR studies were performed by using a single 1.5-T magnetic resonance system (Avanto, Siemens Healthcare, Forchheim, Germany) according to standard and previously published methods. A complete stack of short-axis (SA) images were obtained during breath-hold and cardiac gating for cine, pre-contrast (native) T1 mapping, T2-weighted, and LGE imaging. T1 mapping was performed by using the shortened modified Look-Locker inversion recovery sequence, and T2-weighted CMR was performed with the black-blood short-tau inversion recovery (STIR) sequence. Three SA (basal, mid-ventricular, and apical) scans and a single long-axis (horizontal) scan were obtained for tagging. Native T1 maps and T2-weighted and cine-tagged images were acquired before administration of gadolinium contrast. LGE imaging was performed by using a T1-weighted phase-sensitive inversion recovery sequence 8 to 12 min after intravenous administration of a contrast agent (gadoterate meglumine [Dotarem, Guerbet LLC, Paris, France]; 0.15 mmol/kg of body weight). A single mid-ventricular SA slice was acquired for post-contrast T1 maps at 1, 2, 3, 4, 8, 15, and 20 min after the administration of contrast (gadoterate meglumine). Typical imaging parameters for the sequences used were as previously published (15) and are detailed in the Online Appendix.

CMR IMAGE ANALYSIS. All CMR images and maps were analyzed offline and in a blinded fashion.

For cine images, analysis of LV ejection fraction was performed by using Argus software version VB17 (Siemens Healthcare). LV SA epicardial and endocardial borders were manually contoured at end-diastole and end-systole. LV end-systolic and end-diastolic volumes were used to calculate stroke volume and LV ejection fraction as stroke volume/end-diastolic volume. LV myocardial mass was calculated by subtracting the endocardial volume from the epicardial volume, based on earlier knowledge of myocardial specific gravity (1.05 g/cm^3). Left atrial (LA) diameter was measured in the LV outflow tract (3-chamber) view.

For tagged cine images, post-processing and semiautomated analysis was performed by using Cardiac Image Modeler software (CIMTag2D, University of Auckland, Auckland, New Zealand) by aligning a grid to the myocardial tagging planes in end-diastole. End-systole was determined visually, and tags were adjusted at each frame through the cardiac cycle. From the mid-SA slice, peak circumferential systolic strain and peak diastolic strain rate were derived.

For STIR images, semiquantitative analysis was performed by comparing the LV myocardium in the SA against adjacent skeletal muscle in the same slice, verified on a corresponding steady-state free precession image. The T2 signal intensity (SI) ratio was calculated as T2 $SI_{myocardium:skeletal} = SI_{myocardium}/SI_{skeletal\ muscle}$. Myocardial edema was diagnosed when the myocardial T2 SI ratio was >1.9. Care was taken to exclude nonsuppressed blood pool signal due to slow-flow adjacent to the subendocardium and to avoid using areas with abnormally low signal for normalization.

LGE images were evaluated qualitatively for the presence or absence, pattern (e.g., subendocardial, mid-wall, subepicardial, transmural), and regional distribution of LGE areas by 3 observers, each with at least 4 years of CMR experience. The detection of LGE was made by consensus of all 3 observers. In addition, focal areas of LGE were defined semiquantitatively as those with SI ≥2.0 SDs above the mean SI of normal myocardium according to MC-ROI software (programmed by S.K.P. in Interactive Data Language version 6.1, Exelis Visual Information Solutions, Boulder, Colorado).

For T1 maps, they were manually contoured by using in-house software MC-ROI to outline the endocardium and epicardium. They were then divided into 6 segments per slice by using the anterior right ventricular-LV insertion point as reference for comparing segments among sequences.

Consistent with earlier reports on ECV estimation (10,12), we measured pre-contrast and post-contrast myocardial and blood T1 values, and the estimation of ECV and lambda was based on multipoint regression, incorporating all available pre-contrast and post-contrast points, to increase the robustness of the estimates by increasing the number of underlying data points. ECV was calculated as: (1 - hematocrit). For calculation of post-contrast T1 values, the post-contrast T1 map acquired at 20 min was utilized for ECV calculation.

