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Absence of Fibrosis and Inflammation by Cardiac Magnetic Resonance Imaging in Rheumatoid Arthritis Patients with Low to Moderate Disease Activity

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Abstract

Objective—The prevalence of heart failure is increased 2-fold in patients with rheumatoid arthritis (RA); this is not explained by ischemic heart disease or other risk factors for heart failure. We hypothesized that in patients with RA without known heart disease, cardiac magnetic resonance imaging (CMR) would detect altered cardiac structure, function, and fibrosis.

Methods—We performed 1.5-T CMR in 59 patients with RA and 56 controls frequency-matched for age, race, and sex and compared CMR indices of structure, function, and fibrosis (late gadolinium enhancement (LGE), native T1 mapping, and extracellular volume fraction (ECV)) using Mann-Whitney U tests and linear regression adjusting for age, race, and sex.

Results—Most patients with RA had low-to-moderate disease activity (DAS28-CRP median [interquartile range] 3.16 [2.03, 4.05]), and 49% were receiving anti-tumor necrosis factor alpha agents. Left ventricular (LV) mass, LV end diastolic and systolic volumes indexed to body surface area, and LV ejection fraction and left atrial size were not altered in RA compared to controls (all P>0.05). Measures of fibrosis were not increased in RA: LGE was present in 2 patients with RA and 1 control subject; native T1 mapping was similar comparing RA and control subjects (P=0.55) and ECV (median [IQR]) was lower (26.6% [24.7, 28.5%]) in patients with RA compared to control subjects (27.5% [25.4, 30.4%], P=0.03).

Conclusion—CMR measures of cardiac structure and function were not significantly altered, and measures of fibrosis were similar or lower in RA patients with low to moderate disease activity compared to a matched control group.

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with premature mortality caused largely by cardiovascular disease[1,2]. Initial research efforts focused on the

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increased risk of ischemic heart disease in RA[3–5]; however, heart failure is a major understudied problem that accounts for a substantial portion of the increased cardiovascular mortality[6]. Prevalence of heart failure is increased in RA with a relative risk of 1.6 to 2.0[1,7,8], and the outcomes are worse[9].

The pathogenesis of heart failure in RA is not known. Although the prevalence of some heart failure risk factors (e.g., ischemic heart disease)[10] is increased in RA, increased risk of heart failure is independent of conventional risk factors[7,11]. Thus, factors more specific to RA, such as inflammation, have been implicated[11]. In keeping with this idea, indicators of RA severity and disease activity are associated with increased risk of heart failure[2,7,12].

Concentrations of amino-terminal prohormone brain-type natriuretic peptide (NT-proBNP), a sensitive marker of myocardial stretch for which even minimally increased concentrations are associated with future risk of heart failure and cardiovascular events[13,14], were significantly higher in RA compared with controls[15,16]. Moreover, NT-proBNP concentrations were associated with RA disease activity, tumor necrosis factor alpha (TNF), interleukin-6 and C-reactive protein (CRP) concentrations, but not coronary atherosclerosis[15]. Furthermore, concentrations of troponin I (Tn-I), a marker of myocardial necrosis, measured by an high sensitivity assay, were also significantly higher in patients with RA than control subjects[16, 17].

The findings of increased concentrations of markers of myocardial stress and damage in cross-sectional studies of patients with RA suggest the possibility of ongoing subtle subclinical structural and functional myocardial dysfunction. Echocardiographic findings in RA have generally shown preserved systolic function, but an increased prevalence of diastolic dysfunction[1,18]. Cardiac magnetic resonance (CMR) imaging, however, provides additional information about myocardial structure, as well as fibrosis and inflammation. An early CMR study suggested smaller left ventricular size in RA[19] and several other small studies suggested that some patients with RA have focal scarring detected by late gadolinium enhancement (LGE) and diffuse fibrosis detected by T1 mapping and increased extracellular volume (ECV)[20–24]. However, these studies have been small and have included few patients on biologic therapy.

We hypothesized that patients with RA have altered cardiac structure and function and increased myocardial fibrosis detectable by CMR and that this is related to underlying inflammation.

