Editorial

# 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 paper[12], 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 detect[13].

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 group[14]. 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 drugs[15]. 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 thromboembolism[16]. 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 population[17].

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 overload[13]. 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

*See* Absence of cardiomyopathy by cMRI in RA, *page 1078*

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 risk[19]. 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 reconsidered[20].

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.

**SOPHIE I. MAVROGENI**, MD, PhD, FESC;
**GEORGE MARKOUSIS-MAVROGENIS**, BSc (Hons);
**GENOVEFA D. KOLOVOU**, MD, PhD, FESC, SFASA;
Onassis Cardiac Surgery Center,
Athens, Greece.

Address correspondence to Dr. S.I. Mavrogeni, 50 Esperou St., 175-61, P. Faliro, Athens, Greece. E-mail: soma13@otenet.gr

## REFERENCES

1. Giles JT, Fernandes V, Lima JA, Bathon JM. Myocardial dysfunction in rheumatoid arthritis: epidemiology and pathogenesis. Arthritis Res Ther 2005;7:195-207.
2. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722-32.
3. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005;52:3045-53.
4. Chung CP, Avalos I, Raggi P, Stein CM. Atherosclerosis and inflammation: insights from rheumatoid arthritis. Clin Rheumatol 2007;26:1228-33.
5. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737-45.
6. Mavrogeni S, Bratis K, Sfendouraki E, Papadopoulou E, Kolovou G. Myopericarditis, as the first sign of rheumatoid arthritis relapse, evaluated by cardiac magnetic resonance. Inflamm Allergy Drug Targets 2013;12:206-11.
7. Mavrogeni S, Dimitroulas T, Bucciarelli-Ducci C, Ardoin S, Sfikakis PP, Kolovou G, et al. Rheumatoid arthritis: an autoimmune disease with female preponderance and cardiovascular risk equivalent to diabetes mellitus: role of cardiovascular magnetic resonance. Inflamm Allergy Drug Targets 2014;13:81-93.
8. Ntusi NA, Piechnik SK, Francis JM, Ferreira VM, Matthews PM, Robson MD, et al. Diffuse myocardial fibrosis and inflammation in rheumatoid arthritis: insights from CMR T1 mapping. JACC Cardiovasc Imaging 2015;8:526-36.
9. Holmstrom M, Koivuniemi R, Korpi K, Kaasalainen T, Laine M, Kuuliala A, et al. Cardiac magnetic resonance imaging reveals frequent myocardial involvement and dysfunction in active rheumatoid arthritis. Clin Exp Rheumatol 2016;34:416-23.
10. Kobayashi Y, Giles JT, Hirano M, Yokoe I, Nakajima Y, Bathon JM, et al. Assessment of myocardial abnormalities in rheumatoid arthritis using a comprehensive cardiac magnetic resonance approach: a pilot study. Arthritis Res Ther 2010;12:R171
11. Kobayashi H, Kobayashi Y, Yokoe I, Akashi Y, Takei M, Giles JT. Magnetic resonance imaging detected myocardial inflammation and fibrosis in rheumatoid arthritis: associations with disease characteristics and N-terminal pro-brain naturetic peptide levels. Arthritis Care Res 2017;69:1304-11.
12. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). Cardiovasc Magn Reson 2017;9:75.
13. Mavrogeni S, Apostolou D, Argyriou P, Velitsista S, Papa L, Efentakis S, et al. T1 and T2 mapping in cardiology: "mapping the obscure object of desire". Cardiology 2017;138:207-17.
14. Bradham W, Ormseth MJ, Elumogo C, Palanisamy S, Liu CY, Lawson MA, et al. Absence of fibrosis and inflammation by cardiac magnetic resonance imaging in rheumatoid arthritis patients with low to moderate disease activity. J Rheumatol 2018;45:1078-84.
15. Low AS, Symmons DP, Lunt M, Mercer LK, Gale CP, Watson KD, et al. British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) and the BSRBR Control Centre Consortium. Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76:654-60.
16. Tocci G, Goletti D, Marino V, Matucci A, Milano GM, Cantini F, et al. Cardiovascular outcomes and tumour necrosis factor antagonists in chronic inflammatory rheumatic disease: a focus on rheumatoid arthritis. Expert Opin Drug Saf 2016;15 Suppl 1:55-61.
17. Ljung L, Rantapää-Dahlqvist S, Jacobsson LT, Askling J. Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis. Ann Rheum Dis 2016;75:2087-94.
18. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. J Cardiovasc Magn Reson 2016;18:89.
19. Myasoedova E, Crowson CS, Maradit Kremers H, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482–7.
20. Mascitelli L, Pezzetta F. High iron stores and ischemic heart disease in rheumatoid arthritis and systemic lupus erythematosus. Am J Cardiol 2004;94:981.

J Rheumatol 2018;45:1073–4; doi:10.3899/jrheum.180242