# Cardiovascular Magnetic Resonance in Autoimmune Rheumatic Diseases: Translating the Greek Experience to the International Arena

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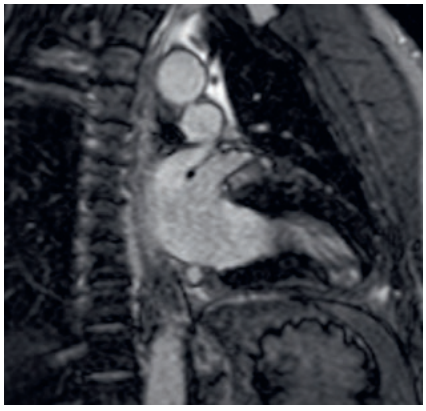
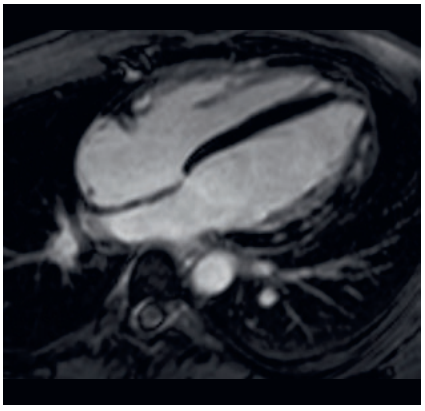
## Introduction

Autoimmune rheumatic diseases (ARDs) are a diverse group of diseases that result from the dysregulation of immune tolerance and the subsequent generation of inappropriate immune responses to self-antigens [1]. ARDs can be localized to individual organ systems or may manifest with generalized multi-system involvement and/or multi-organ dysfunction [1]. Recent years have seen a considerable increase in our understanding of the molecular processes underlying the pathophysiology of ARDs and clinical management has changed dramatically with the advent of novel monoclonal antibodies and small molecule inhibitors that can effect targeted immunomodulation in these patients [2]. Yet despite improvements in overall prognosis and quality of life, ARD patients are still more likely to die than the general population [3–10].

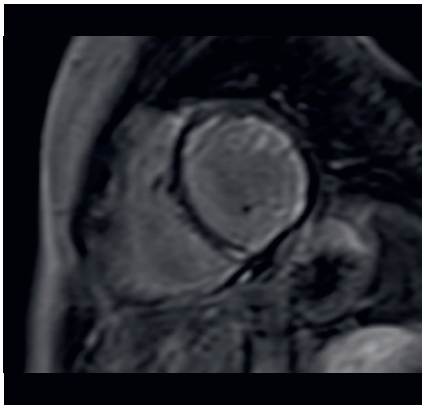
This increased mortality has partially been attributed to a higher incidence of cardiovascular disease (CVD) in ARD patients. Traditionally, most practice guidelines suggest that the additional CVD risk observed in these patients is a consequence of systemic inflammation compounded by uncontrolled comorbidities such as hypertension, diabetes mellitus/metabolic syndrome, dyslipidemia etc. [5]. The guidelines therefore advise appropriate control of these comorbidities as the optimal method for combating CVD in ARD patients [11]. However, it has also become apparent that autoimmune cardiomyopathy is not an uncommon disease manifestation in ARD patients, and in some cases is accompanied by autoimmune vasculitis, microvascular dysfunction or other vascular pathology, valvular disease, pericarditis, or non-bacterial endocarditis [9]. Interestingly, many of these types of autoimmune CVD can be completely asymptomatic. Even when they start causing symptoms, such as reduced functional capacity or fatigue, these might simply be attributed to constitutional symp-



**1** Transmural apical late gadolinium enhancement (LGE) due to myocardial infarction in a patient with rheumatoid arthritis.



**2** Subepicardial LGE in the lateral wall of the left ventricle in a patient with lupus myocarditis.



**3** Diffuse subendocardial LGE due to small-vessel vasculitis in a patient with systemic sclerosis.

toms caused by the administered treatments and/or the patient's overall inflammatory state [7]. When overt signs of cardiac or vascular dysfunction do manifest, it may often be too late to prevent permanent cardiac damage and/or deterioration to heart failure [9]. It is therefore imperative to maintain a high index of suspicion in the clinical setting and to ensure early identification of these manifestations, as initiation of additional immunomodulatory treatment might be necessary to bring them under control [12].