PATIENTS AND METHODS

Study population

We performed a cross-sectional study of 59 patients with RA and 56 controls, frequency-matched for age (within 2 years), race, and sex. Inclusion criteria included ability to provide informed consent, age 18 years or older, meeting ACR classification criteria for RA[25] (RA subjects), and no inflammatory disease (control subjects). Exclusion criteria included previous or current heart failure or ischemic cardiovascular disease (e.g., stroke, myocardial infarction, angina, prior coronary artery bypass grafting or percutaneous coronary

intervention), atrial fibrillation, known structural or functional cardiac abnormality including pulmonary hypertension, an estimated glomerular filtration rate < 60 ml/min, pregnancy or breast feeding, inability to undergo CMR imaging, and hypersensitivity to gadolinium. Participants were recruited from the Vanderbilt Clinic Rheumatology practice, responses to advertisements, and word of mouth. The study was approved by the Vanderbilt Institutional Review Board (IRB#120314) and registered with ClinicalTrials.gov (#NCT01589770). All subjects gave written informed consent.

Clinical and laboratory data

Clinical details and a cumulative medication history with particular attention to RA therapies and cardiovascular drugs were obtained from participants and the electronic medical record, as we have previously done[4]. Tender and swollen joint counts were measured in patients with RA. Fasting venous blood was drawn and ESR and high sensitivity CRP measured in the hospital clinical laboratory. RA disease activity was measured by DAS28 score[26].

Cardiac magnetic resonance imaging (CMR)

Study participants underwent CMR using a 1.5 T Siemens Magnetom Avanto scanner (Siemens Healthcare Sector, Erlangen, Germany). Subjects were scanned using a phased array torso receiver coil, and imaging protocols included cine imaging for ventricular structure and function, native (without contrast) and post contrast modified Look-Locker (MOLLI) imaging for T1 mapping, and LGE imaging for myocardial fibrosis and inflammation. Cine imaging was performed using steady-state free-precession sequences aligned to the horizontal and vertical long axis of the heart. Typical acquisition parameters for cine images were: field of view 300×340 mm, matrix 156×192, slice thickness 8 mm, flip angle 80 degrees, and echo time (TE) 1.1 ms, and usually 30 phases per cardiac cycle to maintain repetition time (TR) below 50 ms. Parallel imaging was employed using the generalized autocalibrating partially parallel acquisition (GRAPPA) technique with an acceleration factor of 2. For T1 mapping MOLLI images were obtained in three left ventricular (LV) short axis (base, mid, and apical) planes before contrast injection and 12 and 25 minutes after contrast injection. Gadolinium (0.15 mmol/kg body weight gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, IN)) was injected intravenously through an antecubital vein. The timing of the contrast injection and MOLLI sequences were chosen to be comparable with the Multi-Ethnic Study of Atherosclerosis (MESA) study[27].

Phase velocity encoded flow imaging was performed through-plane in the ascending aorta and the main pulmonary arteries as a second measure of LV and right ventricular (RV) output and quantification of any valvular regurgitation. Twelve minutes after gadolinium injection, short and long axis myocardial LGE imaging was performed using both single-shot inversion recovery (IR) and phase sensitive inversion recovery (PSIR) true fast imaging with steady-state precession imaging. The third set of MOLLI images were obtained at 25 minutes post contrast, as detailed above.

CMR analyses of structure, function were performed by individuals specialized in CMR (WB and JHS) blinded to disease status. CMR LV and RV measurements were calculated

from manually traced endocardial and epicardial end-diastolic and end-systolic contours from a stack of contiguous short-axis images from the apex to the base of the LV. Left and right atrial dimensions were obtained by caliper measurements of the major axis of the atria, and calculated on a Leonardo workstation using Argus software, V.B17 (Siemens, Erlangen, Germany). Measures of focal and diffuse fibrosis/inflammation including the presence or absence of LGE, myocardial T1 mapping and ECV calculations were determined using a commercial software (CVI42 version 5.3, Circle cardiovascular imaging, Calgary, Canada) and by a third blinded specialist in CMR (DAB, with the assistance of NKB and CL), who has led efforts to standardize image acquisition and developed techniques to minimize inter and intra-observer variation for many large CMR studies[27–30]. Additionally, LGE was assessed by WB, with consensus of all reads. ECV was calculated as ECV = (1-hematocrit)× $(1/T1_{\text{myocardium post contrast}}) - (1/T1_{\text{myocardium pre contrast}})/(1/T1_{\text{blood post contrast}}) - (1/T1_{\text{blood pre contrast}})$[31].

