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

William Bradham, Michelle J. Ormseth, Comfort Elumogo, Srikanth Palanisamy, Chia-Ying Liu, Mark A. Lawson, Jonathan H. Soslow, Nadine Kawel-Boehm, David A. Bluemke, and C. Michael Stein

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 (cMRI) would detect altered cardiac structure, function, and fibrosis.

Methods. We performed 1.5-T cMRI in 59 patients with RA and 56 controls frequency-matched for age, race, and sex, and compared cMRI indices of structure, function, and fibrosis [late gadolinium enhancement (LGE), native T1 mapping, and extracellular volume (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 [28-joint count Disease Activity Score–C-reactive protein median 3.16, interquartile range (IQR) 2.03–4.05], and 49% were receiving anti-tumor necrosis factor 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, 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. cMRI 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. (J Rheumatol First Release April 15 2018; doi:10.3899/jrheum.170770)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
HEART FAILURE
HEART DISEASE
MAGNETIC RESONANCE IMAGING

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with premature mortality caused largely by cardiovascular (CV) disease[1,2]. Initial research efforts focused on the increased risk of ischemic heart disease in RA[3,4,5]; however, heart failure is a major understudied problem that accounts for a substantial portion of the increased CV 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 inflam-

From the Vanderbilt University Medical Center; Veterans Health Administration Tennessee Valley Healthcare System, Nashville, Tennessee; Radiology and Imaging Sciences, National Institutes of Health, Bethesda, Maryland, USA.

This study was funded by the Arthritis Foundation Innovative Research Grant (Stein), Veterans Administration CDA IK2CX001269 (Ormseth), US National Institutes of Health (NIH) Grants: US National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) K23 AR068443 (Ormseth), NIAMS P60 056116 (Stein), US National Heart, Lung and Blood Institute K23 HL123938 (Soslow), and Clinical and Translational Science Awards UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS) and the NIH Intramural Research Program. The contents of this article are solely the responsibility of the authors and do not necessarily represent official views of the NCATS or the NIH.

W. Bradham, MD, PhD, Vanderbilt University Medical Center; M.J. Ormseth, MD, MSCI, Vanderbilt University Medical Center, and Veterans Health Administration Tennessee Valley Healthcare System; C. Elumogo, BS, Radiology and Imaging Sciences, NIH; S. Palanisamy, BS, Radiology and Imaging Sciences, NIH; C.Y. Liu, PhD, Radiology and Imaging Sciences, NIH; M.A. Lawson, MD, Vanderbilt University Medical Center; J.H. Soslow, MD, MSCI, Vanderbilt University Medical Center; N. Kawel-Boehm, MD, Radiology and Imaging Sciences, NIH; D.A. Bluemke, MD, PhD, Radiology and Imaging Sciences, NIH; C.M. Stein, MBChB, Vanderbilt University Medical Center. W. Bradham and M.J. Ormseth contributed equally to this work.

Address correspondence to Dr. M.J. Ormseth, 1161 21st Ave. South, T-3113 MCN, Nashville, Tennessee 37232-2681, USA.
E-mail: michelle.ormseth@vanderbilt.edu

Accepted for publication January 3, 2018.

mation, 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 aminoterminal 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 CV events[13,14], were significantly higher in RA compared with controls[15,16]. Moreover, NT-proBNP concentrations were associated with RA disease activity, anti-tumor necrosis factor (anti-TNF), interleukin 6, and C-reactive protein (CRP) concentrations, but not coronary atherosclerosis[15]. Further, concentrations of troponin I, a marker of myocardial necrosis measured by a 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 increased prevalence of diastolic dysfunction[1,18]. Cardiac magnetic resonance imaging (cMRI), however, provides additional information about myocardial structure, as well as fibrosis and inflammation. An early cMRI study suggested smaller left ventricular (LV) 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)[20,21,22,23,24]. However, these studies have been small and included few patients receiving biologic therapy.

