

Left Ventricular Regional Dysfunction Using Cardiac Magnetic Resonance Imaging in Rheumatoid Arthritis Patients Without Cardiac Symptoms: Comparison Between Methotrexate and Biologics Treatment Groups

To the Editor:

In patients with rheumatoid arthritis (RA), cardiac involvement such as myocarditis and myocardial infarction is common. This cardiac involvement may have serious consequences and can contribute to worsening of a patient's cardiac-related morbidity and mortality^{1,2}. Importantly, myocardial disease is typically clinically silent³, only manifesting as myocardial dysfunction after an extended preclinical phase. Cardiovascular magnetic resonance (CMR) is a sensitive noninvasive diagnostic technique that can identify subclinical myocardial structural and functional abnormalities. No systematic studies of left ventricular (LV) regional function by CMR have been conducted in patients with RA. We sought to use a CMR approach to detect LV regional dysfunction in RA patients without cardiac symptoms compared to healthy volunteers. Further, we compared LV regional function between patients with RA who were treated with methotrexate (MTX) plus biologics compared to those treated only with MTX.

Consecutive patients with RA as defined by the American College of Rheumatology classification criteria were recruited from the outpatient rheumatology clinic at Itabashi Chuo Medical Center between September 2009 and December 2012. Healthy volunteers were also included in the study. Because the regional myocardial function is related to age, we have included only subjects less than 70 years old. All patients with RA received either MTX or MTX plus the biologics infliximab (IFX) or tocilizumab (TCZ). All patients and volunteers underwent nonenhanced CMR with steady-state free-precession (SSFP) cine magnetic resonance imaging (MRI) on a 1.5 Tesla MRI scanner. Peak radial strain (Err, %) of the left ventricle in the middle cavity on the short axis was calculated by dedicated software (QI Imaging) using SSFP cine MRI. Strain measurements are expressed as the fractional change in length from the resting state to the state following myocardial contraction⁴. Strain analysis using this feature tracking method^{5,6} of cine MRI is a feasible and unique approach for comprehensive clinical assessment of regional cardiac function.

We compared 41 patients with RA (85.4% female; mean age 56.8 ± 12.1 yrs) with 10 healthy volunteers (100% female; mean age 55.7 ± 4.5 yrs). A total of 24, 7, and 10 of those received MTX (8.2 ± 1.7 mg), MTX (8.6 ± 1.8 mg) plus IFX (3 mg/kg), or TCZ (8 mg/kg), respectively. The Disease Activity Score in 28 joints (DAS28) was significantly higher in the MTX group than in the biologics group (4.5 ± 1.10 vs 2.9 ± 1.6; *p* = 0.002). There were no significant differences in baseline characteristics such as age, sex, RA duration, anticitrullinated peptide antibodies, rheumatoid factor, dosage of MTX, and the proportion of prednisolone users (Table 1). Mean peak Err of all segments was significantly lower in patients with RA than in control subjects (0.56 ± 0.17 vs 0.69 ± 0.10, *p* = 0.028; Figure 1). Mean peak Err in the MTX group was significantly lower than in the control group (*p* = 0.014), and there was not any significant difference in mean peak Err between the biologics and the control group (*p* = 0.424). Mean peak Err was significantly higher in the TCZ group than the MTX group (*p* = 0.036). Abnormal peak Err in patients with RA was significantly associated with longer duration (*r* = -0.69, *p* = 0.001), and was mildly correlated to erythrocyte sedimentation rate (ESR; *r* = -0.44, *p* = 0.36; data not shown).

To our knowledge, this is the first investigation showing that myocardial radial strain of LV as calculated by cine CMR was impaired in RA patients who had no clinical evidence of cardiovascular (CV) disease. Cardiac dysfunction may arise from a number of distinct processes, including microvascular and macrovascular coronary ischemia, myocardial inflammation (myocarditis), and/or myocardial fibrosis, any of which may be active in RA. Regional dysfunction might be observed with CMR prior to myocarditis, myocardial fibrosis or myocardial infarction, electrocardiogram abnormalities, and chest pain. Therefore, strain measurement by

Table 1. Baseline characteristics of patients with DMARD and biologics used, and of controls. Data are mean ± SD unless otherwise specified.

