Myocardial T1 mapping by cardiac magnetic resonance imaging shows early myocardial changes in treatment-naive patients with active rheumatoid arthritis and positive autoantibodies

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Abstract

Objective

We aimed to study whether myocardial changes are already detectable by cardiac magnetic resonance (CMR) imaging at the time of rheumatoid arthritis (RA) diagnosis.

Methods

This single-centre prospective study included 39 treatment-naive patients with early rheumatoid arthritis (ERA, symptom duration <1 year) without any history of heart disease, and 38 age- and sex-matched healthy volunteers. The disease severity was assessed with clinical evaluation (Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP) score) and serological testing (rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)). The ERA patients were classified into group A (DAS28-CRP score ≥3.2, positive RF and ACPA; n=17) and group B (not fulfilling the group A criteria). The ERA patients and healthy controls underwent 1.5T CMR.

Results

Group A patients had significantly higher myocardial global T1 relaxation times than the healthy controls, 987 [965, 1003] ms vs. 979 [960, 991] ms (median [IQR]; p=0.041). A significant difference in T1 was found in the basal, mid inferior and mid anterolateral segments. In a multivariate analysis, prolonged global T1 relaxation time was independently associated with female sex (95% CI [5.62, 51.31] ms, p=0.016), and group A status (95% CI [4.65, 39.01] ms p=0.014).

Conclusion

At the time of diagnosis, ERA patients with a higher disease activity (DAS28-CRP score ≥3.2) and both positive RF and ACPA showed prolonged T1 relaxation times in basal myocardial segments. These segments could be most susceptible to the development of myocardial fibrosis, and a segmental reporting style could be useful when estimating the first signs of myocardial fibrosis.

Key words

cardiac magnetic imaging, myocardial fibrosis, early rheumatoid arthritis, severe disease form, T1 mapping, segmental analyses.

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease, resulting in articular and extra-articular manifestations. Compared with healthy controls, RA patients have a significantly increased risk for coronary artery disease (CAD) (1), congestive heart failure (CHF), and even sudden cardiac death (2-7). This risk is not only explained by traditional risk factors, but RA has also been proven to serve as an independent risk factor, similar to diabetes mellitus (3, 8-11). RA patients are more likely to show focal and diffuse myocardial fibrosis and inflammation, which correlate with RA disease activity (12). Furthermore, the presence of autoantibodies, i.e. rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), have been linked to impaired cardiac function in patients with severe RA (13).

Cardiac magnetic resonance (CMR) is a great diagnostic tool for studying the myocardium, and is considered the gold standard for the quantification of focal myocardial fibrosis (14). The late gadolinium enhancement (15) sequence identifies even small myocardial scars. The extent of enhancement has been proven to be an independent risk factor for cardiovascular mortality (16, 17), but LGE imaging struggles to identify interstitial diffuse myocardial fibrosis (18). T1 mapping either with or without contrast administration, in turn, is a relatively novel native CMR method for detecting diffuse fibrosis, especially when combined with post-contrast extracellular volume (ECV) quantification and T2 mapping (18-20).

Patients with RA are at increased risk of developing cardiovascular disease (CVD) within the first year of clinical RA symptom onset or even prior to that (7, 21). The overall CVD mortality is increased amongst RA patients in comparison to general population, and clinical guidelines are emphasising the early characterisation, management, and risk reduction of the CVD burden (22). The exact time of appearance of the early cardiac manifestations in RA has remained unclear, as well as how their detection could be improved and if their manifestation could be postponed, prevented, or even attenuated with effective anti-rheumatic medication. Therefore, the aim of this study was to explore early myocardial manifestations in treatment-naive patients with early RA (ERA), focusing on the novel CMR mapping techniques and disease severity, including autoantibodies.

Patients and methods

Patients

This single-centre prospective, blinded study comprised 39 consecutive, recently diagnosed, (duration of symptoms ≤12 months at diagnosis) adult ERA patients fulfilling the ACR/EULAR 2010 classification criteria for RA (23), awaiting to start treatment with a combination of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). The recruitment took place in the Department of Rheumatology in the Helsinki University Hospital and Lohja Hospital, Finland, between October 2018 and August 2021. The patient cohort consisted of individuals without pre-existing cardiovascular diseases such as clinical CAD, cardiomyopathy, ischaemic heart disease, or CHF. Importantly, diabetes mellitus, hypercholesterolaemia, and clinical hypertension were not grounds for exclusion in the study. Consequently, the study included seven patients with clinical hypertension and four with diabetes. Single blood pressure registrations were taken prior to the CMR scan during rheumatologist evaluations. A history of hypertensive disease was recorded separately. Other autoimmune diseases with possible cardiac manifestations and contraindications to CMR also served as exclusion criteria. All 39 patients underwent a thorough medical examination, comprehensive laboratory tests and gadolinium-enhanced CMR. Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP) (24) was calculated. A DAS28-CRP level of <2.6 was considered a threshold for remission, 2.6-3.2 as low disease activity, and ≥3.2 moderate to severe disease activity (13). In this study we divided the ERA patients into two groups; Patients with a DAS28-CRP score ≥3.2, positive RF and positive ACPA formed group A (n=17), and those with less than three