For areas of myocardial involvement by STIR and native T1 mapping, the following was used: on dark-blood T2-weighted images, edema was diagnosed when myocardial T2 SI was >1.9 times that of remote skeletal muscle. On T1 maps, acute myocardial injury was diagnosed when T1 was >990 ms. For all quantitative analyses of T2-weighted and T1-mapping images, only regions of myocardium with a contiguous area of ≥40 mm^2 above the specified thresholds were considered relevant (to reduce the detection of noise as positive findings). To calculate the extent of a subject's myocardial involvement detected by using tissue characterization techniques, the percentage of abnormal myocardium (as defined earlier) was determined for each segment and then averaged for that subject (16).

RA DISEASE ACTIVITY AND DURATION. Disease activity was assessed by using a disease activity score that incorporates a 28 tender joint and swollen joint count in addition to a measure of general health, together with the serum C-reactive protein level (DAS28-CRP). An absolute level of disease activity can be selected as a clinically meaningful goal for therapeutic intervention; a value of ≤3.2 was defined as the threshold for a low disease activity state and <2.6 as the threshold for remission. CMR biomarkers were also correlated with disease duration. In keeping with clinical practice, a cutoff of 2 years was used to distinguish early RA disease duration from established duration.

STATISTICAL ANALYSIS. Normality of data was tested by using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD and nonparametric data as median (interquartile range); categorical data are presented as number (percentage). The chi-square test or the Fisher exact test was used to compare dichotomous data. The unpaired Student *t* test (when normally distributed) or Mann-Whitney *U* test (for nonparametric data) was used to compare continuous variables between RA patients and control subjects, as appropriate. Segmental data were averaged on a per-subject basis

TABLE 2 CMR Findings

	Control Subjects (N = 39)	RA Patients (N = 39)	p Value
LVEDV indexed to BSA, ml/m^2	78 ± 15	80 ± 16	0.63
LVESV indexed to BSA, ml/m^2	24 ± 16	23 ± 9	0.62
LVEF, %	73 ± 5	72 ± 7	0.25
LV mass indexed to BSA, g/m^2	52 ± 11	54 ± 12	0.34
LA size, mm	27 ± 5	32 ± 5	<0.001
Mid-SA circumferential strain	-18.7 ± 1.2	-16.9 ± 1.3	<0.001
Peak diastolic circumferential strain rate, s^{-1}	112 ± 20	83 ± 21	<0.001
Presence of LGE, %	0	18 (46)	–
Volume fraction of LGE >2 SDs, %	0	3.7 ± 0.4	–
Global myocardial T2 SI ratio	1.5 ± 0.1	1.6 ± 0.2	0.70
Volume fraction of edema by T2, %	0	10 (2-18)	–
Average myocardial T1, ms	961 ± 18	973 ± 27	0.03
Volume fraction of T1 >990 ms, %	2 (1-8)	35 (19-51)	<0.001
Post-contrast T1, ms	468 ± 32	450 ± 40	0.04
ECV, %	27.9 ± 2.0	30.3 ± 3.4	<0.001

Values are n (%), mean ± SD, or median (interquartile range).

BSA = body surface area; CMR = cardiac magnetic resonance; ECV = extracellular myocardial volume; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; SA = short-axis; SI = signal intensity; STIR = short-tau inversion recovery; other abbreviation as in Table 1.