Characteristic	Controls, n = 10	DMARD, n = 24	Biologics, n = 17	p
Age, yrs*	55.7 ± 4.5	59.0 ± 2.2	53.7 ± 2.7	0.278
Male/female, n††	0:10	2:22	4:13	0.144
RA duration, mos†	—	79.5 ± 108.3	50.1 ± 73.5	0.643
Anti-CCP, u/ml†	—	102.9 ± 19.2	44.9 ± 45.3	0.104
RF, u/ml†	—	56.3 ± 26.4	90.0 ± 31.4	0.672
DAS28-ESR†	—	4.5 ± 1.0	2.9 ± 1.6	0.002
MTX, mg†	—	8.2 ± 1.7	8.6 ± 1.8	0.434

†: Wilcoxon rank sum test. ††: Fisher's exact test. *: Kruskal-Wallis test. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; DAS-28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; MTX: methotrexate; anti-CCP: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor.

CMR could be a more sensitive method to assess early myocardial involvement in RA. MRI provides a highly accurate and sensitive method for evaluating changes in regional ventricular function. There has been a constructive report that assessed subclinical atherosclerosis using imaging modality⁷. By combining CMR and other imaging modality methods, we might be able to predict and evaluate CV diseases at an early stage. Our preliminary data lend support for a high prevalence of LV regional dysfunction in patients with active RA versus control subjects. Regional dysfunction was significantly more prominent in the MTX group than in the TCZ group (*p* = 0.036). There are reports that treatment with MTX reduces CV events⁸. However, there are no reports that analyzed the effect of MTX on regional myocardial function. Consequently, it is necessary to further explore this matter with an increased number of patients. In our study, there were many patients with high disease activity who were treated with MTX, and severe inflammation in patients with high activity might be the reason for low regional myocardial function in those taking MTX. However, there was no significant difference between regional myocardial function in the TCZ group and the control group, suggesting that myocardial abnormality was normalized as TCZ lessened the disease activity of RA. Further, changes in ESR were mildly associated with changes in Err. These data suggest that the reduction of inflammation may also help inhibit the progression of myocardial dysfunction.

Our previous study has shown that cardiac abnormalities indicating microvascular and macrovascular coronary ischemia, myocarditis, and/or myocardial fibrosis are frequent in asymptomatic patients with RA, as revealed by pharmacological stress perfusion and delayed-enhanced MRI⁹. Our present study has suggested that nonenhanced CMR with cine MRI, analyzing LV regional function, may be useful to detect subclinical myocardial involvement in RA. Noninvasive CMR would have the potential to diagnose cardiac involvement in RA.

Previous work on assessing the mortality rate of CV disease has looked at inflammatory markers and traditional risk factors¹⁰. We showed that longer duration was significantly associated with LV regional dysfunction. ESR was mildly associated with LV regional dysfunction. Early diagnosis of regional dysfunction and therapy to reduce inflammation might be useful to improve myocardial abnormalities.

Our study suggested a high prevalence of subclinical LV regional dysfunction in active RA patients without cardiac symptoms, and that the reduction of disease activity of RA may help inhibit the progression of myocardial involvement. Evaluation of LV regional function by CMR appears to be useful for detecting subclinical myocardial involvement in patients with RA, allowing the selection of patients who may benefit from more aggressive therapies to reduce RA activity and contributing to the improvement of patient outcomes.