Statistics

The study was powered to detect differences in LV mass index and post-contrast T1 mapping comparing RA to control subjects based on previous data from published studies. Based on previously reported mean ± standard deviation (SD) of 67.6 ± 12.6 g/m^2 for LV mass index[32] and 564 ± 103 msec for post-contrast T1 mapping[33], at least 55 subjects in each group would provide approximately 80% power to detect a difference of at least 10% in both parameters with a two-sided significance of 5%.

CMR indices of structure, function, and fibrosis (LGE, T1 values, and ECV) were compared between RA and control subjects using Mann-Whitney U tests and linear regression adjusting for age, race, and sex. Skewed variables were log-transformed to normalize residuals. Spearman correlation was used to assess relationship between CMR indices and RA-specific variables.

RESULTS

Subject characteristics

Patients with RA (median age 53 years) and control subjects (median age 52 years) were of similar age, race (98% Caucasian in both), and sex (76% and 79% female in RA and controls, respectively) (Table 1). Patients with RA had low-to-moderate disease activity (DAS28-CRP (median and interquartile range (IQR) 3.16 units [2.03, 4.05 units], and established disease (disease duration 10 years [5, 15 years], range <1 month to 47 years). Approximately 63% of patients with RA were taking methotrexate and 49% were taking an anti-TNF agent (Table 1).

Myocardial structure and function

Left ventricular mass indexed to body surface area (BSA) was similar in patients with RA (43.8 g/m^2 [40.0, 49.5 g/m^2]) and control subjects (42.2 g/m^2 [36.4, 48.5 g/m^2]), P=0.19 (Table 2). Right atrial major axis dimension was significantly smaller in RA (30 mm [25, 34 mm]) compared to control subjects (34 mm [30, 38 mm]), P=0.001. Heart rate was significantly higher in RA (72 beats per minute (bpm) [66, 79 bpm]) compared to control

subjects (68 bpm [59, 73 bpm], P=0.01) (Table 2). Left ventricular ejection fraction, end diastolic volume and end systolic volume indexed to BSA did not differ significantly in RA and control subjects (Table 2). Patients with RA had lower right ventricular (RV) end diastolic volume indexed to BSA (58.3 ml/m^2 [50.7, 69.5 ml/m^2]) compared to control subjects (63.3 ml/m^2 [59.1, 72.3 ml/m^2], P=0.004) (Table 2). Similarly, patients with RA had lower RV end systolic volume indexed to BSA compared to control subjects (20.4 ml/m^2 [15.7, 27.9 ml/m^2] vs 26.6 ml/m2 [20.8, 33.6 ml/m^2], P=0.002) (Table 2).

Myocardial fibrosis or inflammation

Assessing focal fibrosis or inflammation, two patients with RA (3%) and one control subject (2%) had LGE (Table 2). Among RA, one had subepicardial patchy LGE and the other had inferior RV insertion patchy LGE. The control subject had a subendocardial scar.

Assessing diffuse fibrosis or inflammation of the heart, native T1 mapping (P=0.45) and post contrast T1 values (25-minute) (P=0.37) were not significantly different in patients with RA and control subjects (Table 2). ECV was significantly lower in patients with RA (26.6% [24.7, 28.5%]) compared to control subjects (27.5% [25.4, 30.4%]), P=0.03, contrary to our hypothesis.

Native T1 value was weakly correlated with tender joint count (Rho=0.29, P=0.03), but not swollen joint count, CRP, patient reported global health or overall DAS28-CRP score (all P>0.05). ECV was not correlated with tender or swollen joint counts, CRP, global health or DAS28-CRP score (all P>0.05). There was a trend for an inverse association between age and native T1 time in patients with RA (Rho=−0.25, P=0.06); the opposite of what was observed in control subjects (Rho=0.20, P=0.15). Native T1 time did not correlate with duration of RA (Rho=−0.05, P=0.74). Patients taking anti-TNF agents had lower native myocardial T1 and ECV than non-users but differences were not significant (Table 3).