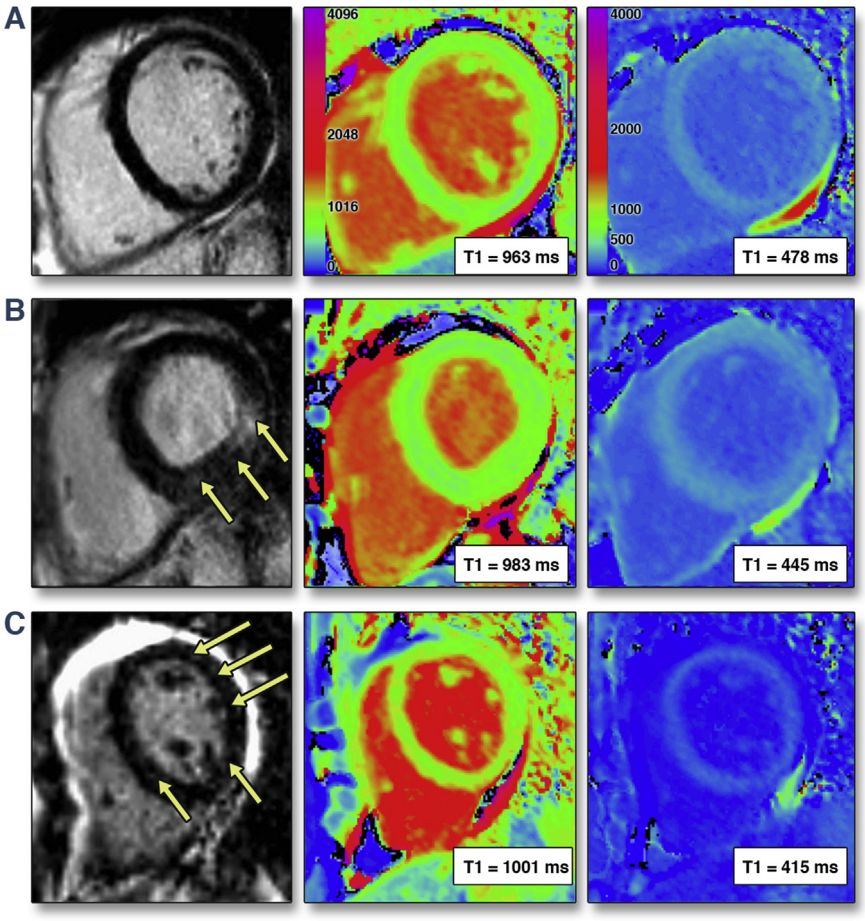
before group comparisons versus control for clustering of segments within each subject. Bivariate correlations were assessed by using the Pearson's (R) or the Spearman's (R_S) coefficient, as appropriate. All statistical tests were 2-tailed, and a p value <0.05 was considered statistically significant. All analyses were performed using SPSS version 20 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. The patients with RA were well matched with the control subjects for age, sex, and comorbidities (Table 1). A majority of the RA patients were on methotrexate and chloroquine. Most patients had been diagnosed with RA for a median of 7 years (interquartile range: 4 to 11 years). The median duration of anti-inflammatory treatment was 4 years (interquartile range: 3 to 6). The mean DAS28-CRP score was 3.3 ± 1.3, which signifies ongoing disease activity in most patients.

LV AND RIGHT VENTRICULAR STRUCTURE AND FUNCTION. There was no significant difference in LV size, mass, or ejection fraction between RA patients and control subjects (Table 2). However, peak systolic circumferential strain (-16.9 ± 1.3 vs. -18.7 ± 1.2; $p < 0.001$) and diastolic strain rate (83 ± 21 s^{-1} vs. 112 ± 20 s^{-1}; $p < 0.001$) at mid-SA were impaired in RA patients compared with control subjects. In keeping with diastolic dysfunction, the LA diameter

FIGURE 2 Representative Examples of Pre-Contrast and Post-Contrast T1 Maps With Corresponding LGE Images



(A) Normal control with no late gadolinium enhancement (LGE): pre-contrast T1, 963 ms; post-contrast T1, 478 ms; extracellular volume (ECV), 27.4%. **(B)** Rheumatoid arthritis (RA) patient with basal inferior and lateral mid-wall LGE **(arrows)**: pre-contrast T1, 983 ms; post-contrast T1, 445 ms; ECV, 31.6%. **(C)** RA patient with multiple, near-circumferential, small patches of mid-wall LGE **(arrows)**; native T1, 1,001 ms; post-contrast T1, 415 ms; ECV, 37.9%. Values in graphic indicate myocardial T1 values.

was larger in RA patients compared with control subjects (32 ± 5 mm vs. 27 ± 5 mm; p < 0.001).

