Cardiac magnetic resonance imaging reveals frequent myocardial involvement and dysfunction in active rheumatoid arthritis

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Abstract

Objective

In rheumatoid arthritis (RA), cardiac involvement is common and often subclinical. We used cardiovascular magnetic resonance (CMR) to identify myocardial abnormalities in patients with active RA, free of clinical cardiac disease.

Methods

Sixty female patients with active RA aged <70 years and 21 sex- and age-matched control subjects underwent either 1.5T or 3T CMR imaging for analyses of T1 relaxation times, late gadolinium enhancement (LGE), and the volumes, and function of both ventricles.

Results

Determined using 1.5T CMR, the native left ventricular (LV) septal T1 time averaged 1011 (range 973–1046) ms in 20 patients with RA vs. 976 (range 970–988) ms in 10 control subjects (p=0.045). With 3T CMR, the T1 time measured 1173 (range 1154–1187) ms in 29 RA patients vs. 1053 (range 942–1148) ms in 9 control subjects (p=0.002). Myocardial LGE was detected in 55% of the RA patients. LV ejection fraction averaged 58 (range 56–61)% vs. 66 (61–74)% (p<0.001) in the RA (n=60) and control groups (n=21), respectively, and corresponding means for LV peak filling rate were 2.99 (range 2.32–3.33) s^{-1} vs. 3.39 (range 2.96–3.70) s^{-1} (p=0.012). The end-diastolic volumes of either ventricle were enlarged in RA compared to the control group (p<0.05 for both).

Conclusion

In active RA, myocardial T1 relaxation times are prolonged suggesting diffuse inflammation or fibrosis. Local myocardial scars and inflammation, visible as LGE, are also common, as are impairments of LV systo-diastolic function.

Key words

rheumatoid arthritis, cardiovascular disease, cardiac magnetic resonance, T1 mapping, late gadolinium enhancement

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Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory disease characterised by severe articular and extra-articular manifestations. RA is associated with an increased prevalence of cardiovascular diseases (CVD) and has similarities with CVD in diabetes mellitus (1). The known cardiac manifestations include premature atherosclerosis with ischaemic heart disease, pericardial effusion, valvular thickening and insufficiency, aortic root alterations, myocarditis, coronary vasculitis, cardiac amyloidosis, and congestive heart failure (2-4). In addition patients with RA have higher prevalence of diastolic dysfunction and increased left ventricular mass have been documented (5-6).

The mechanisms of cardiovascular involvement in RA are not fully understood. Different immunological processes and an excess of inflammatory cytokines have been incriminated in the development of myocardial dysfunction, and chronic inflammation is also suggested as leading to endothelial dysfunction and accelerated atherosclerosis (7). Myocardial biopsy studies have shown a high occurrence of endothelial lesions, inflammatory changes in the coronary microvasculature and in the cardiomyocytes, and even myocardial fibrosis (8-11).

Cardiac involvement in RA portends a poor prognosis (12-14) which raises the importance of its early detection. It is known that increased CVD risk begins even prior to or within one year of the clinical onset of RA. The significance of evaluating cardiovascular risk factors and recognising high-risk RA patients should be emphasised because CVD is still the major cause of mortality in RA (15-16). Myocardial abnormalities can be assessed using different modes of echocardiography, single-photon emission computed tomography, and cardiovascular magnetic resonance (CMR) (1, 17-20). Standard CMR imaging with contrast enhancement enables an accurate assessment of left ventricular (LV) and right ventricular (RV) volumes and function as well as the detection of focal myocardial replacement fibrosis or infiltration as areas of late gadolinium enhancement (LGE). Previous CMR findings have shown the existence of subclinical myocardial LGE in RA and its association with disease activity (14, 21).

Following recent technical improvements in CMR, pixel by pixel mapping of myocardial T1 relaxation times has become a promising tool for the non-invasive evaluation of diffuse myocardial fibrosis and inflammation (22, 23). Abnormal myocardial T1 maps have been found in dilated and hypertrophic cardiomyopathies (24) as well as in inflammatory (25) and infiltrative diseases (26) of the heart muscle. Prolonged myocardial T1 relaxation times have also been reported in systemic lupus erythematosus (SLE) (27) and in one earlier study of patients with RA (21).