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

MATERIALS AND METHODS

Study population. We performed a cross-sectional study of 59 patients with RA and 56 controls, frequency-matched for age (within 2 yrs), race, and sex. Inclusion criteria consisted of age ≥ 18 years, the ability to provide informed consent, meeting of ACR classification criteria for RA[25] (RA subjects), and no inflammatory disease (control subjects). Exclusion criteria included previous or current heart failure or ischemic CV 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 breastfeeding, inability to undergo cMRI, and hypersensitivity to gadolinium. Participants were recruited from the Vanderbilt Clinic Rheumatology practice, responses to advertisements, and word of mouth. This 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 CV 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 erythrocyte sedimentation rate (ESR) and high sensitivity CRP were measured in the hospital clinical laboratory. RA disease activity was measured by 28-joint count Disease Activity Score (DAS28)[26].

Details of cMRI scanning. Study participants underwent cMRI using a 1.5 T Siemens Magnetom Avanto scanner (Siemens Healthcare Sector). 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 postcontrast 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 settings for cine images were the following: field of view 300 × 340 mm, matrix 156 × 192, slice thickness 8 mm, flip angle 80°, echo time 1.1 ms, and usually 30 phases per cardiac cycle to maintain repetition time below 50 ms. Parallel imaging was done using the generalized autocalibrating partially parallel acquisition technique with an acceleration factor of 2. For T1 mapping, MOLLI images were obtained in 3 LV short axis (base, mid, and apical) planes before contrast injection, and 12 and 25 min after contrast injection. Gadolinium [0.15 mmol/kg body weight gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals)] 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[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 IR true fast imaging with steady-state precession imaging. The third set of MOLLI images were obtained at 25 min postcontrast, as detailed above.

Individuals specialized in cMRI (WB and JHS) performed the cMRI analyses of structure and function and were blinded to disease status. LV and RV measurements from cMRI 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 version VB17 (Siemens). Measures of focal and diffuse fibrosis/inflammation, including the presence or absence of LGE, myocardial T1 mapping, and ECV calculations, were determined using commercial software (CVI42 version 5.3, Circle Cardiovascular Imaging) and by a third blinded specialist in cMRI (DAB, with the assistance of NKB and CL), who has led efforts to standardize image acquisition and developed techniques to minimize inter- and intraobserver variation for many large cMRI studies[27,28,29,30]. Additionally, LGE was assessed by WB, with consensus of all reads. ECV was calculated as ECV = (1-hematocrit) × (1/T1 myocardium postcontrast) – (1/T1 myocardium precontrast) / (1/T1 blood postcontrast) – (1/T1 blood precontrast)[31].

Statistics. Our study was powered to detect differences in LV mass index and postcontrast T1 mapping comparing RA to control subjects, based on previous data from published studies[32,33]. Based on previously reported mean ± SD of 67.6 ± 12.6 g/m^2 for LV mass index[32] and 564 ± 103 ms for postcontrast T1 mapping[33], ≥ 55 subjects in each group would provide about 80% power to detect a difference of ≥ 10% in both measures with a 2-sided significance of 5%. Data are expressed as median [interquartile range (IQR)].

The cMRI 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 (r) was used to assess the relationship between cMRI indices and RA-specific variables.

RESULTS

Subject characteristics. Patients with RA (median age 53 yrs) and control subjects (median age 52 yrs) were of similar age, race (98% white 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 3.16 units, IQR 2.03–4.05 units), and established disease (disease duration 10 yrs, IQR 5–15 yrs, range < 1 mo to 47 yrs). About 63% of patients with RA were taking methotrexate and 49% were taking an anti-TNF agent (Table 1).

Table 1. Patient demographics. Values are n (%) or median (IQR) unless otherwise specified.