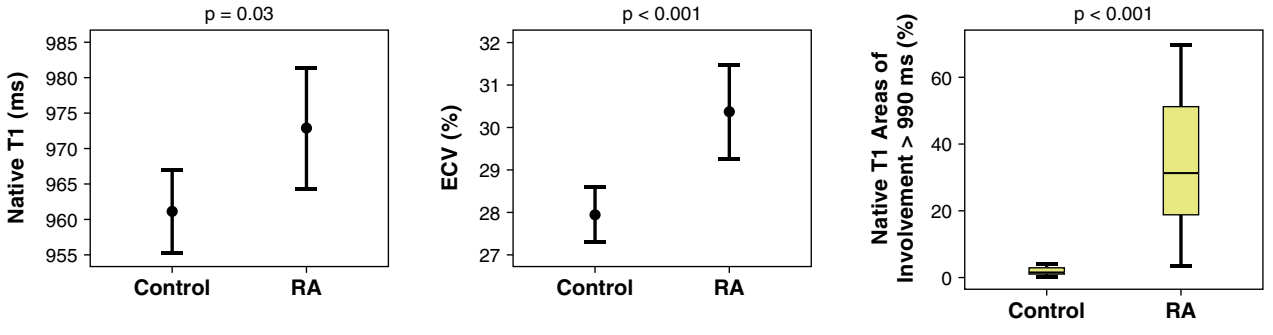
FOCAL MYOCARDIAL FIBROSIS (LGE IMAGING). As previously reported by others (7), we found an increased incidence of LGE in RA patients compared with control subjects (46% vs. 0%), as shown in Table 2. The majority of LGE was nonischemic in nature: 28% of RA patients had patchy mid-wall enhancement in the basal inferior and lateral walls (Figure 2); 13% had patchy or linear enhancement involving the septum; and 5% had evidence of previously unknown MI. In these 2 patients with previous MI, subsequent coronary angiography confirmed epicardial coronary artery disease. Quantitative analysis of LGE revealed that, overall, RA patients had a small volume of scarring (3.7 ± 0.4% of total LV mass).

MYOCARDIAL EDEMA (T2-WEIGHTED CMR). On conventional dark-blood T2-weighted imaging, there was no significant difference in the overall global myocardial T2 SI ratio between RA patients and control subjects (1.6 ± 0.2 vs. 1.5 ± 0.1; p = 0.7). However, patients with RA had significantly more areas of focal myocardial edema within the left ventricle (median 10% vs. 0% in control subjects; p < 0.001).

DIFFUSE MYOCARDIAL FIBROSIS (T1 MAPPING). Native T1 mapping and post-contrast T1 mapping were performed in all patients with RA. The 2 RA patients with MI were excluded from this analysis. RA patients had significantly higher native shortened modified Look-Locker inversion recovery T1 values (973 ± 27 ms vs. 961 ± 18 ms; p = 0.03) and expanded ECV (30.3 ± 3.4 vs. 27.9 ± 2.0; p < 0.001) (Figure 3). Patients with RA had significantly larger areas of myocardial involvement detected by using native T1 mapping (median 35% vs. 2% in control subjects; p < 0.001). When RA patients were stratified according to the presence of LGE, there was no significant difference in native T1 and ECV values (Table 3). However, patients with LGE had greater areas of myocardial involvement on volume fraction of T1 >990 ms (median 33% vs. 13%; p < 0.001). When grouped according to duration of RA diagnosis, there was no difference in native T1 values (966 ± 27 vs. 963 ± 36; p = 0.79) and ECV (29.8 ± 3.8 vs. 30.4 ± 4.0; p = 0.59) between RA patients with disease duration <2 years and those with disease duration >2 years, respectively. Finally, there were also no differences in native T1 and ECV when RA patients were separated according to rheumatoid factor positivity or the presence of anti-cyclic citrullinated peptide antibodies.

FUNCTIONAL AND CLINICAL CORRELATES OF DIFFUSE MYOCARDIAL FIBROSIS. Both native T1 (R = 0.54, p < 0.001) and ECV (R = 0.61, p < 0.001) were moderately correlated with disease activity. Native T1 and ECV also correlated with peak systolic strain (R = 0.46, p = 0.003; and R = 0.52, p = 0.001) and peak diastolic strain rate (R = -0.44, p < 0.001; and R = -0.49, p < 0.001), respectively (Figure 4). In addition, the DAS28-CRP score was associated with peak systolic strain (R = 0.41, p = 0.01) and peak diastolic strain rate (R = -0.37, p = 0.02) (Figure 5). Finally, areas of myocardial injury detected by using T1 mapping correlated with peak systolic strain (R_S = 0.62, p < 0.001), peak diastolic strain rate (R_S = -0.68, p < 0.001), and DAS28-CRP score (R_S = 0.44, p = 0.006), respectively.

FIGURE 3 Myocardial Involvement in RA Patients as Detected by T1 and ECV Quantification Compared With Control Subjects



Note that native T1-mapping using the quantitative threshold of T1 >990 ms **(third panel)** demonstrates a range (from mild to more severe forms) of myocardial involvement within the RA patient group. **Error bars** indicate 95% confidence intervals. Data refer to RA patients only and not to control subjects. In the **box and whisker plot**, the **horizontal bar** indicates the median; the **box** denotes the interquartile range, and the **whiskers** refer to the range of value measured. Abbreviations as in Figures 1 and 2.