The present case-control study herein was designed to characterise subclinical myocardial involvement in patients with active RA, free of any clinical cardiac disease. The effort utilised CMR with cine imaging, T1 mapping, and LGE assessment.

Materials and methods

Patients and control subjects

In this case-control study the 60 patient population comprised two groups of females under the age of 70 years with active RA: 31 patients with newly diagnosed disease awaiting the start of treatment with conventional disease-modifying anti-rheumatic drugs and 29 patients with long-lasting RA awaiting the start of treatment with biological therapy. All patients were prospectively recruited from the Department of Rheumatology, Helsinki University Central Hospital. The exclusion criteria were clinical coronary artery disease or cardiomyopathy, heart failure, significant valvular heart disease, chronic arrhythmias, untreated hypertension (>180/110 mmHg), renal failure (GFR <60 ml/min/m^2), severe obesity (BMI >35 kg/m^2), history of thyroid disease, medication for diabetes, and smoking within the last 10 years. The RA population was then compared with an age- and sex-matched control group comprising healthy volunteers: n=11, median age 49 (range 39–52) y, height 171 (range 165–174) cm, weight 67 (range 63–74) kg and patients with fibromyalgia: n=10, median age 53

(range 42–57) y, height 167 (range 158–170) cm, weight 74 (range 69–79) kg, all of whom were non-smokers.

Each study participant underwent CMR imaging for the purposes of the present research. Patients with RA or fibromyalgia also underwent 12-lead electrocardiography and echocardiography. The study protocol was approved by the Ethics Review Board of the Joint Authority for the Hospital District of Helsinki and Uusimaa, and written informed consent was obtained from each participant.

CMR technique

All RA patients and controls were studied with a clinical scan protocol; however, the healthy volunteers did not receive a contrast agent. CMR was performed either with a 1.5T MR (Avantofit; Siemens, Erlangen, Germany) or a 3T MR scanner (Verio; Siemens, Erlangen, Germany) using a 32-channel receiver cardiac coil, as our institution had T1 Modified Look-Locker Inversion-recovery (MOLLI) sequence available for years 2012-2013 only in 3T and afterwards only in 1.5T scanner. Fibromyalgia patients were imaged with 3T and healthy volunteers with 1.5T scanner. Breath-hold cine MR was performed by using retrospectively electrocardiographically gated segmented true fast imaging with a balanced steady-state free precession (bSSFP) sequence. To assess LV and RV volumes and ejection fractions (EF), cine CMR images were obtained in vertical and horizontal long-axis, and a stack of short-axis planes that covered both ventricles. The typical imaging parameters were TR/TE 3.0/1.6 ms, flip angle 52º, 256 x 256 matrix, and a 240 x 340 mm field of view (FOV). Slice thickness was 6 mm, and the interslice gap was 20%. The temporal resolution was 33–36 ms.

Myocardial T1 mapping was performed in a mid-ventricular short-axis slice, using a shortened Modified Look-Locker Inversion-recovery (shMOLLI) sequence. Typical acquisition parameters for the shMOLLI sequence were TR/TE 2.1/1.1 ms, flip angle 35º, 236 x 256 matrix and 331 x 360 mm FOV; inversion times varied from 90 ms to circa 5000 ms, and 8 mm slice thickness.

Ten minutes after injection of a contrast agent (gadoteratemeglumine, Dotarem® 0.2 mmol/kg) LGE images were acquired in the same views as for cine images, using inversion a recovery-spoiled gradient echo (IR-SPGR) sequence. The imaging parameters were TR/TE 2.58/2.3 ms, flip angle 50º, 256 x 256 matrix, and 240 x 340 FOV. Slice thickness was 8 mm and interslice gap 0%. Inversion time was optimised for each measurement to null the signal intensity of a normal myocardium (240-360 ms).

Image analysis

Images were analysed in consensus with two experienced (>10 years of experience) cardiac radiologists and a medical physicist (SK, MH, TK). CMR image analysis was performed using QMass MR Software® (v. 7.6, Medis Medical Imaging Systems, Leiden, Netherlands). Measurements of LV and RV volumes, EF and diastolic filling were segmented semi-automatically by tracking the endocardial borders of both ventricles with a segmentation tool developed for this purpose.