Demographics	RA, n = 59	Controls, n = 56	p
General			
Age, yrs	53 (40–59)	52 (38–57)	0.73
White	58 (98)	55 (98)	0.97
Female	45 (76)	44 (79)	0.77
Current smoker	10 (17)	4 (7)	0.11
Alcohol use, drinks/wk	0 (0–2)	2 (1–5)	< 0.001
Diabetes mellitus type 2	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, yrs	10 (5–15)	–	–
Tender joints	3 (0–10)	–	–
Swollen joints	1 (0–4)	–	–
VAS global health, mm	25 (10–50)	–	–
ESR, mm/h	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
Current medications			
NSAID†	44 (75)	33 (59)	0.08
Aspirin	9 (15)	10 (18)	0.71
Statin	10 (17)	10 (18)	0.90
β blocker	5 (9)	1 (2)	0.11
Ca channel blocker	6 (10)	2 (4)	0.16
ACE-I	7 (12)	7 (13)	0.92
ARB	6 (10)	2 (4)	0.16
Corticosteroids	20 (34)	2 (4)	< 0.001
MTX	37 (63)	–	–
HCQ	9 (15)	–	–
Anti-TNF	29 (49)	–	–
RTX	2 (3)	–	–
ABA	2 (3)	–	–
Tofacitinib	1 (2)	–	–

*RF available in 53 patients, anti-CCP in 26 patients, and radiographs in 40 patients. † Current use of NSAID is use within 1 week prior. IQR: interquartile range; RA: rheumatoid arthritis; BP: blood pressure; BMI: body mass index; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28-CRP: 28-joint count Disease Activity Score based on CRP; NSAID: nonsteroidal antiinflammatory drug; Ca: calcium; ACE-I: angiotensin converting enzyme inhibitor I; ARB: angiotensin receptor blocker; MTX: methotrexate; HCQ: hydroxychloroquine; TNF: tumor necrosis factor; RTX: rituximab; ABA: abatacept.

Myocardial structure and function. LV 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 bpm; 66–79 bpm) compared to control subjects (68 bpm, 59–73 bpm, p = 0.01). LV 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 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/m^2 (20.8–33.6 ml/m^2), p = 0.002; Table 2].

Myocardial fibrosis or inflammation. Assessing focal fibrosis or inflammation, 2 patients with RA (3%) and 1 control subject (2%) had LGE (Table 2). Among RA, 1 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 postcontrast T1 values (25-min; 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 (r = –0.25, p = 0.06); the opposite of what was observed in control subjects (r = 0.20, p = 0.15). Native T1 time did not correlate with duration of RA (r = –0.05, p = 0.74). Patients taking anti-TNF agents had lower native myocardial T1 and ECV than nonusers, but differences were not significant (Table 3).

DISCUSSION

To our knowledge, our study represents one of the largest cMRI 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 cMRI by LGE (representing focal fibrosis or inflammation) or by increased ECV and native T1 time (representing diffuse fibrosis or

Table 2. Cardiac MRI findings in RA and control subjects. Values are median (IQR) unless otherwise specified.

Variables	RA, n = 59	Controls, 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
Left atrium 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
Right atrium 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, n (%)	2 (3)	1 (2)	–	–
Native myocardial T1, ms	973 (928–995)	973 (945–1001)	0.45	0.60
Postcontrast T1, ms	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. MRI: magnetic resonance imaging; RA: rheumatoid arthritis; LV: left ventricular; BSA: body surface area; EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; CI: cardiac index; RV: right ventricle; LGE: late gadolinium enhancement; ECV: extracellular volume.

Table 3. Cardiac MRI findings in patients with RA based on anti-TNF use. Values are median (IQR) unless otherwise specified.

Variables	Anti-TNF		p	Adjusted p
	Users, n = 29	Nonusers, n = 30		
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/m^2	2.84 (2.66–3.17)	2.65 (2.20–3.03)	0.35	0.14
Left atrium 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
Right atrium size, mm	30 (27–35)	29 (24–35)	0.31	0.21
Presence of LGE, n (%)	1 (3.4)	1 (3.3)	–	–
Native myocardial T1, ms	946 (919–995)	979 (948–996)	0.19	0.10
Postcontrast T1, ms	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. MRI: magnetic resonance imaging; RA: rheumatoid arthritis; TNF: tumor necrosis factor; LV: left ventricular; BSA: body surface area; EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; CI: cardiac index; RV: right ventricle; LGE: late gadolinium enhancement; ECV: extracellular volume.

inflammation) in RA. However, we found little LGE and no evidence of increased diffuse fibrosis or inflammation in patients with RA.