TABLE 3 Measures of Subclinical Myocardial Involvement by T1 Mapping and ECV in RA Patients With and Without LGE

	RA Without LGE (N = 21)	RA With LGE (N = 18)	p Value
Volume fraction of LGE >2 SDs, %	0	4.2 (0.7)	–
Pre-contrast T1 (ms)	972 ± 31	974 ± 22	0.82
Volume fraction of T1 >990 ms, %	13 (3-8)	33 (8-53)	<0.001
Post-contrast T1, ms*	440 ± 33	462 ± 45	0.07
ECV, %	30.6 ± 4	30.1 ± 2.9	0.66
STIR T2 ratio	1.6 ± 0.1	1.5 ± 0.1	0.78
Volume fraction of edema (T2 STIR SI >1.9), %	5 (2-13)	8 (2-20)	0.06

Values are mean ± SD or median (interquartile range). *At 20 min after gadolinium administration.
Abbreviations as in Tables 1 and 2.

DISCUSSION

The principal finding of the current study is that CMR detects diffuse and focal myocardial fibrosis, as well as inflammation, in patients with RA. Second, in these RA patients with no known cardiovascular disease, indexes of diffuse myocardial fibrosis and inflammation were elevated regardless of the presence of LGE and correlate with the DAS28-CRP score, a measure of disease activity in RA as well as with systolic and diastolic strain. Third, diffuse myocardial fibrosis is unrelated to RA disease duration and is not associated with the presence of rheumatoid factor or anticyclic citrullinated peptide antibodies. Our results indicate that assessment of novel tissue characteristics with T1-mapping CMR can provide novel imaging biomarkers of disease activity, beyond those provided by standard techniques such as STIR T2-weighted and LGE imaging.

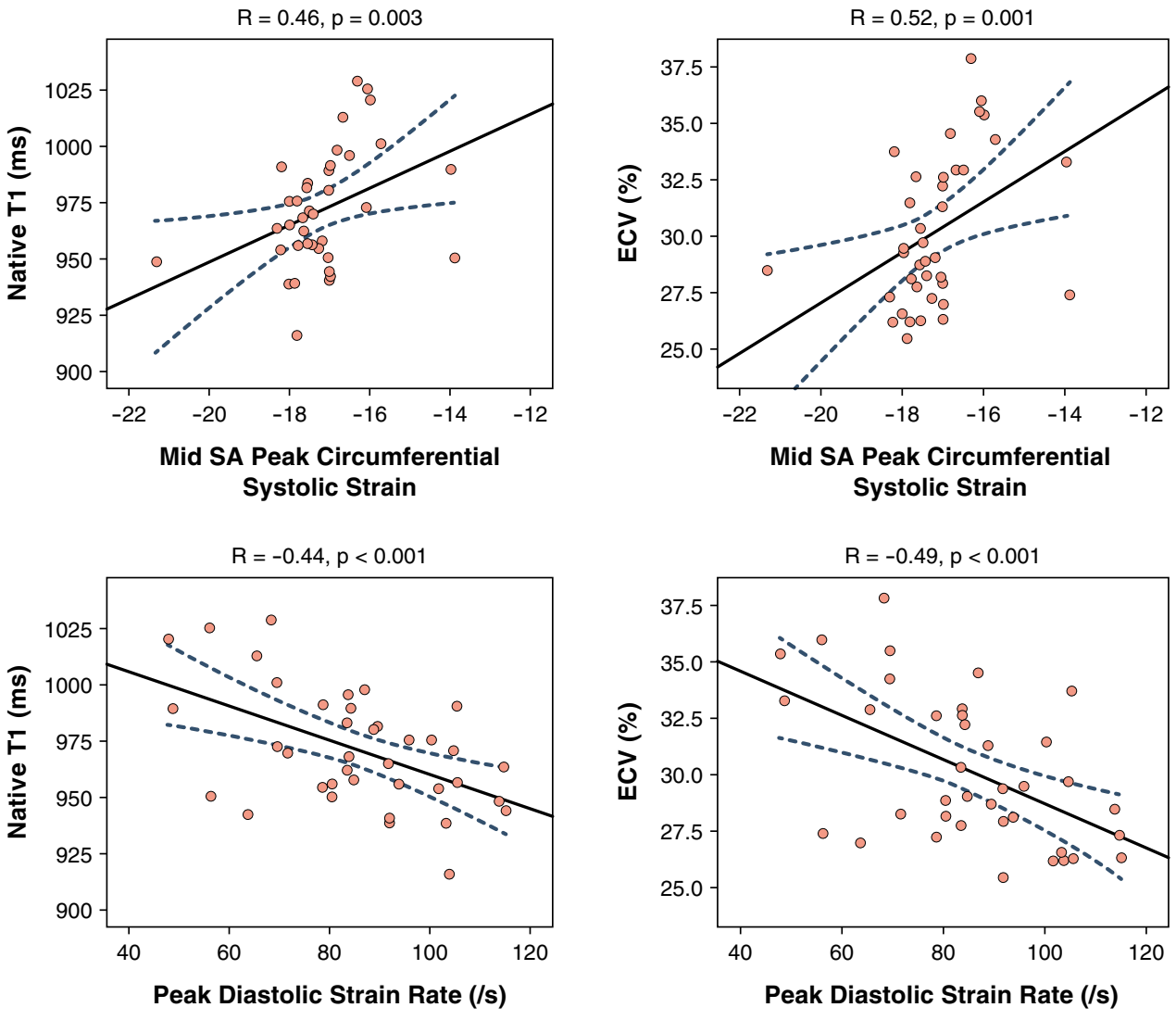
Myocardial fibrosis is due to deposition of extracellular matrix proteins, including collagen (17), and has been shown to be associated with adverse cardiovascular outcomes (18). Myocardial fibrosis in RA likely represents the final common expression of microvascular disease, macrovascular coronary artery disease, and chronic myocardial inflammation (myocarditis and cardiomyopathy) (6). The pathophysiology of LGE is premised on the combination of increased volume of distribution for gadolinium-based contrast agent and prolonged washout related to the decreased capillary density within the scarred myocardium (19). The increase in gadolinium concentration within fibrotic tissue results in T1 shortening, and the fibrotic myocardium appears as bright SI on inversion recovery images compared with the dark, nonfibrotic myocardium. We found that the prevalence of focal LGE in RA was 46%, with most patients having a nonischemic pattern of patchy midwall enhancement. Similarly, a previous study reported LGE in 7 (39%) of 18 RA patients with no symptomatic cardiac disease (7). We also documented 2 RA patients with previously undiagnosed MIs. Although the risk of coronary artery disease is higher in patients with RA (2,3), RA patients are less likely to report symptoms of angina and are more likely to experience silent MIs and sudden cardiac death (5).