DISCUSSION

This study represents one of the largest CMR studies in RA and matched controls to date. Our findings were unexpected. Based on previous reports, we hypothesized there would be structural abnormalities and increased fibrosis or inflammation detected on CMR by LGE (representing focal fibrosis or inflammation) or by increased ECV and native T1 time (representing diffuse fibrosis or inflammation) in RA. However, we found little LGE and no evidence of increased diffuse fibrosis or inflammation in patients with RA.

LGE CMR can be used to assess myocardial tissue for scarring and fibrosis and inflammation[34] because the residence time for gadolinium in expanded interstitial space is prolonged compared to the intravascular space. LGE CMR is helpful for identifying focal fibrosis, rather than diffuse fibrosis in which the myocardium may be uniformly abnormal with a lack of normal myocardial segments for comparison[35]. LGE CMR can also detect inflammation of the heart, as in myocarditis, where it is present in active disease and resolves over time[34], which is of interest in RA, where some have observed high rates of myopericarditis among patients with cardiac symptoms[36]. Myocardial T1 before (native) and after gadolinium has emerged as a technique to measure diffuse fibrosis[33]. ECV

adjusted for hematocrit is thought to more accurately represent the ratio of interstitial space to total myocardial volume independent of field strength and gadolinium dose and clearance. ECV is increased in infiltrative states such as cardiac amyloid and with both interstitial fibrosis and replacement fibrosis[37]. ECV correlates with the collagen volume measured histologically[37] and increases with age in healthy individuals, a trend in controls but not in RA. The significance of the small reduction in ECV observed in RA patients is not known; although different from controls, the ECV of RA patients was within normal limits[32] and thus could reflect chance. Alternatively, lower ECV in RA could also represent loss of cardiac collagen, dense myocardial space or perhaps failure of typical repair mechanisms, or other uncharacterized alterations in the myocardium.

As also reported by others, heart rate was higher in patients with RA than controls, a finding which may be due to deconditioning[38]. We also observed a non-significant decrease in LV end diastolic and end systolic volumes and significantly decreased RV end diastolic and end systolic volumes. Faster heart rates may be compensating for smaller hearts in RA to maintain cardiac output, which was preserved in RA.

The absence of major cardiac structural and functional alterations in RA and no increase in LGE or ECV suggests that the myocardium is not markedly abnormal in the setting of low-to-moderate disease activity. If the availability of more effective therapies and tighter control of disease activity prevents myocardial fibrosis or treats myocardial inflammation in RA, the effects of such therapy on the incidence of heart failure will be of great significance. This is consistent with recent work in atherosclerosis demonstrating that patients with RA (N=139) with remission or low disease activity for at least 75% of the time over a three year period of follow up had no acceleration of carotid intima-media thickness compared to matched control subjects (n=139)[39].

TNF may be particularly important in heart failure. In animal models of heart failure circulating TNF levels were elevated, and blocking TNF was beneficial[40–42]. However, although humans with heart failure have high circulating TNF levels[43], anti-TNF therapy had no benefit or even increased mortality[44, 45]. Conversely, in some[8, 46–49] but not all[50] large RA observational studies anti-TNF therapy was associated with improved CV outcomes including decreased heart failure. This suggests that although anti-TNF agents can worsen existing heart failure, they might decrease risk of heart failure in RA. Studies with other biologic agents will be of interest.

Differences between the findings of the current study, suggesting that the myocardium is not markedly abnormal in patients with low to moderate disease activity, many of whom were receiving an anti-TNF or another biologic agent, and the findings of other CMR studies are informative (Table 4). CMR performed in patients with RA and matched controls (N=39 each)[20] found LGE in 46% of RA patients and in no controls; ECV and native T1 time were also higher in RA suggesting an increase in both focal and diffuse fibrosis. Patients were similar to those in the current study with regard to age, prevalence of rheumatoid factor, and DAS28 scores. However, median CRP concentrations were significantly higher in RA (9 mg/L) compared to controls (1 mg/L), whereas in the current study CRP was similar in RA and controls (1.7 mg/L in both). Moreover, no anti-TNF use was reported, whereas 49% of

RA patients in the current study were taking an anti-TNF agent. Thus, differences in findings between the two studies may be related to earlier and more aggressive therapy of RA. We examined this idea by stratifying CMR measures based on any biologic use and anti-TNF use; patients using anti-TNF agents had lower native T1 and ECV, but these differences were not significant.