Motion-corrected, native T1 maps were generated, and T1 estimates were computed on a per-pixel basis by performing a non-linear curve fitting using the 3-parameter signal model. We performed "midwall myocardial" T1 assessments by measuring the native T1 relaxation values from the septum. First, we evaluated the LGE images to exclude focal enhancement in the same area and to avoid false elevated T1 values. The comparisons of T1 relaxation times between the RA group and the control subjects were assessed separately for the measurements made by the 3T and 1.5T field strength scanners. The pattern and distribution of LGE were identified visually using the 17-segment LV model of the American Heart Association (AHA) (28), and in addition, any presence of RV free wall LGE was evaluated.

Statistical analysis

The T1 relaxation times determined by 1.5T CMR were compared between patients with RA and healthy volunteers while those measured with 3T CMR were compared between the RA and fibromyalgia groups. The measurements of LV and RV volumes, mass, and function were compared between all RA patients and the combined control groups. Volumetric parameters and T1 values were also compared between newly diagnosed and chronic RA patients.

Data are presented as median (interquartile range, IQR). To compare continuous and categorical variables between RA patients and control subjects or between RA groups, Mann-Whitney U-test and Chi-square test were used, respectively. Spearman correlation was used to compare statistical dependence between two continuous variables. Univariate and multivariate binary logistic regression was performed to ascertain the effects of disease activity (DAS28-CRP), age, RA group (newly diagnosed *vs*. chronic), ACPA positivity, and presence of extra-articular manifestations on the likelihood that patients with RA show LGE.

All statistical tests were two-sided and a *p*-value of 0.05 was considered indicative of statistical significance. Statistical analyses were performed with NCSS 8 (NCSS, LLC, Kaysville, Utah, USA) and SPSS 22 (IBM Corp., Armonk, New York, USA).

Results

Clinical characteristics of the participants

Clinical characteristics of the 60 RA patients are summarised in Table I. All participants were female. RA duration ranged from one month to 5.7 years in newly diagnosed patients (n=31) and 1.5 to 36 years in chronic patients (n=29). The DAS28-CRP, corresponded to moderate or high disease activity (DAS28-CRP ≥3.2) in 22 patients (73%) and 17 patients (61%), respectively.

Diffuse fibrosis and inflammation (T1 mapping)

As measured by 1.5T CMR, the native septal T1 relaxation time averaged 1011 (range 973–1046) ms in 20 patients with RA and 976 (range 970–988) ms in 10 control subjects (p=0.045). With 3T CMR, the corresponding T1 relaxation time averaged 1173 (range 1154–1187) ms *vs*. 1053 (range 942–1148) ms in the

Table I. Clinical features of rheumatoid arthritis (RA) patients.

Clinical feature	Patients with newly diagnosed RA n=31	Patients with chronic RA n=29	*p*-value
Age, years; median (IQR)	51 (39-62)	50 (39-60)	0.589
RF positivity; n (%)	26 (84)	23 (85)	1.000
ACPA positivity; n (%)	27 (87)	26 (93)	0.673
Number of swollen joints; median (IQR)*	8 (4-10)	6 (2-7)	0.037
Number of tender joints; n, median (IQR)*	7 (3-12)	6 (2-11)	0.726
DAS28 (CRP); median (IQR)	3.9 (3.1-4.2)	3.7 (2.7-4.4)	0.566
Extra-articular manifestations; n (%)	5 (16)**	14 (48)***	0.007
Erosions on radiographs; n (%)	5 (17)	23 (85)	<0.001
Duration of RA symptoms, years; median (IQR)	0.4 (0.3-0.8)	13.0 (4-26)	<0.001
Height, cm; median (IQR)	169 (164-172)	163 (170-171)	0.023
Weight, kg; median (IQR)	63 (59-77)	68 (61-75)	0.391
BMI, kg/m^2; median (IQR)	21.8 (20.7-25.6)	24.8 (23.3-27.6)	0.027
Mean blood pressure; median (IQR)	108 (98-121)	110 (103-127)	0.569

RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibody; IQR: interquartile range, DAS28 (CRP): Disease Activity Score (CRP): low disease activity ≤3.2; moderate disease activity 3.2 < and ≤5.1; high disease activity >5.1; CRP: C-reactive protein; BMI: body mass index; *: 66/68 joints evaluated; **secondary sicca syndrome in five patients, ***secondary sicca syndrome nine patients, rheumatoid nodules in five patients.

