

Cardiac Disease in Rheumatoid Arthritis — Can Cardiovascular Magnetic Resonance Imaging Depict the Janus Duality?



Rheumatoid arthritis (RA) is associated with premature mortality mainly attributed to cardiovascular disease (CVD)^{1,2}. Although ischemic heart disease was initially considered as the main cause of heart failure (HF) in this population^{3,4,5}, it failed to completely explain the high incidence of HF in RA. Over time, myocardial inflammation and/or fibrosis have become increasingly recognized as important pathophysiologic components underlining HF in patients with RA^{6,7}.

Cardiovascular magnetic resonance imaging (cMRI) is a noninvasive modality capable of using radiowave pulse sequences to characterize myocardial tissues regarding fibrosis and inflammation without the need for ionizing radiation exposure. Studies of cMRI suggested that a subset of patients with RA have focal scarring detected by late gadolinium enhancement (LGE) and diffuse fibrosis and increased extracellular volume (ECV) detected by T1 mapping^{8,9,10,11}. However, these studies were small and included few patients taking biological therapy. The inclusion of new cMRI indices in clinical practice, as proposed by the joint Society for Cardiovascular Magnetic Resonance/European Association for Cardiovascular Imaging paper¹², opened up new horizons in cardiovascular medicine. It is now clear that T1 and T2 mapping and ECV provide important knowledge into disease processes affecting the myocardium that otherwise can be difficult to detect¹³.

In ancient Roman religion, Janus was the god of duality. He was usually presented as having 2 faces, looking both to the future and the past, to beginning and end, good and bad. In this issue of *The Journal*, Bradham, *et al* documented using cMRI that the percentage of myocardial fibrosis in RA patients with low to moderate disease activity was similar to or less than that of a matched control group¹⁴. However, RA, like Janus, has 2 faces: one of low to moderate and another of severe activity. The authors claim that their results are further supported by clinical studies showing that patients with RA receiving tumor necrosis factor- α (TNF- α)

inhibition had a decreased risk of myocardial infarction, compared with those receiving only disease-modifying antirheumatic drugs¹⁵. It is nevertheless unclear whether this is due to reduced systemic inflammation or a specific anti-TNF effect at the atherosclerotic plaque level. The observed cardiovascular improvement appears to be associated with anti-TNF response, but anti-TNF agents have also been associated with an increased incidence of HF and/or rapid deterioration of heart function, potentially due to adverse events such as vasculitis and venous thromboembolism¹⁶. Further, European League Against Rheumatism (EULAR) moderate responders had equal risk of developing an acute coronary syndrome to that of EULAR nonresponders, that is, twice the risk compared with the general population¹⁷.

Another important point in the study by Bradham, *et al* is that LGE, native T1, and ECV are lower in patients with RA, when pathophysiologically one would expect greater burden of inflammation and subclinical myocardial involvement in patients with RA, as seen in previous studies^{6,8}. The 2 most important known factors of an increase in native T1 are edema (increase of tissue water due to acute infarction of inflammation) and expansion of the interstitial space (fibrosis due to myocardial infarction, cardiomyopathy, and amyloidosis)⁸. In contrast, the 2 most important known determinants of low native T1 values are lipid overload (as in Anderson-Fabry disease or lipomatous metaplasia, seen in chronic myocardial infarction) and iron overload¹³. Further, it is important to emphasize that native T1 values are a composite signal of myocytes and ECV with the potential of pseudonormalization of abnormal values (e.g., low native T1 values of Anderson-Fabry disease can be canceled out by inferolateral fibrosis)¹⁸. This indicates that the normal or lower-than-normal T1 mapping, presented by the authors as a proof of lack of cardiomyopathy, in RA could potentially be the result of lipomatous metaplasia, iron overload, or pseudonormalization. It should also be acknowledged that the association between lipid measures and the

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risk of CVD in RA is paradoxical, whereby lower total cholesterol and low-density lipoprotein (LDL) levels and lower atherogenic ratios are associated with increased cardiovascular risk¹⁹. Further, it is worth mentioning that ferritin, a protein involved in iron metabolism and a good indicator of iron stores in the body, is related to the development of atherosclerosis and this relationship is strengthened by the synergistic action between LDL cholesterol and elevated iron stores. Therefore, ferritin should be considered as an adjunctive risk factor for ischemic heart disease in RA and the potential role of iron in the development of RA cardiomyopathy should be reconsidered²⁰.

Until the aforementioned issues are clarified, the only clear finding from the study by Bradham, *et al* is that patients with RA who are well-controlled by biological agents have normal or lower T1 mapping values. However, normal cMRI values do not necessarily demonstrate the absence of cardiomyopathy. Further comparative studies, including cardiac autopsy and contrast-enhanced MRI, are needed to understand the underlying pathophysiology of cardiac disease in RA, and until more evidence becomes available, seemingly normal cMRI indices should not automatically be assumed to indicate the absence of cardiomyopathy.

The only imaging modality capable of illustrating the underlying “Janus-duality” in various diseases, including RA, is cMRI using T1 mapping and ECV. However, technical limitations, pseudonormalization patterns, and the specific pathophysiologic background of each disease should be carefully considered before final conclusions are drawn.

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