LGE cMRI can be used to assess myocardial tissue for scarring, fibrosis, and inflammation[34] because the residence time for gadolinium in expanded interstitial space is prolonged compared to the intravascular space. LGE cMRI 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 cMRI 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 patients with RA is not known; although different from controls, the ECV of patients with RA 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 that may be due to deconditioning[38]. We also observed a nonsignificant 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 suggest 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 prevent myocardial fibrosis or treat 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 ≥ 75% of the time over a 3-year period of followup 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[40,41,42]. However, although humans with heart failure have high circulating TNF levels[43], anti-TNF therapy had no benefit or even resulted in increased mortality[44,45]. Conversely, in some[8,46,47,48,49] 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 our 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 cMRI studies are informative (Table 4). Ntusi, *et al* performed cMRI in patients with RA and matched controls (n = 39 each)[20], and found LGE in 46% of patients with RA 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 our 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 our 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 our current study were taking an anti-TNF agent. Thus, differences in findings between the 2 studies may be related to earlier and more aggressive therapy of RA. We examined this idea by stratifying cMRI 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 cMRI 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 (FM)[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 our 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 FM. In RA, LGE was associated with higher DAS28-CRP. More patients with early RA (duration 0.4 yrs) than established RA (duration 13 yrs) 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 our 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, 1 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 showed that 19 of 60 (32%) patients with RA had LGE[24]. These patients had similar demographics compared to the earlier study, with slightly older patients who had shorter disease duration and disease activity compared to our 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 our current study and its findings with previous work suggests that 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 cMRI may also be important, because the rate is > 2-fold lower in the United States[29] than in Iceland[51] and Sweden[52], which is probably a result of 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, patients with RA 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.

Table 4. Comparison between current study and prior cardiac MRI studies.

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

* 31 new RA, 29 established RA starting biologics. ◊ Values are for early (established) RA. ** LGE assessed globally. † Disease duration presented in median or mean years. MRI: magnetic resonance imaging; RA: rheumatoid arthritis; DAS: Disease Activity Score; SJC: swollen joint count; CRP: C-reactive protein; TNF: tumor necrosis factor; LGE: late gadolinium enhancement.

Our study did have limitations. The cross-sectional features of the study preclude us from knowing whether aggressive treatment and control of disease explains the differences between our current study and some previous studies. Moreover, given that we studied primarily RA patients with low to moderate disease activity, we cannot extrapolate the findings of our study to patients with uncontrolled RA. Similarly, small numbers precluded us from evaluating whether anti-TNF use in the presence of persistently active disease was associated with abnormal cMRI findings.