RA (n=29) and control (n=9) groups, respectively (p=0.002). T1 relaxation times could not be determined due to ECG gating problems, or they were not acquired, in a total of 11 RA patients and two control subjects. Representative images of T1 maps in the healthy control and RA patient are presented in Figure 1. There were no statistically significant differences in T1 relaxation times measured by either 1.5T or 3T CMR between patients with newly diagnosed and chronic RA, or patients with or without extra-articular manifestations, T1 relaxation times did not correlate significantly with the disease activity score (DAS28-CRP) or with age. As measured by 1.5T CMR, the T1 relaxation time averaged 958 (range 925–958) ms in the three anti-citrullinated protein antibodies (ACPA) negative RA patients and 1019 (range 995-1051) ms in the 17 ACPA positive patients (p=0.019), whereas no such difference was seen in those patients investigated by 3T CMR.

Local fibrosis and inflammation (LGE)

Among the 60 RA patients, myocardial LGE was detected in 33 individuals (55%). We found an increased incidence of myocardial LGE in newly diagnosed RA patients (68%) compared to chronic RA patients (41%) (p=0.040). Figure 2 demonstrates the distribution of LGE by the AHA model of LV segmentation. LGE was most common in the septal, inferior, and inferolateral segments of the basal and middle parts of the LV walls. It was typically subepicardial or intramyocardial and linear or patchy. Subepicardial and patchy enhancement involved inferior and inferolateral segments and RV insertions in particular. In the interventicular septum, LGE had a linear pattern. Representative images of septal and RV insertion LGE are presented in Figure 3. One patient had subendocardial and circular LGE reminiscent of cardiac amyloidosis. Another patient exhibited lateral transmural LGE suggestive of a myocardial infarction scar. This finding is demonstrated in Figure 4. There was no LGE of the RV free wall. None of the patients with fibromyalgia had myocardial LGE. There were no statistically significant correlations between T1 relaxation times and LGE.

In univariate binary logistic regression analyses, increased likelihood of LGE was statistically significantly associated with increasing DAS28-CRP (OR 1.81, 95% CI 1.06 to 3.10, p=0.029), and RA group (newly diagnosed compared to chronic); OR 2.98, 95% CI 1.04 to 8.55, p=0.043), but not with age, ACPA positivity, or presence of extra-articular manifestations. In multivariate binary logistic regression analysis with DAS28-CRP and RA group as predictors, increased likelihood of LGE was associated with increasing DAS28-CRP (OR 1.76, 95% CI 1.01 to 3.05, p=0.044) but not with RA group (OR 2.42, 95% CI 0.80 to 7.33, p=0.119).

Left and right ventricular volumetric results

Table II summarises the data on LV and RV volumes, mass, and function and shows that the patients with RA had statistically significantly larger ventricular volumes and lower LVEF and a peak filling rate when compared with the control subjects.

There were no statistically significant differences between the newly diagnosed and chronic RA patients in the LV volumetric measurements (Table III). The RV measurements were also comparable, expect for RVEF, which was lower (p=0.008), and RV end-systolic volume, which was larger (p=0.02), in the newly diagnosed RA group.

Discussion

The present work focused on myocardial tissue characterisation in patients with RA using standard and novel CMR techniques. We found that patients with active RA free of any clinical cardiac disease commonly have prolonged native septal T1 relaxation times, suggesting diffuse fibrosis or inflammation of the myocardium. Further, more than 50% of the patients with RA, but none of those with fibromyalgia, exhibited local myocardial LGE indicative of replacement fibrosis. Importantly, these abnormalities of the heart muscle were associated with relative dilatation of either ventricle and with impairment LV systolic contractions and diastolic filling. Furthermore, the presence of LGE was associated with increasing disease activity score and age.