of these characteristics formed group B (n=22).

The control group comprised 38 age- and sex-matched healthy volunteers without a self-reported history of heart disease, any other cardiovascular diseases, or any autoimmune disease. The volunteers were recruited among healthcare professionals and their relatives.

All study participants gave written informed consent. The ethics committee of the Helsinki University Hospital provided a favourable opinion on the study protocol (HUS/2691/2017), and the declaration of Helsinki was followed.

CMR imaging

All 39 ERA patients underwent 1.5T CMR (Avantofit; Siemens, Erlangen, Germany) at Meilahti University Hospital, using a combination of 30-channel receiver body and 32-channel receiver spine coils. Images were acquired in breath-hold to minimise breathing artifacts. To assess left ventricle (LV) and right ventricle (RV) volumes and ejection fractions (EF), a retrospectively electrocardiographically (ECG) gated balanced steady-state free precession (bSSFP) cine sequence was scanned in vertical and horizontal long-axis, and also in short-axis planes covering the whole heart. Typical Imaging parameters for cine imaging were repetition time (TR) of 2.8 ms and echo time (TE) of 1.2 ms, flip angle 55°, 192 × 154 matrix, and a 280 × 230 mm field of view (FOV). Slice thickness was 6 mm, inter-slice gap was 20% in long-axis directions and 30% in short-axis planes, and 30 phases of the cardiac cycle were reconstructed. The temporal resolution was 34–40 ms. Similar parameters were also used for the left (LVOT) and right (RVOT) ventricle outflow tract cine imaging.

T2-STIR images were acquired in the short-axis direction at three levels of the LV (apex, mid-ventricular and basal planes). Typical scan parameters for T2 STIR imaging were TR of two heartbeats, TE of 45 ms, 192 × 148 matrix, 270 × 245 mm FOV, and slice thickness of 8 mm, mid-diastolic acquisition, and echo-train length of 17.

T2-mapping images were acquired in the short-axis direction of the LV (apex, mid-ventricular, and basal) using a T2-prepared bSSFP sequence. Three single-shot bSSFP images with different T2 preparation times (0 ms, 25 ms, and 55 ms) were obtained at mid-diastolic phase during one breath-hold. Typical imaging parameters were TR of 2.4 ms, TE of 1.1 ms, slice thickness of 8 mm, flip angle 70°, 192 × 144 matrix, and 360 × 290 mm FOV.

Pre- and post-contrast T1 mapping of the myocardium was performed in a short-axis direction at three levels of the LV (apex, mid-ventricular, and basal) using a shortened Modified Look-Locker Inversion-recovery (shMOLLI) sequence. Briefly, the typical acquisition parameters for the shMOLLI sequence were TR/TE of 2.4/1.2 ms, slice thickness of 8 mm, flip angle 35°, 256 × 169 matrix, 300 × 256 mm FOV, and data acquisition in mid-diastolic phase. Post-contrast T1 mapping was performed 12 minutes after the injection of a contrast agent (gadoteratemeglumine, Dotarem® 0.2 mmol/kg).

Starting from five minutes after the injection of the contrast agent, LGE images were acquired in the long-axis and short-axis directions of the LV using a multi-slice single shot phase-sensitive inversion recovery (PSIR) sequence with bSSFP readout. The typical imaging parameters of the PSIR sequence were TR/TE of 2.5/1.1 ms, inversion time (TI) to suppress the signal intensity of a normal myocardium of 350-400 ms, triggering performed once every two heartbeats, flip angle 40°, 144 × 144 matrix, and 270 × 200 FOV. Slice thickness was 8 mm and inter-slice gap was 25%. The CMR protocol used with our healthy