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

REFERENCES

1. Giles JT, Fernandes V, Lima JA, Bathon JM. Myocardial dysfunction in rheumatoid arthritis: epidemiology and pathogenesis. Arthritis Res Ther 2005;7:195-207.
2. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722-32.
3. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005;52:3045-53.
4. Chung CP, Avalos I, Raggi P, Stein CM. Atherosclerosis and inflammation: insights from rheumatoid arthritis. Clin Rheumatol 2007;26:1228-33.
5. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737-45.
6. Nicola PJ, Crowson CS, Maradit-Kremers H, Ballman KV, Roger VL, Jacobsen SJ, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum 2006;54:60-7.
7. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52:412-20.
8. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med 2004;116:305-11.
9. Davis JM 3rd, Roger VL, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. Arthritis Rheum 2008;58:2603-11.
10. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-7.
11. Crowson CS, Nicola PJ, Kremers HM, O'Fallon WM, Therneau TM, Jacobsen SJ, et al. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum 2005;52:3039-44.
12. Myasoedova E, Crowson CS, Nicola PJ, Maradit-Kremers H, Davis JM 3rd, Roger VL, et al. The influence of rheumatoid arthritis disease characteristics on heart failure. J Rheumatol 2011;38:1601-6.
13. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. New Engl J Med 2006;355:2631-9.
14. Smith JG, Newton-Cheh C, Almgren P, Struck J, Morgenthaler NG, Bergmann A, et al. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. J Am Coll Cardiol 2010;56:1712-9.
15. Solus J, Chung CP, Oeser A, Avalos I, Gebretsadik T, Shintani A, et al. Amino-terminal fragment of the prohormone brain-type natriuretic peptide in rheumatoid arthritis. Arthritis Rheum 2008;58:2662-9.
16. Avouac J, Meune C, Chenevier-Gobeaux C, Dieude P, Borderie D, Lefevre G, et al. Inflammation and disease activity are associated with high circulating cardiac markers in rheumatoid arthritis independently of traditional cardiovascular risk factors. J Rheumatol 2014;41:248-55.
17. Bradham WS, Bian A, Oeser A, Gebretsadik T, Shintani A, Solus J, et al. High-sensitivity cardiac troponin-I is elevated in patients with rheumatoid arthritis, independent of cardiovascular risk factors and inflammation. PloS One 2012;7:e38930.
18. Rudominer RL, Roman MJ, Devereux RB, Paget SA, Schwartz JE, Lockshin MD, et al. Independent association of rheumatoid arthritis with increased left ventricular mass but not with reduced ejection fraction. Arthritis Rheum 2009;60:22-9.
19. Giles JT, Malayeri AA, Fernandes V, Post W, Blumenthal RS, Bluemke D, et al. Left ventricular structure and function in patients with rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Arthritis Rheum 2010;62:940-51.
20. Ntusi NA, Piechnik SK, Francis JM, Ferreira VM, Matthews PM, Robson MD, et al. Diffuse myocardial fibrosis and inflammation in