Autopsy studies have shown that diffuse myocardial abnormalities are not uncommon in RA (7), and works also exist to suggest that reduction of RA activity may inhibit the progression of myocardial involvement (29). Modern CMR imaging, including the assessment of LGE and T1 relaxation times, provides a new tool to identify myocardial abnormalities, such as oedema, inflammation, myocyte damage, and fibrosis. While LGE exposes focal scars

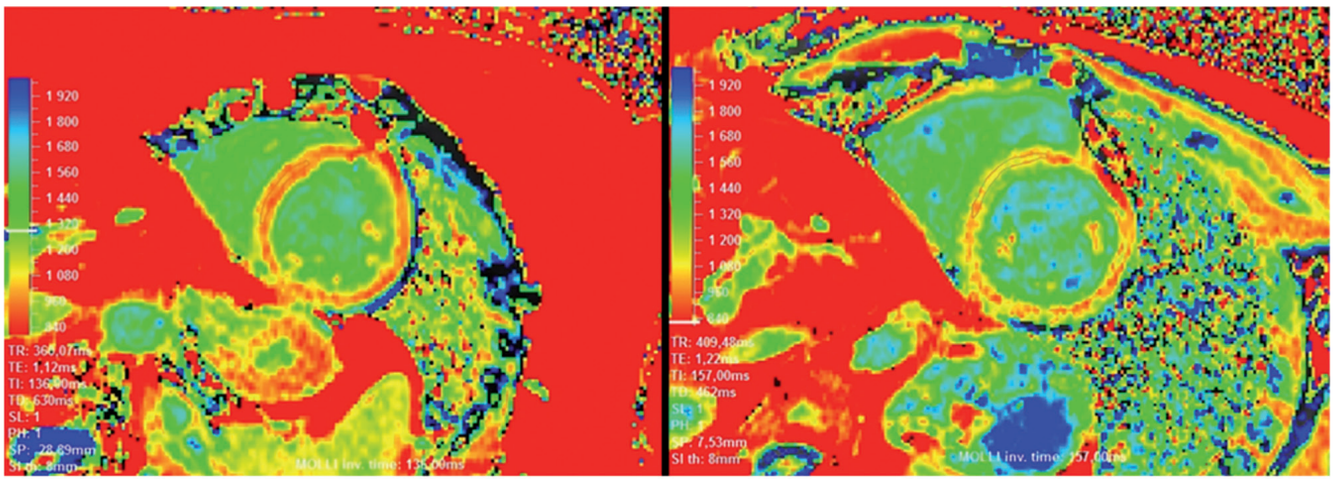

Fig. 1 A. Pre-contrast T1 mapping of 60-year old healthy control shows normal T1 relaxation value (T1 971 ms) of the left ventricular septum.
B. T1 relaxation value of a 20-year old patient with newly diagnosed rheumatoid arthritis is significantly higher (T1 1051 ms), thus referring to diffuse fibrosis or chronic inflammation of the myocardium.

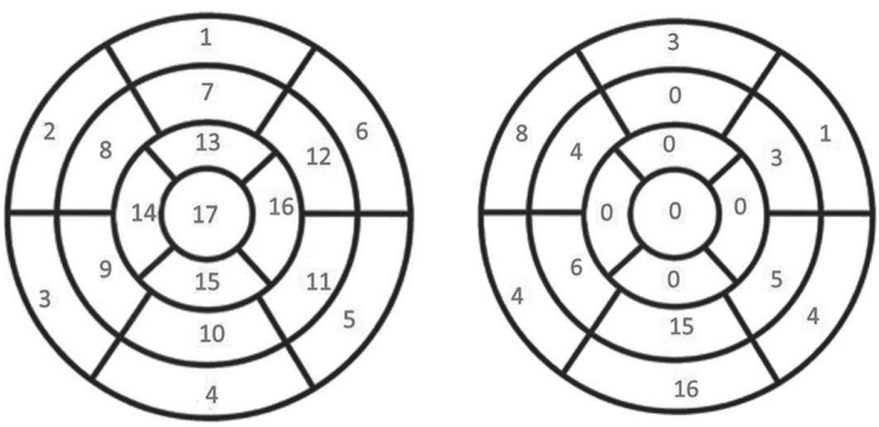

Fig. 2 A. Left ventricular segments according to the American Heart Association (AHA).
B. Location and distribution of late gadolinium enhancement (LGE) of the left ventricle in patients with chronic and newly diagnosed rheumatoid arthritis.