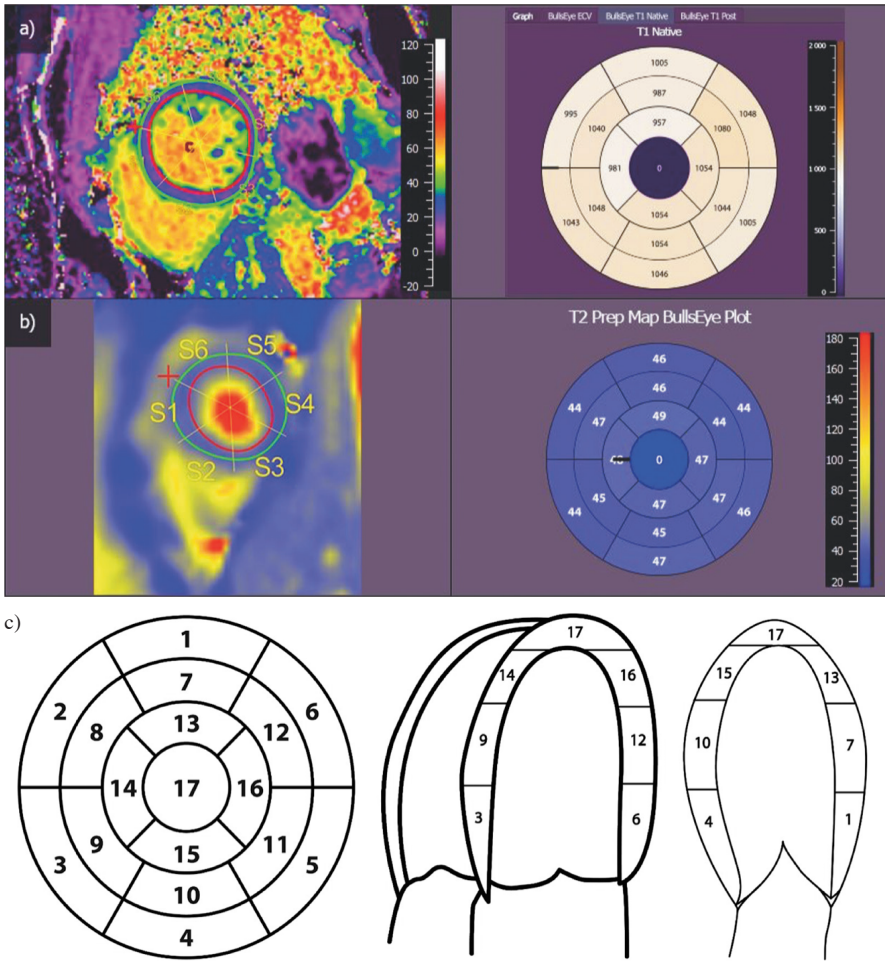

Fig. 1. a: T1 native relaxation time, extracellular volume fraction (ECV); **b**: T2 relaxation time analyses using Medis software. Manual drawing of the endomyocardial and epimyocardial borders of the left ventricle marks the midmyocardium for relaxation time analyses and ECV calculation.
c: an example picture of the American Heart Association (AHA) 17-segment model on a bull's-eye display (left), in the four-chamber plane and two-chamber plane (right) (25, 41).

control group was otherwise identical, but gadolinium-enhanced sequences were excluded for ethical reasons.

Image analysis

Experienced cardiac radiologists (certified EACVI level 3, S.K. or M.H.) approved all the reports and measurements blindly without clinical data. The volumetric analyses, segmental T1 and T2 mapping according to the American Heart Association 17-segment model (25), and ECV quantification were performed with Medis Suit MR (version 4.0.24.4, Medis Medical Imaging systems, Leiden, Netherlands) (Figure 1). Left atrium (LA) volume was calculated using a standard biplane method (26, 27). Two independent analysts completed T1, T2 and ECV mapping analyses. Segments with obvious artifacts were excluded. In T1 and T2 mapping, the agreement between the observers was excellent (ICC for global T1 0.9, segmental variance 0.7-0.9; for global T2 0.9, segmental variance 0.7-0.9). For ECV quantification, the agreement was not sufficient, and the ECV maps were generated in consensus.

Statistical analysis

All statistical analyses were performed using SPSS software (v. 28, IBM SPSS Statistics, Corp., Armonk, New York, USA). An age- and sex-matched (with 10-year tolerance) control for each patient with complete CMR data was selected from a pool of 69 controls using SPSS. One patient remained unmatched. Data are described with median with interquartile range (IQR, [Q_1, Q_3]). Due to non-normal distribution of the data and small sample size nonparametric tests were used.