LGE CMR is an accurate method for measuring focal myocardial fibrosis. However, its sensitivity is limited for the assessment of diffuse myocardial fibrosis, in which the difference in SI between normal and fibrotic myocardium may not be a discriminator. T1 mapping, before and after contrast, directly measures the underlying T1 relaxation times with high spatial resolution. T1 mapping also allows direct parametric signal quantification on a standardized scale for each myocardial voxel, and it provides better characterization of myocardial tissue composition on a global and regional level than conventional LGE (19). ECV is derived from the ratio of T1 change in the blood and myocardium, taking into account the hematocrit level. In the absence of MI, infiltration, or edema, increases in ECV quantitatively depict the extent of diffuse myocardial fibrosis (20). We found increased pre-contrast T1 values and expanded ECV in RA patients, indicating the presence of subclinical myocardial disease. Our group has previously published research on the use of volume fraction of T1 as a sensitive biomarker of myocardial involvement in patients with myocarditis and systemic sclerosis (11,15). Elevation in the volume fraction of native T1 above a threshold of 990 ms may indicate myocardial fibrosis or myocardial inflammation not detected by using standard techniques such as T2-weighted STIR or LGE.

Native T1 and ECV were correlated with abnormal systolic and diastolic strain parameters in these patients with RA. Myocardial fibrosis has been linked to abnormal indexes of myocardial strain (21). The pathophysiology and sequence of events occurring before the development of structural heart disease in RA remain unclear. Others have postulated that myocardial fibrosis detected by using CMR likely precedes the development of myocardial relaxation abnormalities (22). Our study adds to the growing body of evidence regarding the association between diffuse myocardial fibrosis and impaired myocardial strain (in the context of adverse structural remodeling in inflammatory heart disease).