rheumatoid arthritis: insights from CMR T1 mapping. JACC Cardiovasc Imaging 2015;8:526-36.
21. Holmstrom M, Koivuniemi R, Korpi K, Kaasalainen T, Laine M, Kuuliala A, et al. Cardiac magnetic resonance imaging reveals frequent myocardial involvement and dysfunction in active rheumatoid arthritis. Clin Exp Rheumatol 2016;34:416-23.
22. Kobayashi Y, Giles JT, Hirano M, Yokoe I, Nakajima Y, Bathon JM, et al. Assessment of myocardial abnormalities in rheumatoid arthritis using a comprehensive cardiac magnetic resonance approach: a pilot study. Arthritis Res Ther 2010;12:R171.
23. Puntmann VO, Taylor PC, Barr A, Schnackenburg B, Jahnke C, Paetsch I. Towards understanding the phenotypes of myocardial involvement in the presence of self-limiting and sustained systemic inflammation: a magnetic resonance imaging study. Rheumatology 2010;49:528-35.
24. Kobayashi H, Kobayashi Y, Yokoe I, Akashi Y, Takei M, Giles JT. Magnetic resonance imaging-detected myocardial inflammation and fibrosis in rheumatoid arthritis: associations with disease characteristics and N-terminal pro-brain natriuretic peptide levels. Arthritis Care Res 2017;69:1304-11.
25. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
26. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
27. Liu CY, Liu YC, Wu C, Armstrong A, Volpe GJ, van der Geest RJ, et al. Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2013;62:1280-7.
28. Yi CJ, Wu CO, Tee M, Liu CY, Volpe GJ, Prince MR, et al. The association between cardiovascular risk and cardiovascular magnetic resonance measures of fibrosis: the Multi-Ethnic Study of Atherosclerosis (MESA). J Cardiovasc Magn Reson 2015;17:15.
29. Turkbey EB, Nacif MS, Guo M, McClelland RL, Teixeira PB, Bild DE, et al. Prevalence and Correlates of Myocardial Scar in a US Cohort. JAMA 2015;314:1945-54.
30. Raman FS, Kawel-Boehm N, Gai N, Freed M, Han J, Liu CY, et al. Modified look-locker inversion recovery T1 mapping indices: assessment of accuracy and reproducibility between magnetic resonance scanners. J Cardiovasc Magn Reson 2013;15:64.
31. Arheden H, Saeed M, Higgins CB, Gao DW, Bremerich J, Wyttenbach R, et al. Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats. Radiology 1999;211:698-708.
32. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, et al. Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson 2015;17:29.
33. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574-80.
34. Mavrogeni S, Karabela G, Stavropoulos E, Gialafos E, Sfendouraki E, Kyrou L, et al. Imaging patterns of heart failure in rheumatoid arthritis evaluated by cardiovascular magnetic resonance. Int J Cardiol 2013;168:4333-5.
35. Sado DM, Flett AS, Moon JC. Novel imaging techniques for diffuse myocardial fibrosis. Future Cardiol 2011;7:643-50.
36. Mavrogeni S, Bratis K, Sfendouraki E, Papadopoulou E, Kolovou G. Myopericarditis, as the first sign of rheumatoid arthritis relapse, evaluated by cardiac magnetic resonance. Inflamm Allergy Drug Targets 2013;12:206-11.
37. White SK, Sado DM, Fontana M, Banypersad SM, Maestrini V, Flett AS, et al. T1 mapping for myocardial extracellular volume measurement by CMR: bolus only versus primed infusion technique. JACC Cardiovasc Imaging 2013;6:955-62.
38. Piha SJ, Voipio-Pulkki LM. Elevated resting heart rate in rheumatoid arthritis: possible role of physical deconditioning. Br J Rheumatol 1993;32:212-5.
39. Arida A, Protogerou AD, Konstantonis G, Fragiadaki K, Kitas GD, Sfikakis PP. Atherosclerosis is not accelerated in rheumatoid arthritis of low activity or remission, regardless of antirheumatic treatment modalities. Rheumatology 2017;56:934-9.
40. Kadokami T, Frye C, Lemster B, Wagner CL, Feldman AM, McTiernan CF. Anti-tumor necrosis factor-alpha antibody limits heart failure in a transgenic model. Circulation 2001;104:1094-7.
41. Li YY, Feng YQ, Kadokami T, McTiernan CF, Draviam R, Watkins SC, et al. Myocardial extracellular matrix remodeling in transgenic mice overexpressing tumor necrosis factor alpha can be modulated by anti-tumor necrosis factor alpha therapy. Proc Natl Acad Sci USA 2000;97:12746-51.
42. Bradham WS, Moe G, Wendt KA, Scott AA, Konig A, Romanova M, et al. TNF-alpha and myocardial matrix metalloproteinases in heart failure: relationship to LV remodeling. Am J Physiol Heart Circ Physiol 2002;282:H1288-95.
43. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. New Engl J Med 1990;323:236-41.
44. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133-40.
45. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594-602.
46. Westlake SL, Colebatch AN, Baird J, Curzen N, Kiely P, Quinn M, et al. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology 2011;50:518-31.
47. Listing J, Strangfeld A, Kekow J, Schneider M, Kapelle A, Wassenberg S, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum 2008;58:667-77.
48. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007;27:369-73.
49. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. Rheumatology 2005;44:677-80.
50. Setoguchi S, Schneeweiss S, Avorn J, Katz JN, Weinblatt ME, Levin R, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J 2008;156:336-41.
51. Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. JAMA 2012;308:890-6.
52. Barbier CE, Themudo R, Bjerner T, Johansson L, Lind L, Ahlstrom H. Long-term prognosis of unrecognized myocardial infarction detected with cardiovascular magnetic resonance in an elderly population. J Cardiovasc Magn Reson 2016;18:43.