Statistical significance between variables was evaluated using independent-samples Mann-Whitney U, Kruskal-Wallis test, Wilcoxon's test for paired samples, Chi-Square, Fisher's exact and McNemar tests, where appropriate. A univariate and multivariate general linear model were drafted from clinical factors; age, sex, heart rate, body mass index (BMI), body surface area (BSA), blood pressure, hypertension, Diabetes mellitus, smoking status, duration of symptoms, group A status, DAS28-CRP score, number of swollen joints, CRP, RF and ACPA. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant.

Table I. Baseline characteristics.

	RA patients (n=39)	Controls (n=38)	p-value
Age (years)	58.1 [47.0, 66.1]	54.0 [42.1, 60.6]	<0.001
Gender (males), n (%)	14 (35.9)	14 (36.8)	
Current smokers, n (%)	9 (24.3)	1 (3.8)	0.167
Ex-smokers, n (%)	12 (32.4)	5 (20.8)	0.293
Type 1 diabetes, n (%)	2 (5.4)	0	
Type 2 diabetes, n (%)	2 (5.4)	0	
Hypertensive disease, n (%)	7 (18.9)	1 (4.2)	0.909
BMI (kg/m^2)	26.4 [23.5, 29.1]	25.0 [22.6, 27.8]	0.204
BSA (m^2)	1.96 [1.74, 2.10]	1.94 [1.75, 2.09]	0.446
Heart rate (bpm)	73.3 [67.0, 83.0]	66.3 [61.0, 78.0]	0.015
Systolic blood pressure (mmHg)	150 [139, 165]		
Diastolic blood pressure (mmHg)	87 [83, 93]		
DAS28-CRP	3.86 [2.99, 4.72]		
Number of tender joints (28)	4.0 [2.0, 6.5]		
Number of swollen joints (28)	3.0 [2.0, 7.0]		
RF seropositivity, n (%)	31 (83.8)		
RF level (IU/ml)	58.0 [25.0, 167]		
ACPA seropositivity, n (%)	31 (88.6)		
ACPA level (U/ml)	300 [106, 300]		
ESR (mm/h)	16.0 [8.5, 29.0]		
CRP (mg/l)	4.0 [1.8, 12.5]		

Values are median [Q1, Q3] for continuous variables and number (%) for categorical variables.
RA: rheumatoid arthritis; DAS28-CRP: Disease Activity Score-28 with CRP; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; BMI: body mass index; BSA: body surface area; bpm: beats per minute; mmHg: millimetre of mercury; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Cardiac magnetic resonance (CMR) imaging results of patients and controls.

	RA patients (n=39)	Controls (n=38)	p-value
LV EDV index (ml/m^2)	77.9 [69.1, 88.8]	80.9 [71.9, 90.3]	0.690
LV ESV index (ml/m^2)	32.0 [24.3, 36.3]	28.8 [25.1, 34.4]	0.286
LV EF (%)	61.2 [56.2, 64.6]	61.6 [59.5, 65.1]	0.071
LV mass index (g/m^2)	46.9 [43.6, 54.9]	48.1 [44.1, 52.7]	0.712
Left atrium volume (biplane)	71.0 [57.0, 84.0]	63.5 [47.0, 72.0]	**0.020**
Left atrium (cm^2)	23.0 [20.0, 26.0]	21.7 [19.7, 24.0]	0.312
RV EDV index (ml/m^2)	74.1 [65.5, 83.8]	87.2 [76.1, 102.5]	**<0.001**
RV ESV index (ml/m^2)	28.6 [22.1, 32.9]	36.0 [28.1, 42.1]	**0.002**
RV EF (%)	61.7 [55.9, 69.2]	58.9 [52.9, 62.8]	**0.034**
Right atrium (cm^2)	21.0 [18.0, 23.0]	20.0 [18.3, 23.3]	0.743
Oedema n (%)	0		
Myocardial scars n (%)	2 (5.1)		
Pericardial effusion n (%)	0	0	
Pleural effusion n (%)	2 (5.1)	0	

Values are median [Q1, Q3] for continuous variables and number (%) for categorical variables.
LV: left ventricle; RV: right ventricle; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction; SV: stroke volume.

Results

Baseline characteristics

The baseline characteristics of both the ERA patient and control groups are presented in Table I. The median time from the onset of RA symptoms to CMR was 139 [104, 256] days. The majority of ERA patients were RF positive (83.8%) and ACPA positive (88.6%). The median value of DAS28-CRP was 3.86; 12 patients had a value <3.2 (remission or low disease activity), 19 patients ≥3.2 but <5.1 (moderate disease activity), and 6 patients ≥5.1 (high disease activity).