Holmstrom et al performed CMR in 60 patients with RA (N=31 newly diagnosed RA and N=29 established RA about to start biologic therapy), 11 healthy controls, and 10 patients with fibromyalgia [21]. Patients had a median of 8 and 6 swollen joints in the early and chronic RA groups, respectively; this compares to a median of 1 swollen joint in the current study. LGE was present in 55% of patients with RA (68% in newly diagnosed RA and 41% in established RA). LGE was not measured in the healthy controls and was absent in fibromyalgia. In RA, LGE was associated with higher DAS28-CRP. More patients with early RA (duration 0.4 years) than established RA (duration 13 years) had LGE suggesting that it may not be due to fibrosis, which accumulates over time, but more likely represents inflammation or edema of the myocardium.

In an early study 7 of 18 RA patients (39%) had LGE[22]. Compared to the current study, patients were slightly older and had shorter disease duration, higher DAS28-CRP scores and higher ESR and CRP. Those with LGE had higher CRP, ESR, and DAS28-CRP scores. Of the 7 patients with LGE, one was taking an anti-TNF agent, whereas 6 of 11 patients without LGE were taking an anti-TNF. In another early study LGE was higher in RA patients (n=24, all with DAS28>7 and none on anti-TNF drugs) compared to healthy controls and patients with myocarditis[23]. Recently, another study show that 19 of 60 (32%) RA patients had LGE[24]. These patients had similar demographics compared to the earlier study, with slightly older patients with shorter disease duration and disease activity compared to the current study. The authors found that those with LGE had higher disease activity (median DAS28 score= 5.1) compared to those without (median DAS28 score= 3.5). Comparing the current study and its findings with previous work suggests key differences in patient populations (low RA disease activity, low concentration of CRP, low swollen joint count, and high prevalence of biologic therapy use) contributed to the low prevalence of LGE. Population differences in rate of focal fibrosis (LGE) by CMR may also be important, since the rate is more than 2-fold lower in the United States[29] than Iceland[51] and Sweden[52], probably due to underlying risk factors in the population. Reports of LGE being particularly prominent in early RA suggest that inflammation may be more important than permanent fibrosis. Thus, RA patients may have cardiac inflammation and LGE in the setting of high disease activity, and this could resolve with aggressive treatment. Further studies will be necessary to test this hypothesis.

This study did have limitations. The cross-sectional nature of the study precludes us from knowing if aggressive treatment and control of disease explains the differences between the current study and some previous studies. Moreover, given that we studies primarily RA patients with low to moderate disease activity, we cannot extrapolate the findings of this study to patients with uncontrolled RA. Similarly, small numbers precluded us from evaluation if anti-TNF use in the presence of persistently active disease was associated with abnormal CMR findings.

CONCLUSION

CMR measures of cardiac structure and function and fibrosis were not significantly altered in RA patients with low to moderate disease activity compared to a matched control group.

