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EDITORIAL COMMENT

# Rheumatoid Arthritis: Mapping the Future*

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*Prediction is very difficult.*
*Especially if it is about the future.*
—Niels Bohr (1)

Rheumatoid arthritis (RA) is a common autoimmune condition presenting with symmetric polyarticular arthritis and affecting 0.5% to 1.0% of the population (2). It is associated with significant and progressive disability, extra-articular systemic complications, high socioeconomic costs, and early death (3). Cardiac manifestations occur in up to 60% of patients with RA and include pericarditis, myocarditis, ischemic heart disease, and heart failure, leading to a doubling of the cardiac mortality risk compared with that of healthy control subjects (4). Life expectancy is reduced by ~5 to 10 years, and 35% to 50% of this excess mortality seems to result from cardiovascular disease (5). Despite this finding, conventional cardiac risk factors only partly explain the increased risk, making the identification of individuals likely to experience a future cardiac event challenging. Detecting cardiac disease at an early stage (before the heart is permanently damaged) has important clinical implications because targeted pharmacotherapy has the potential to improve prognosis.

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In this issue of *iJACC*, Ntusi et al. (6) present findings from a cardiac magnetic resonance (CMR) study of 39 patients with RA and no known cardiac involvement compared with 39 matched control subjects. The authors' goal was to identify a novel CMR biomarker for assessing cardiac involvement in patients with RA. The authors should be commended for completing a well-designed prospective study and undertaking careful myocardial tissue characterization. Using a previously validated sequence (7), native and post-contrast T1 maps were acquired, enabling calculation of extracellular volume fraction, with T2-weighted and late gadolinium enhancement (LGE) imaging for identification of edema and replacement fibrosis, respectively. In addition, routine CMR parameters (including ventricular dimensions and volumes, ejection fractions, and myocardial strain) were acquired.

LGE is a marker of adverse prognosis in many patient populations, including those with cardiomyopathy (8), valvular disease (9), coronary artery disease, and congenital heart disease (10). However, the presence of LGE correlates histologically with replacement fibrosis; it commonly occurs late in the disease process and is believed to be irreversible. Because LGE relies on the differential signal intensity between normal and abnormal myocardium, it can only usually detect focal fibrosis. It has a relatively low sensitivity in identifying homogeneously abnormal diffuse myocardial fibrosis secondary to progressive accumulation of collagen in the interstitial space (11). The novel T1-mapping methods are based on a modified Look-Locker sequence, as described by Messroghli et al. (12); these methods have emerged as promising CMR techniques that enable the identification of diffuse fibrosis. The importance of identifying diffuse fibrosis is that it is potentially reversible with appropriate therapy, with a more tangible possibility for improvement in prognosis (11).

Studies in this area have expanded rapidly over the past few years, with differences in diffuse fibrosis burden seen between normal control subjects and patients with amyloid heart disease, Fabry's disease, valvular heart disease, cardiomyopathy, myocardial infarction, and other connective tissue diseases (including systemic lupus erythematosus and systemic sclerosis) (10). Importantly, the combination of native and post-contrast T1 maps and hematocrit enable calculation of extracellular volume (ECV) fraction, which has correlated well with expansion in ECV due to deposition of extracellular matrix proteins, including collagen and histologically identified diffuse fibrosis (7).

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Ntusi et al. (6) found that diffuse fibrosis, focal fibrosis, and inflammation can all be identified reliably with CMR in RA. In this study, 18 patients with RA (46%) had evidence of LGE, mostly of a patchy, nonischemic mid-wall pattern, although 2 patients (5%) had evidence of a previous silent myocardial infarction; epicardial coronary disease was confirmed on subsequent coronary angiography. There was a small difference observed in native T1 between RA patients and control subjects (973 ± 27 ms vs. 961 ± 18 ms; $p = 0.03$), but, more important, patients with RA had higher ECV than control subjects (30.3 ± 3.4% vs. 27.9 ± 2.0 ms; $p < 0.001$). At the same time, patients with RA had more areas of focal myocardial edema within the left ventricle (10% vs. 0%; $p < 0.001$), acknowledging that the increase in ECV, in the absence of infarction, could be either secondary to myocardial diffuse fibrosis or inflammation or possibly a combination of the 2 factors. Recent studies have also suggested that independent of etiology, an increase as small as 3% in ECV can be associated with significantly worse short-term outcomes in the general population and in patients with diabetes (13). Therefore, the findings by Ntusi et al. (6) have the potential to correctly identify early cardiac involvement in asymptomatic patients with RA, allowing stratification of patients into high- and low-risk groups. Furthermore, the authors found that both the degree of diffuse fibrosis and inflammation were elevated independently of the presence of LGE and correlated well with a validated RA disease activity score and diastolic and systolic myocardial strain; this supports the notion that T1 mapping could be used independently as a novel biomarker.

However, some limitations of the current study (6) prevent generalization of the results at this point. The aim is to produce a robust biomarker to predict outcome, whether from CMR and other imaging modalities or using blood biomarkers such as high-sensitivity troponin, B-type natriuretic peptide, ST2 cells, transforming growth factor-beta, or C-reactive protein. Comparison of T1 mapping with these markers will identify whether it can provide additional prognostic information. A simple blood biomarker is preferable to an expensive and lengthy CMR in identification of cardiac involvement, and its additive value against blood markers therefore needs to be established.

At a clinical level, it remains to be demonstrated that an increased ECV portends worse outcome in RA. The next step is therefore a prospective longitudinal outcome study. On the basis of the current data from other populations (13), one would expect this to be the case, but it needs to be confirmed. Finally, assuming that this is the case, it would be important to undertake CMR studies and serially monitor ECV in patients "on" and "off" treatment to establish whether additional therapies can alter ECV and improve prognosis as well as identify potential fluctuations in ECV with disease activity. However, "additional treatment" could arguably be immunomodulatory or cardioprotective in nature. We do not know at present which option, if any, might reduce ECV, and we need to investigate both avenues before we can establish what would be most beneficial for the RA population. Some answers will come from the CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) study, which is currently actively recruiting (14). Without a prospective outcome-driven multicenter study involving a pharmacological intervention showing benefit, it would be difficult to fully embrace T1 mapping for prognostic purposes in this cohort. To predict the future of patients with RA by using T1 mapping, as Niels Bohr would put it, "is difficult;" however, that future is potentially bright. At present, and while further supportive data are awaited, the threshold of undertaking CMR in RA patients could be appropriately lowered as the combination of T1 mapping, T2-weighted imaging, and LGE described by Ntusi et al. (6) can confirm silent coronary disease and identify early cardiac involvement.

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