After the CMR scan, 37 (94.9%) of ERA patients began mono- and/or combination therapy with csDMARDs (methotrexate, sulfasalazine, hydroxy-

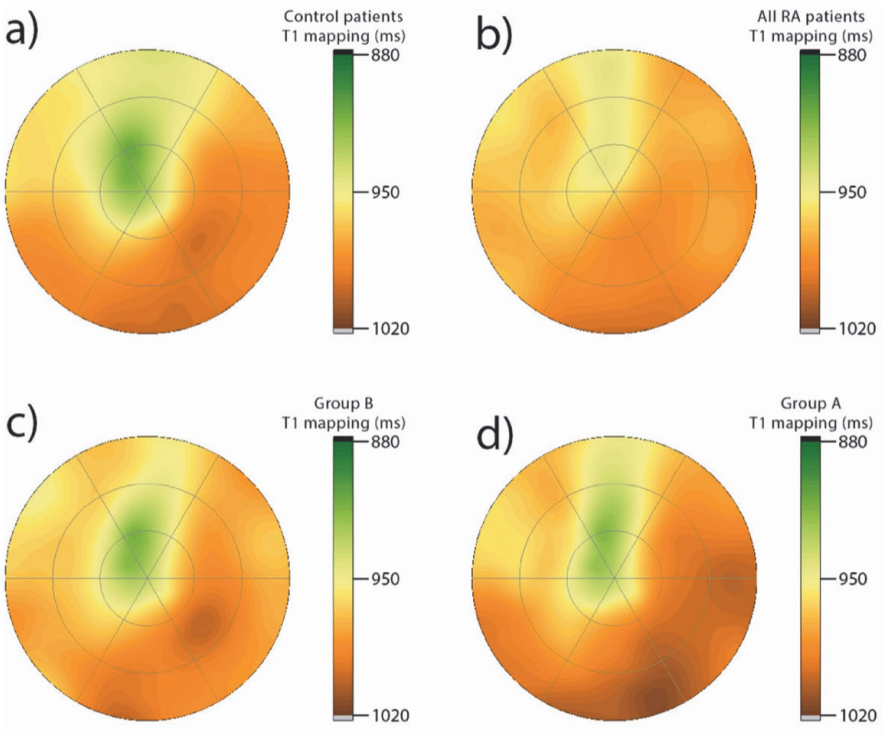

Fig. 2. Myocardial heat map AHA 16 segment bull's-eye diagrams of the median differences (ms) between segmental T1 relaxation time in **a**) healthy control subjects, **b**) all early rheumatoid arthritis (ERA) patients, **c**) ERA group B and **d**) ERA group A (DAS28-CRP ≥ 3.2 with positive autoantibodies ACPA and RF).

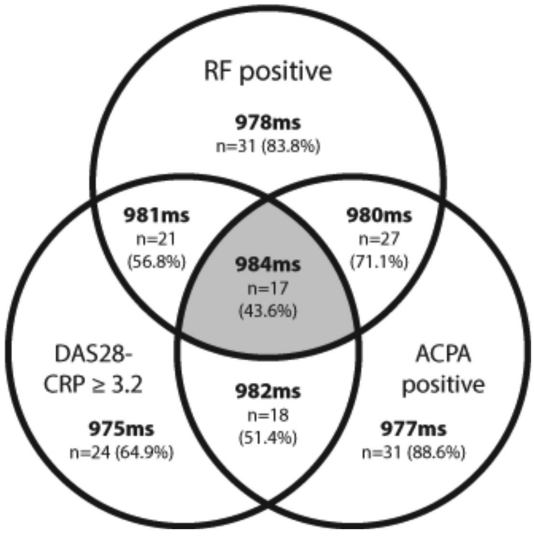

Fig. 3. Venn diagram of global T1 relaxation times in early rheumatoid arthritis (ERA) patients with seropositive rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) and/or Disease Activity Score-28 with CRP score ≥3.2.
Group A is coloured grey; group B is represented by the white background.

chloroquine and oral glucocorticoids), none of the RA patients began treatment with biological disease-modifying anti-rheumatic drugs (bDMARDs).