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Table 1

Patient demographics

	RA (N= 59)	Control (N=56)	P
General demographics			
Age, years	53 [40, 59]	52 [38, 57]	0.73
Race, # (%) Caucasian	58 (98)	55 (98)	0.97
Sex, # (%) female	45 (76)	44 (79)	0.77
Smoker (current), # (%)	10 (17)	4 (7)	0.11
Alcohol use, drinks/week	0 [0, 2]	2 [1, 5]	<0.001
Diabetes Mellitus II, # (%)	3 (5.1)	0 (0)	0.09
Hypertension, # (%)	16 (27)	9 (16)	0.15
Systolic BP, mmHg	130 [119, 144]	123 [116, 134]	0.06
Diastolic BP, mmHg	75 [67, 83]	76 [68, 83]	0.90
BMI, kg/m^2	27.5 [23.5, 33.9]	26.5 [23.5, 30.5]	0.33
RA related			
RF positive, # (%)	40 (75)	-	-
Anti-CCP positive, # (%)	20 (77)	-	-
Erosions, # (%)	17(29)	-	-
Disease duration, years	10 [5, 15]	-	-
Tender joints, # (%)	3 [0, 10]	-	-
Swollen joints, # (%)	1 [0, 4]	-	-
Global health VAS, mm	25 [10, 50]	-	-
ESR, mm	12 [5, 22]	7 [3, 12]	0.004
CRP, mg/L	1.7 [0.7, 6.7]	1.7 [0.5, 3.1]	0.16
DAS28-CRP, units	3.16 [2.03, 4.05]	-	-
Hematocrit, %	40 [37, 42]	41 [39, 42]	0.22
Medications			
NSAID (current), # (%)	44 (75)	33 (59)	0.08
Aspirin (current), # (%)	9 (15)	10 (18)	0.71
Statin (current), # (%)	10 (17)	10 (18)	0.90
Beta Blocker (current), # (%)	5 (9)	1 (2)	0.11
Ca Channel Blocker (current), # (%)	6 (10)	2 (4)	0.16
ACE-I (current), # (%)	7 (12)	7 (13)	0.92
ARB (current), # (%)	6 (10)	2 (4)	0.16
Corticosteroids (current), # (%)	20 (34)	2 (4)	<0.001
Methotrexate (current), # (%)	37 (63)	-	-
Hydroxychloroquine (current), # (%)	9 (15)	-	-
Anti-TNF (current), # (%)	29 (49)	-	-
Rituximab (current), # (%)	2 (3)	-	-
Abatacept (current), # (%)	2 (3)	-	-

	RA (N= 59)	Control (N=56)	P
Tofacitinib (current), # (%)	1 (2)	-	-

Data are expressed as median [interquartile range] or number (#) and percent (%). BP= blood pressure, BMI= body mass index, RF= rheumatoid factor, CCP= anti-cyclic citrullinated peptide antibody, VAS= visual analog scale, ESR= erythrocyte sedimentation rate, CRP= C-reactive protein, DAS28-CRP= disease activity score based on 28 joint count and CRP, NSAID= non-steroidal anti-inflammatory drug, Ca= calcium, ACE-I= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, TNF= tumor necrosis factor alpha. RF available in 53 patients, CCP in 26 patients, and X-rays in 40 patients. Current use of NSAID is use within the past week.

Table 2

CMR findings in RA and control subjects

	RA (N=59)	Control (N=56)	P	Adjusted P
Heart rate, bpm	72 [66, 79]	68 [59, 73]	0.01	0.02
LV mass indexed to BSA, g/m^2	43.8 [40.0, 49.5]	42.2 [36.4, 48.5]	0.19	0.21
LVEF, %	67.9 [62.4, 74.4]	66.7 [60.1, 70.3]	0.09	0.07
LVEDV indexed to BSA, ml/m^2	59.3 [46.9, 66.9]	61.1 [55.0, 66.3]	0.23	0.13
LVESV indexed to BSA, ml/m^2	18.0 [11.7, 24.5]	20.9 [16.0, 26.3]	0.06	0.05
LV ci, l/min/m^2	2.79 [2.43, 3.15]	2.62 [2.19, 3.00]	0.14	0.13
LA size, mm	29 [24, 32]	29 [26, 32]	0.40	0.19
RVEF, %	62.0 [56.9, 67.2]	59.5 [54.3, 63.5]	0.03	0.001
RVEDV indexed to BSA, ml/m^2	58.3 [50.7, 69.5]	63.3 [59.1, 72.3]	0.004	0.004
RVESV indexed to BSA, ml/m^2	20.4 [15.7, 27.9]	26.6 [20.8, 33.6]	0.002	0.001
RA size, mm	30 [25, 34]	34 [30, 38]	0.001	0.001
Interventricular septum, mm	7 [6, 8]	7 [6, 8]	0.08	0.15
Presence of LGE, # (%)	2 (3)	1 (2)	-	-
Native myocardial T1, msec	973 [928, 995]	973 [945, 1001]	0.45	0.60
Post-contrast T1, msec	453 [427, 476]	457 [424, 486]	0.37	0.13
ECV, %	26.6 [24.7, 28.5]	27.5 [25.4, 30.4]	0.03	0.04

Adjusted for age, race and sex. BPM= beats per minute, LV= left ventricular, BSA= body surface area, EF= ejection fraction, EDV= end diastolic volume, ESV= end systolic volume, ci= cardiac index, LA= left atrium, RV= right ventricle, RA=right atrium, LGE= late gadolinium enhancement, ECV=extracellular volume.