We also found that native T1 and ECV correlated with disease activity in RA. Our data support the hypothesis that systemic inflammatory response is critical to development of cardiovascular complications. Early epidemiological observational and clinical studies are commensurate with this

FIGURE 4 Correlation Between Myocardial Involvement in RA as Detected by Using T1 Parameters and LV Systolic and Diastolic Strains

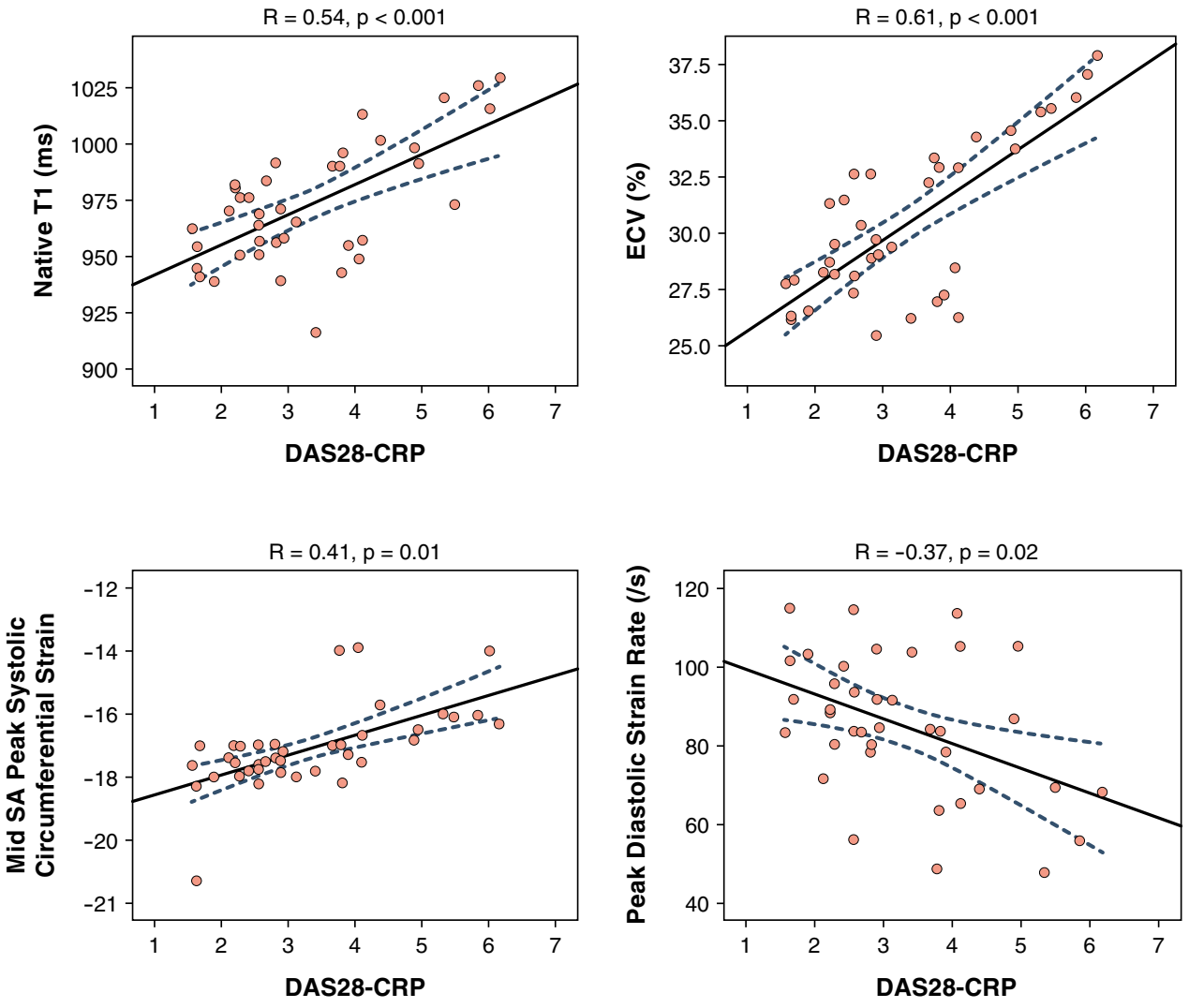


LV = left ventricular; SA = short axis; other abbreviation as in Figure 1.

proposition (23). Elevated DAS28-CRP scores in RA correlate with elevations in pro-inflammatory cytokines, including interleukin-1-alpha, interleukin-1-beta, interleukin-6, tumor necrosis factor-alpha, leptin, and vascular endothelial growth factor (24); these factors play a crucial role in mediating pathophysiologically important effector functions within the cardiovascular system, including up-regulation of vascular adhesion molecules, oxidization of low-density lipoprotein cholesterol, increased oxidative stress, endothelial and microvascular dysfunction, and promotion of atherothrombosis.