Conventional CMR results

No significant differences in LV volumetric parameters were detected between patients and controls (Table II). Left atrium volume was larger in the ERA patients than in controls (71.0 [57, 84] ml *vs*. 63.5 [47, 72] ml, p=0.020), respectively. Right ventricle (RV) end-diastolic volume index (87.2 [76, 103] ml/m^2 *vs*. 74.1 [66, 84] ml/m^2, p<0.001) and RV end-systolic volume index (36.0 [28, 42] ml/m^2 *vs*. 28.6 [22, 33] ml/m^2, p=0.002) were significantly reduced in ERA patients compared to healthy controls, but ERA patients had better RV EF (61.7 [56, 69] % *vs*. 58.9 [53, 63] %, p=0.034).

Two of the ERA patients (5.1%) presented with myocardial scars and two (5.1%) with pleural effusions at the CMR. One of the patients had a non-ischaemic scar suspect for previous myocarditis. The second patient had a non-ischaemic scar that remained unspecific. One patient with minor unilateral pleural effusion had a possible history of pleuritis, and the other patient had a minor bilateral non-specific effusion.

CMR T1 mapping

The distribution of global T1 relaxation times in the myocardium in ERA patients and healthy controls is demonstrated as a heat map diagram in Figure 2. The ERA patients and controls had no difference in the global T1 relaxation time (Table III). In more detailed analyses according to myocardial segments T1 relaxation time of the basal

Table III. Results of global myocardial mapping analyses.

	All ERA patients (n=39)	Controls (n=38)	p *	ERA group A (n=17)	ERA group B (n=22)	p **	p ***
T1 (ms)	972 [957, 989]	979 [960, 991]	0.769	987 [965, 1003]	970 [947, 985]	0.052	**0.041**
T2 (ms)	46.3 [44.5, 47.3]	47.5 [45.5, 49.2]	0.078	46.4 [44.2, 47.4]	46.2 [44.9, 47.1]	0.715	0.100
ECV (%)	25.3 [23.6, 26.1]	-	-	25.4 [24.9, 25.9]	24.9 [23.0, 26.3]	0.328	-

Values are median [Q1, Q3].
ERA: early rheumatoid arthritis; ECV: extracellular volume fraction.
p*: p-value of all ERA patients *vs*. controls; p**: p-value of ERA group A *vs*. group B; p***: p-value of ERA group A *vs*. healthy controls.

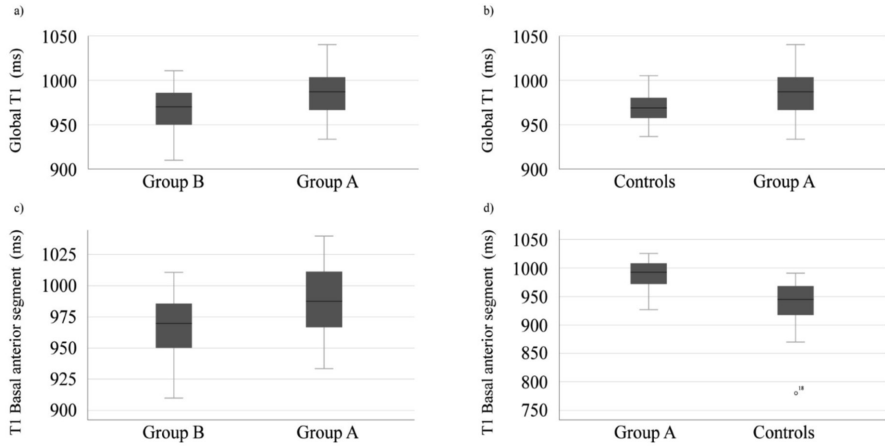

Fig. 4. Global T1 relaxation time in treatment-naive **a**) group B and group A of early rheumatoid arthritis (ERA) patients and **b**) group A and their age- and sex-matched controls and **c**) in basal anterior segment in group A and B.

anterior segment was statistically significantly longer in ERA patients than in controls (978 [933, 1004] ms *vs*. 960 [924, 977] ms, p=0.035, respectively. For details, see Supplementary Table S1, Fig. 1 a-b.). Figure 3 demonstrates the global T1 values according to disease activity and autoantibody positivity. Patients with DAS28-CRP score ≥3.2, positive RF, and positive ACPA (group A) had higher global T1 than patients with just one or two of these characteristics (group B).