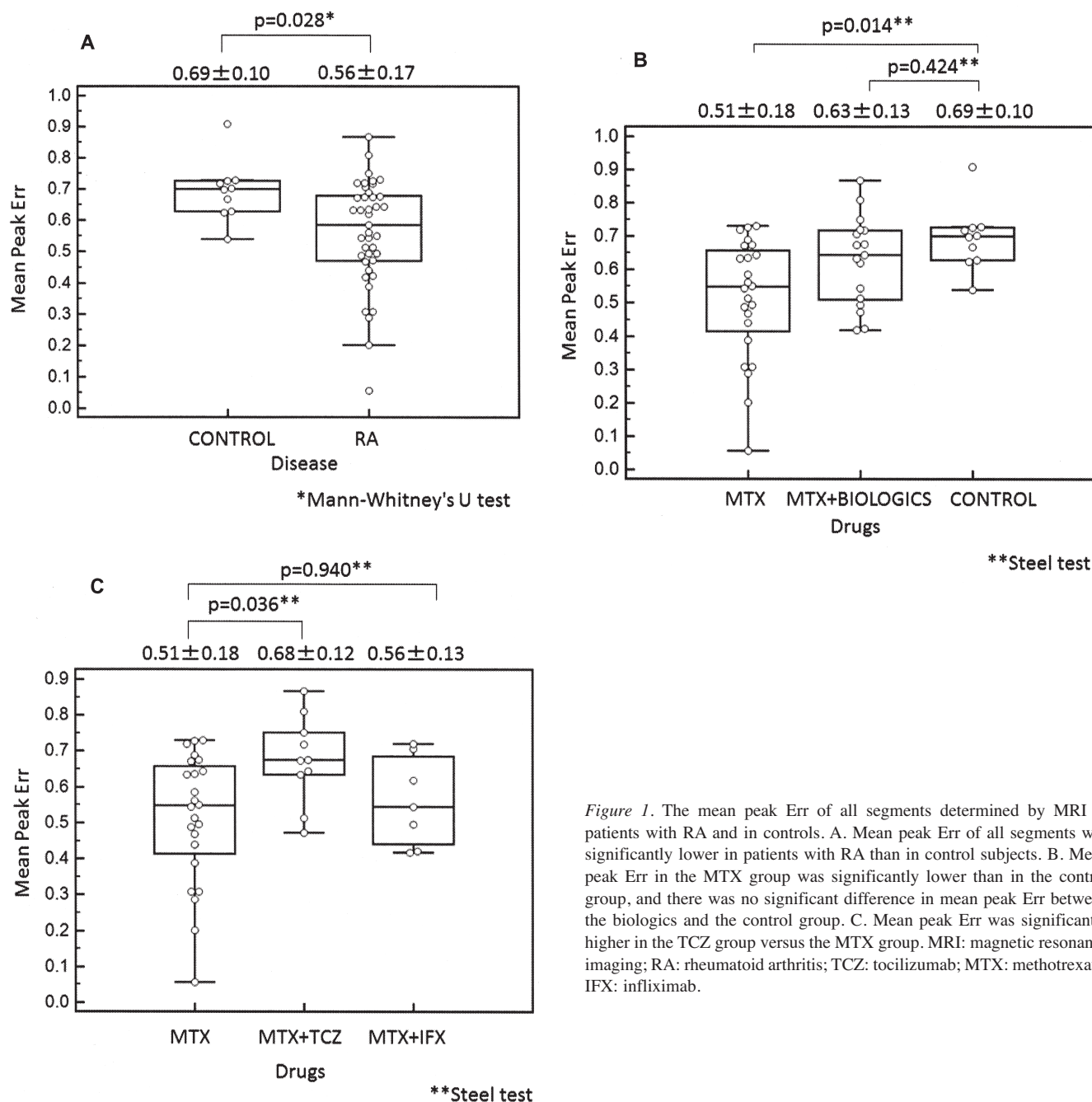


Figure 1. The mean peak Err of all segments determined by MRI in patients with RA and in controls. A. Mean peak Err of all segments was significantly lower in patients with RA than in control subjects. B. Mean peak Err in the MTX group was significantly lower than in the control group, and there was no significant difference in mean peak Err between the biologics and the control group. C. Mean peak Err was significantly higher in the TCZ group versus the MTX group. MRI: magnetic resonance imaging; RA: rheumatoid arthritis; TCZ: tocilizumab; MTX: methotrexate; IFX: infliximab.

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