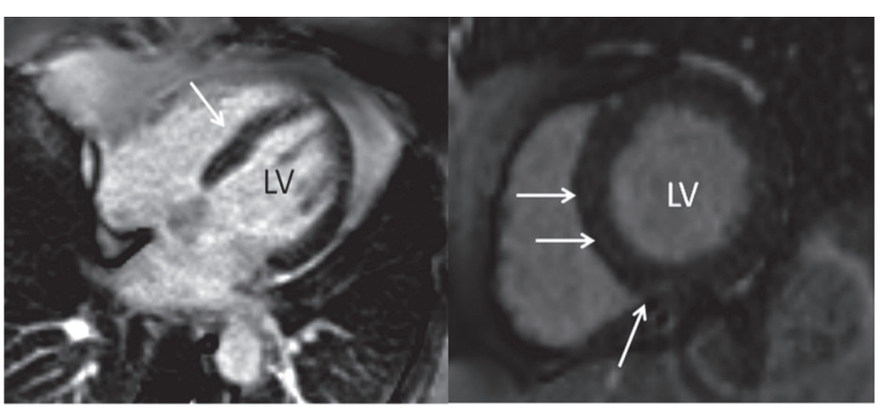

Fig. 3. Cardiac magnetic resonance images of 64-year old patient with chronic and active rheumatoid arthritis. Four-chamber (**A**) and short-axis views (**B**) of the heart show linear, late gadolinium enhancement of the basal interventricular septum (arrow) and patchy enhancement of right ventricular insertion (arrow head), LV: left ventricle.

and replacement fibrosis, T1 mapping is able to identify diffuse interstitial fibrosis and inflammation. Native T1 relaxation times reflect both intra- and extracellular signals in the myocardium and become prolonged due to increased water content referring to diffusely diseased myocardium.

Abnormally prolonged native T1 relaxation times have been reported in myocardial fibrosis and oedema, and with amyloid infiltration (30), while iron overload and fat infiltration appear to shorten T1 time (23). Several specific myocardial disease entities have been associated with elevated T1 relaxation times (23-26), and recently, studies with native T1 mapping have shown a potential to identify myocardial involvement in SLE (27) and chronic RA as well (21). Our work exposed comparable prolongation of LV septal T1 relaxation times in newly-diagnosed and chronic RA. Without post-contrast T1 mapping, however, it is difficult to tell whether this result was due to inflammation or diffuse fibrosis or a combination thereof. This finding may also explain why the T1 relaxation times of the RA subpopulations were not differ-

Table II. Cardiac magnetic resonance findings in patients with rheumatoid arthritis (RA) and in controls.

Variable	RA patients = 60 Median (IQR)	Controls together = 21 Median (IQR)	*p*-value (significant $p<0.05$)
LVEF, %	58.5 (56-61)	66.7 (61-74)	< 0.001
LVEDV-index, ml/m^2	82 (75-91)	76 (68.5-82)	0.022
LVESV-index, ml/m^2	34 (30-40)	25 (21-29)	< 0.001
LVSV-index, ml/m^2	47 (43-51)	43 (42-46)	0.24
LVPFR/EDV, 1/s	2.99 (2.32-3.33)	3.39 (2.96-3.50)	0.012
LV mass-index, g/m^2	51 (45-56)	54 (47-59)	0.29
RVEF, %	58 (56-60)	58 (51-63)	0.69
RVEDV-index, ml/m^2	80 (75-85)	75 (66-78)	0.03
RVESV-index, ml/m^2	34 (30-38)	33 (24-37)	0.25
RVSV-index, ml/m^2	44 (40-45)	48 (45-49)	0.02

IQR: Interquartile range; LV: Left ventricle; EF: Ejection fraction; EDV: End-diastolic volume; ESV: End-systolic volume; SV: Stroke volume; PFR: Peak filling rate; RV: Right ventricle.