The ERA patients in group A had significantly longer global T1 relaxation time than their age- and sex-matched controls (987 [965, 1003] ms *vs*. 979 [960, 991] ms, p=0.041, respectively (Fig. 4). In segmental analyses, the statistically significant and greatest median differences in T1 relaxation times localised in the basal anterior, basal inferior, basal inferolateral, basal anterolateral, mid inferior and mid anterolateral segments (Suppl. Table S1, Fig. 1c). Group A ERA patients also had a somewhat longer global T1 relaxation time than patients in group B, but the difference remained statistically insignificant (987 [965, 1003] ms *vs*. 970 [947, 985] ms, p=0.052). When analysed segmentally, however, the difference reached statistical significance in basal anterior, basal inferior, and basal inferolateral segments (Suppl. Table S1).

Our study focused on the association between global T1 relaxation times and clinical factors (Table IV). In univariate general linear models, global mean T1 relaxation times were slightly longer in women, in patients with lower body surface area (BSA) and in group A, the differences being statistically significant (p=0.003, p=0.030 and p=0.036, respectively). These associations remained statistically significant, when combined in a multivariate general linear model additionally adjusted for age (p=0.016 for female sex and p=0.014 for group A status). Systolic or diastolic blood pressure showed no correlation with elevated T1 relaxation times in ERA patients.

CMR T2 mapping and ECV quantification

In T2 relaxation times, no statistically significant difference was detected between neither ERA patients and controls (Table III) nor between group A and group B patients. Similarly, ECV values were equal between the two RA patient groups.

Discussion

This prospective cohort study showed that regional myocardial changes were detectable by CMR T1 mapping already at the time of RA diagnosis. The subtle changes in T1 relaxation times were detectable mostly in the basal segments and were most evident in group A patients with moderate to severe disease (DAS28-CRP≥3.2) and both positive RF and ACPA. In a multivariate adjusted model, the changes in global T1 relaxation times were independently associated with female sex and group A status. The ECV and T2 relaxation times were similar both in the two ERA groups and in all the ERA patients compared to controls.

In addition to the global T1 and T2 relaxation times and ECV values of the myocardium, we also present the myocardial T1 mapping results for each myocardial segment, as some segments may be more susceptible to diffuse fibrosis than others. When only global myocardial mean or median T1 and T2 values are presented, the first signs of fibrosis and inflammation may be missed, as the effect of one segment on the mean of 16 segments is small. To address this, we completed the T1 analysis segment by segment. Indeed, in segmental analyses, we demonstrated a more pronounced lengthening of global T1 in the basal anterior, basal inferior, and basal inferolateral segments in group A ERA patients when compared with the other (group B) ERA patients. Between healthy controls and patients in group A, T1 relaxation times were significantly longer in the basal anterior, basal inferior, basal inferolateral, basal anterolateral, mid inferior, and mid anterolateral segments. Our findings indicate that especially the basal anterior, basal inferior, and basal inferolateral regions may be the most vulnerable for diffuse fibrosis in ERA patients.

Some myocardial illnesses manifest with different patterns of localisation, for example, acute myocarditis tends to express subepicardial LGE at the basal inferolateral wall. The mild basal and midventricular local increase in T1 relaxation times in ERA patients could, in fact, be the pathognomonic pattern of cardiac manifestations in RA. However, further studies with larger patient populations are required to evaluate this assumption.

In this study, the ERA patients showed similar T2 and ECV results in both groups and when compared to healthy controls. Studies by Ferreira *et al*. (28, 29) demonstrated the superior sensitivity of native T1 compared to T2-weighted imaging and LGE in detecting inflammation in acute myocarditis. This may, indeed, be one mechanism behind the observed difference, as RA patients have an elevated risk of myo-

Table IV. Associations of clinical factors with the global mean T1 relaxation time. (n=39).

	Univariate models				Multivariate model			
	B	95% CI		P	B	95% CI		B
		Lower	Upper			Lower	Upper	
Age	-0.254	-1.132	0.624	0.561	-0.297	-1.069	0.465	0.440
Female sex	28.076	10.535	45.616	**0.003**	28.466	5.622	51.310	**0.016**
BMI (kg/m^2)	-0.024	-2.240	2.192	0.983				
BSA (m^2)	-47.133	-89.448	-4.818	**0.030**	4.028	-47.881	55.938	0.876
Heart rate (bpm)	0.192	-0.850	1.234	0.711				
Systolic blood pressure (mmHg)	-0.177	-0.750	0.396	0.535				
Diastolic blood pressure (mmHg)	-0.027	-1.046	0.992	0.958				
Hypertension	4.512	-21.827	30.850	0.730				
Diabetes mellitus	17.623	-13.153	48.399	0.253				
Smoking	-5.153	-24.422	14.116	0.591				
Duration of symptoms	1.419	-1.699	4.537	0.361				
ERA Group A*	19.679	1.365	37.993	**0.036**	21.831	4.651	39.011	**0.014**
DAS28-CRP at baseline	-1.705	-10.755	7.344	0.704				
Swollen joints (28)	-0.754	-3.429	1.921	0.570				
CRP	-0.416	-0.811	-0.022	**0.039**				
RF	29.533	4.497	54.570	**0.022**				
ACPA	21.745	-9.779	53.268	0.170				