STUDY LIMITATIONS. In the current study, we concentrated on pre-contrast and post-contrast tissue characteristics in RA. Although native myocardial T1 values and ECV may be increased due to other causes (e.g., cardiac amyloidosis) (15,25), there was no evidence of myocardial infiltration, and none of the RA patients had an LGE pattern suggestive of MI (the 2 patients with MI were excluded from the analysis). Hence, we are confident that the increased native T1 and ECV reflect diffuse myocardial fibrosis and myocardial inflammation. Moreover, we have not validated T1 and ECV measurements against

FIGURE 5 Correlation Between RA Disease Activity and Myocardial Involvement Detected by Using T1 Parameters and LV Systolic and Diastolic Strains



DAS28-CRP = rheumatoid arthritis disease activity score with 28 tender and swollen joint count, incorporating C-reactive protein; other abbreviations as in Figures 1, 2, and 4.

histological assessments; endomyocardial biopsy was not possible in these asymptomatic patients. Although T1 mapping can detect both myocardial edema and fibrosis, the technique is not sufficiently evolved to be able to distinguish the underlying mechanism behind increased extracellular water. Myocardial biopsy is the only certain way to distinguish these 2 pathological features of the myocardium. However, previous publications have shown good correlation between CMR indexes of diffuse myocardial fibrosis and histological fibrosis in other clinical contexts (12,26). Another limitation of this study was the lack of serum biomarkers of myocardial injury, including troponins, CRP, and B-natriuretic peptides. Finally, we report LA diameter, which is less accurate compared with LA volume as a measure of LA size. However, measuring LA volume accurately with CMR would require a complete stack of SA cines through the atria; this was not part of our scanning protocol, which was already long in duration.

We have shown that RA is associated with subclinical myocardial fibrosis. It remains unclear how much of these observations reflect RA disease activity and progression versus the effect of drugs such as methotrexate, which reportedly causes hepatic and pulmonary fibrosis (27,28). Indeed, methotrexate was

associated with mild liver fibrosis in 1% to 52% of patients with RA (27). Some studies have shown that although most methotrexate-induced hepatic enzyme dysfunction is reversible, many patients who develop hepatic fibrosis also have other risk factors for fibrosis, including obesity, excessive alcohol intake, diabetes mellitus, advanced age, and drug-related factors such as high total methotrexate dose and long duration of therapy (29). In humans, methotrexate has not been shown to cause myocardial fibrosis. In an animal model of autoimmune myocarditis, methotrexate was shown to be anti-inflammatory, antifibrotic, and to be associated with significant improvement in ejection fraction (30). These data would support the observed changes being due to the disease rather than to the use of methotrexate.

CONCLUSIONS

Our results demonstrate the potential of CMR to depict diffuse and focal myocardial fibrosis and inflammation in RA patients with apparently normal hearts, in whom indexes of diffuse myocardial fibrosis and inflammation are elevated regardless of the presence of LGE and correlate with disease activity and impaired systolic and diastolic strain indexes. Novel CMR T1-mapping tissue characterization provides added value as promising imaging biomarkers for disease monitoring and the study of therapies aimed at reducing diffuse myocardial fibrosis in RA. Finally, in the future, CMR including T1 mapping may potentially be useful in RA patients at different stages of the disease to assess the extent of myocardial involvement and to delineate myocardial disease progression.

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PERSPECTIVES

CLINICAL COMPETENCY: Subclinical cardiovascular disease is frequent in RA, including focal and diffuse myocardial fibrosis and inflammation, which are associated with impaired strain and RA disease activity. Novel CMR T1-mapping tissue characterization provides added value as a promising imaging biomarker for disease monitoring and the study of therapies aimed at reducing diffuse myocardial fibrosis in RA.

TRANSLATIONAL OUTLOOK: Future studies are warranted to elucidate the relationship between myocardial fibrosis and inflammation with myocardial strain. Studies are also needed to clarify to what extent the earlier observations are due to RA disease activity and progression versus the effect of RA therapies.

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APPENDIX For an expanded description of the imaging parameters for the sequences used, please see the online version of this article.