Table III. Cardiac magnetic findings of newly diagnosed and chronic patients with rheumatoid arthritis (RA).

Variable	Newly diagnosed RA patients = 31 Median (IQR)	Chronic RA patients = 29 Median (IQR)	*p*-value (significant $p<0.05$)
LVEF, %	57 (56-58)	60 (59-61)	0.05
LVEDV-index, ml/m^2	84 (78-89)	80 (75-87)	0.56
LVESV-index, ml/m^2	35 (33-39)	33 (29-36)	0.13
LVSV-index, ml	47 (46-50)	48 (44-51)	0.96
LV PFR/EDV, 1/s	2.65 (2.28-3.15)	3.05 (2.65-3.77)	0.61
LV mass-index, g/m^2	51 (55-58)	51 (49-53)	0.86
RVEF, %	57.5 (55-58)	60 (56-63)	0.008
RVEDV-index, ml/m^2	83 (78-93)	77 (71-89)	0.16
RVESV-index, ml/m^2	36 (33-41)	31 (27-37)	0.02
RVSV-index, ml/m^2	47 (44-49)	48 (44-51)	0.49

IQR: Interquartile range; LV: Left ventricle; EF: Ejection fraction; EDV: End-diastolic volume; ESV: End-systolic volume; SV: Stroke volume; PFR: Peak filling rate; RV: Right ventricle.

ent, notwithstanding the marked difference in their disease duration.

LGE visualises the expansion of extracellular space related to focal myocardial fibrosis or infiltration, myocyte necrosis, fibrosis, oedema or protein deposition. Injured cell membranes and larger extracellular space results in increased accumulation of gadolinium in the myocardium, seen as bright regions in CMR images. The characteristics of myocardial LGE differ according to the underlying myocardial pathology. Lesions due to replacement fibrosis in ischaemic heart disease are typically subendocardial, while non-ischaemic cardiomyopathies often display intramyocardial or subepicardial LGE. The typical pattern in dilated cardiomyopathy is band-like intramyocardial LGE involving the interventricular septum. Hypertrophic cardiomyopathies often display patchy intramyocardial LGE in the anteroseptal region, while acute myocarditis is typically accompanied by intramyocardial or subepicardial LGE in the lateral LV wall. Cardiac amyloidosis, in turn, is characterised by a peculiar pattern of subendocardial circular LGE (32).

Previous studies have shown that abnormal myocardial LGE also appears in patients with inflammatory connective tissue diseases like systemic sclerosis and SLE (33, 34). The myocardial LGE lesions reported hitherto in RA have been mainly intra-myocardial or subepicardial without any predominant localisation in the LV myocardium (14). In our study, LGE lesions were found predominantly in the basal and mid-cavity inferolateral LV segments and in the interventricular septum. A similar pattern of LGE was recently found in the study by Ntusi *et al*. (21). This distribution is close to the pattern reported in

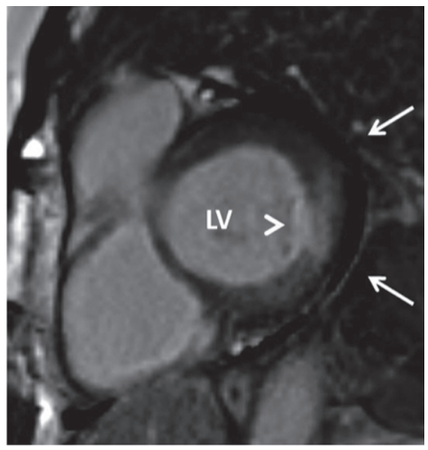

Fig. 4. Cardiac magnetic resonance image of 68-year old patient with chronic and active rheumatoid arthritis. Short- axis views of the LV shows local, transmural late gadolinium enhancement of the basal lateral wall (arrow head). This patient exihibited also pericardial effusion seen as low (black) signal next to lateral wall of the LV (arrows). LV: left ventricle.