*Patients with positive RF and ACPA and DAS28-CRP≥3.2 formed ERA group A.
BMI: body mass index; BSA: body surface area; DAS28-CRP: Disease Activity Score-28 with CRP; DAS28: Disease Activity Score-28; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies.

carditis. The myocardial changes in our ERA population were subtle, possibly explaining why they remained undetectable in T2 and ECV.

Although changes in myocardial function in ERA patients have been previously studied (13, 30, 31), research concerning myocardial mapping in this patient group is limited. Contrary to many previous studies on RA patients, our cohort consists of treatment-naïve ERA patients who completed CMR soon after RA diagnosis. In previous studies RA disease activity and severity have correlated with impaired cardiac function (31, 32), prolonged T1 relaxation times and increased ECV in patients with established RA (12) and impaired myocardial strain in ERA patients (13, 31). Indeed, our ERA patients with an active disease, with DAS28-CRP ≥3.2, together with positive autoantibodies ACPA and RF, presented with longer T1 relaxation times compared to patients with milder findings already at the time of diagnosis.

In a study by Koivuniemi *et al*. (33) female ERA patients exhibited prolonged T1 relaxation times compared to healthy controls one year after starting treatment. In our study, women also presented with slightly higher T1 relaxation times independently of disease activity, possibly portraying previously reported gender-related differences in T1 values (34).

The ERA patients in our study presented with lower RV end-systolic and RV end-diastolic volumes together with higher heart rate when compared to the healthy controls. In a study by Bradham *et al*. (35) RA patients also demonstrated reduced RV end systolic and end-diastolic volumes. Higher heart rate has also been reported previously and may be caused by cardiac deconditioning (36). Of interest, in the study by Bradham *et al*. patients had established RA (disease duration 10 years), whereas our patients had ERA.

Prolonged T1 relaxation times and increased ECV are markers of myocardial fibrosis and inflammation (28). Previous studies have shown that RA patients are at risk of developing focal and diffuse myocardial fibrosis (7, 12) and heart failure (HF) (37, 38). Myocardial fibrosis tends to develop slowly, and it is usually seen years after the disease onset (39). The results on T1 values in RA patients with low to moderate disease activity have remained contradictory, which may be explained by differences in disease activity and treatment, including the use of anti-TNF agents (30, 35, 40).

Our study included only patients without any known CVD, possibly leading to disqualification of the patients most prone to CVD, including some early myocardial changes. In fact, in our study, only those patients with a more active disease form, with DAS28-CRP ≥3.2 with positive autoantibodies ACPA and RF, showed any signs of prolonged T1, while most of the ERA patients had similar T1 values as the healthy controls, demonstrating that the overall myocardial changes in patients without prior CVD are minimal.

Limitations

The main limitation of this study is the relatively small number of study patients. The prospectively recruited cohort is, however, well representative of the eligible patients within the Helsinki University Hospital area. There are also some clinical differences between the two cohorts. The healthy controls were slightly younger than the ERA patients. However, since the T1 relaxation times showed no correlation with age, this does not explain the observed difference in segmental T1 analyses. Also, single blood pressure measurements were not available from the control cohort. A single blood pressure measurement registered in a clinical setting

may be unrepresentative of actual blood pressure levels, however, and a history of hypertensive disease was recorded from both groups. In addition, myocardial mapping is prone to motion artifacts especially in quite thin myocardium, which is a common feature in RA patients.

Conclusions

This study indicates that already at the time of RA diagnosis, ERA patients with DAS28-CRP ≥3.2 with positive autoantibodies ACPA and RF are at risk for myocardial changes, visible in CMR as prolonged T1 relaxation times. These early, mild myocardial changes marked by prolonged T1 relaxation times are mainly located in the basal segments. Thus, a segmental reporting style could be useful when estimating the first signs of myocardial fibrosis. Future studies in larger cohorts will reveal whether effective medical therapy can completely prevent or even attenuate myocardial damage also in patients with a more active disease form.

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