Table 3

CMR findings in RA patients based on anti-TNF use

	Anti-TNF users (N=29)	Anti-TNF non-users (N=30)	P	Adjusted P
Heart rate, bpm	71 [66, 76]	73 [65, 79]	0.83	0.94
LV mass indexed to BSA, g/m^2	42.9 [39.3, 49.5]	44.5 [41.6, 50.0]	0.09	0.33
LVEF, %	69.2 [64.0, 75.9]	67.1 [62.3, 74.7]	0.52	0.70
LVEDV indexed to BSA, ml/m^2	59.3 [52.5, 64.5]	58.9 [44.4, 69.7]	0.85	0.53
LVESV indexed to BSA, ml/m^2	17.7 [12.8, 23.7]	19.2 [10.8, 24.7]	0.78	0.93
LV ci, l/min/m2	2.84 [2.66, 3.17]	2.65 [2.20, 3.03]	0.35	0.14
LA size, mm	29 [25, 33]	29 [24, 31]	0.08	0.15
RVEF, %	62.1 [57.5, 68.2]	61.4 [56.4, 66.2]	0.35	0.33
RVEDV indexed to BSA, ml/m^2	58.9 [52.2, 68.7]	56.6 [46.3, 72.6]	0.74	0.89
RVESV indexed to BSA, ml/m^2	20.4 [15.8, 27.4]	20.5 [15.7, 31.4]	0.78	0.61
RA size, mm	30 [27, 35]	29 [24, 35]	0.31	0.21
Presence of LGE, # (%)	1 (3.4)	1 (3.3)	-	-
Native myocardial T1, msec	946 [919, 995]	979 [948, 996]	0.19	0.10
Post-contrast T1, msec	447 [425, 469]	459 [436, 479]	0.24	0.83
ECV, %	25.6 [24.3, 28.4]	27.1 [25.0, 28.6]	0.21	0.13

Adjusted for age, race and sex. BPM= beats per minute, LV= left ventricular, BSA= body surface area, EF= ejection fraction, EDV= end diastolic volume, ESV= end systolic volume, ci= cardiac index, LA= left atrium, RV= right ventricle, RA=right atrium, LGE= late gadolinium enhancement, ECV=extracellular volume.

Table 4

Comparison between current study and prior CMR studies

Study	Sample size		DAS	SJC	CRP, mg/l		Disease	α-TNF, %	Biologic, %	LGE, % or units		Native T1	Location
	RA	Control			RA	Control	Duration			RA	Control		
Current	59	56	3.16	1	1.7	1.7	10	49%	58%	2%	1	No diff	USA
Ntusi[20]	39	39	3.3	-	9	1	7	0%	5%	46%	0	↑RA	UK
Holmstrom[21]*	31, 29	21	3.9, 3.7	8, 6	-	-	0.4, 13	0%	0%	55%	0	↑RA	Finland
Kobayashi[22]	18	-	3.96	-	2.6	-	2.7	39%	39%	39%	-	-	Japan
Puntmann[23]	24	34	>7.0	-	48.3	4.7	>10	0%	0%	10.5%**	2.3%**	-	UK, Germany
Kobayashi[24]	60	-	3.8	3	7.4		1.75	11%	40%	32%	-	-	Japan

*Data are presented for 31 new RA, 29 established RA starting biologic.

**LGE assessed globally.

DAS = disease activity score. SJC = swollen joint count. CRP= C-reactive protein. Disease duration presented in median or mean years. TNF= tumor necrosis factor. LGE = late gadolinium enhancement. USA = United States of America. UK = United Kingdom.