SLE and resembles distribution of LGE seen in viral myocarditis and in dilated cardiomyopathy (34, 35). In our study, myocardial LGE was more common in newly diagnosed RA patients that had not yet received disease-modifying anti-rheumatic treatment. This finding indicates that local inflammation and even fibrosis of the myocardium are common findings in early stage of the disease. In accordance with earlier studies LGE was also directly related to the disease activity score (14).

Postmortem studies have reported a high prevalence of myocarditis in RA patients free of symptoms and even normal echocardiography results. This confirms that CMR is a modality of choice in tissue characterisation because echocardiography is unable to detect myocardial changes (1).

Patients with RA are more likely to have diastolic dysfunction assessed with echocardiography. Decreased distensibility, impaired relaxation, abnormal diastolic filling and increased left atrial dimensions are suggestive of diastolic dysfunction (5).

RA patients without clinically evident CVD have LV diastolic filling abnormalities by doppler echocardiography in spite of the normal LV systolic function (36). Diastolic dysfunction seems to be related to structural abnormalities of the LV, especially changes in LV

mass, septal and posterior wall thickening. Structural and functional LV changes are clinically significant and correlate to a higher risk of cardiovascular mortality (3). Novel echocardiographic studies, including LV strain analyses by speckle tracing, have also shown both systolic and diastolic LV dysfunction in patients with RA but free of clinical cardiovascular disease (5, 37). Fine *et al*. even reported that abnormalities of LV systolic strain correlated with RA disease severity (19). In study by Schau *et al*. 25% of RA patients revealed diastolic heart failure, predominantly associated with concentric hypertrophy and reduced longitudinal strain. They concluded that prevalence of heart failure was increased in active RA (38).

Our volumetric LV measurements by CMR showed that both LVEF and peak filling rate were reduced in RA compared with the control group. These data indicate a systo-diastolic LV dysfunction in accordance with the earlier echocardiographic studies. They are also in line with our T1 mapping and LGE assessment, suggesting myocardial involvement in RA. Modern speckle tracking echocardiography is exquisite in identifying LV dysfunction, while CMR no doubt can offer more information about direct myocardial changes. The combination of these methods may offer advantages for exposing subclinical cardiac involvement in RA.

We found surprisingly few differences in the CMR measurements between newly diagnosed and chronic RA despite the marked difference in disease duration. There were, however, more LV myocardial LGE and a relative impairment of RV function in the newly diagnosed patients who at the time of our study were still without effective antirheumatic therapy. Unfortunately, we could not perform T1 relaxation time mapping of the RV free wall. Due to the thinness of the RV wall, the motion correction is challenging and the confounding effect of the blood pool next to the myocardium upon the T1 times is very difficult to avoid. In addition, spatial resolution of images is inadequate yet. With technical improvements, T1-mapping of the RV wall should become possible in the future (39).

Limitations of the study

Standard protocols for CMR imaging in myocarditis are well defined by Friedrich *et al*. (40). In addition to function, T1 mapping and LGE imaging, we acquired T2-weighted images. However, in tissue oedema characterisation we found that T2-weighted images exhibited a limited sensitivity and robust image quality do to motion artifacts especially in mild or less severe inflammation. Therefore in this study we did not include analysis of oedema T2-weighted images. Unfortunately, we did not acquire early phase gadolinium images.

We measured only native T1 relaxation times, which reflect both intra- and extracellular signals in the myocardium and do not differentiate active inflammation from diffuse fibrosis. Further studies should include measurements of myocardial extracellular volumes, using both post-contrast and native T1-mapping. We started the CMR studies with a 3T field strength scanner, but then had, for practical reasons, to switch to 1.5T imaging in the later part of our investigation. Our institution had T1 mapping sequence available for years 2012-2013 only in 3T and afterwards only in 1.5T scanner. T1 relaxation times are sensitive to the strength of the static magnetic field, so we were careful to compare the RA and control groups separately for the 3T and 1.5T measurements. It is also important to note that the septal T1 relaxation times were measured in one short axis LV slice only.

Conclusions

We conclude that CMR imaging commonly exposes diffuse and focal myocardial abnormalities, a relative biventricular dilatation and systo-diastolic LV dysfunction in active RA. Future studies are needed to show whether and how modern CMR imaging can help clinicians in the routine care of patients with RA.

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