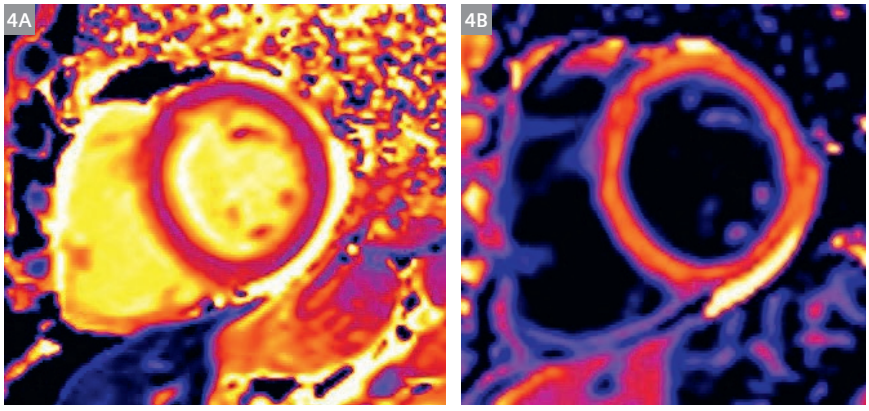
Nevertheless, a high index of suspicion alone cannot ensure early identification of all cases of autoimmune CVD in ARD patients, since such cases are often asymptomatic. Furthermore, an echocardiographic examination, which is often used as a first-line test for evaluating the cardiovascular system, has considerable limitations, such as limited spatial resolution and dependence on a sufficient acoustic window for optimal image acquisition [12]. Lastly, the left ventricular ejection fraction (LVEF) is often used by healthcare professionals as a rough measure of systolic function. However, LVEF is preserved in the majority of ARD patients with autoimmune CVD, and cannot be used reliably as a rule-out indicator [12]. A more sensitive diagnostic tool is therefore required to fill this gap.

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging modality that utilizes non-ionizing, radio-wavelength photons to generate high-quality images of human tissues [12]. CMR offers considerable advantages over other non-invasive imaging modalities when it comes to evaluating the cardiovascular system. It allows the determination of biventricular function with a high degree of accuracy and does not require an acoustic window. CMR can easily identify valvular and vascular abnormalities, enable the evaluation of myocardial perfusion without an exercise-based stress test, and, most importantly, characterize myocardial tissues with regard to edema and fibrosis [12]. The pathophysiological phenomena that should be identified – if present – in ARD patients include macro- or micro vasculopathy [9], myocardial inflammation [11–16], and myocardial fibrosis due to inflammation and/or myocardial infarction [13–16]. Based on the findings of the CMR examination, the acuity of any autoimmune inflammatory processes in the cardiovascular system can be estimated [13–16]. CMR additionally enables the identification of myocardial ischemia and/or subendocardial/transmural replacement or diffuse fibrosis, due to either macro- or micro-vascular coronary artery disease [12–17]. Furthermore, CMR can clarify the etiology of silent or overt heart failure, or cardiac rhythm disturbances [18–21]. Imaging patterns of myocardial replacement fibrosis are presented in Figures 1–3. Recently, the application of T1 and T2 mapping allowed the quantification of myocardial edema and diffuse fibrosis, which are the main pathophysiological phenomena that occur in the cardiovascular system of ARD patients [22–26] (Figs. 4A, B).

## The role of CMR in motivating immunomodulatory treatment

### Initiation/modification in ARD patients

CMR can detect cardiovascular involvement at any stage of the ARD, and often long before the ARD is fully expressed [19]. Unfortunately, echocardiography, which is the most common modality used in cardiology, is unable to detect these early lesions. Consequently, ARD patients with early lesions are not diagnosed and do not receive appropriate treatment, which explains the increased mortality in this population. The incidence of myocardial involvement varies in different ARDs; it is very high in systemic sclerosis, systemic lupus erythematosus, inflammatory myopathies, and vasculitis. However, multicenter studies comparing echocardiography or endomyocardial biopsy with CMR are still lacking.




**4** **(4A)** Short-axis native T1 mapping from a patient with systemic sclerosis; **(4B)** short-axis post-contrast T1 mapping from the same patient.

To our knowledge, there are also few studies coming from individual centers that support CMR's role in the evaluation of immunomodulatory and cardioprotective treatment in ARD patients. A previous study by our group showed that CMR can successfully evaluate the effect of both cardiac and immunomodulatory medication on the CV system. Furthermore, occult cardiac lesions seen on CMR – including myocardial edema, myocarditis, diffuse subendocardial fibrosis, and myocardial infarction – were not unusual in treatment-naïve ARD patients and can be reversed with appropriate treatment [19]. Additionally, stress CMR has successfully detected silent myocardial Raynaud's phenomenon in ARD patients with known peripheral Raynaud's phenomenon, and this resulted in early initiation of relevant cardiac treatment [13]. Moreover, CMR is capable of identifying ARD patients at high risk of cardiac rhythm disturbances that may lead to sudden cardiac death. CMR can therefore inform therapeutic decision-making for both cardiac and immunomodulatory treatment and specific CMR indices may also help to identify patients who might benefit most from implantation of a cardioverter defibrillator [20, 21]. With regard to this, it is worth noting that current criteria require an LVEF of < 35% to warrant implantation of a cardioverter defibrillator [27]. This is particularly problematic in ARD patients because, as mentioned above, they may have cardiovascular lesions with an otherwise preserved LVEF. Although the role of cardioprotective treatment is established for early morphological or functional cardiac changes [20, 21], clear guidelines for immunomodulatory treatment do not yet exist. However, the identification of myocardial inflammation using CMR is considered sufficient to warrant the initiation of immunomodulatory treatment, even if other clinical parameters are non-diagnostic [28].

**When to consider a CMR examination for ARD patients**

A baseline study that includes clinical, electrocardiographic, and echocardiographic evaluation should be performed when a diagnosis of any ARD is made. Based on our experience, a CMR examination may be considered in the following cases [12]:

- There is a mismatch between clinical findings and imaging/laboratory findings.
- The patient has developed new-onset heart failure.
- Cardiac rhythm disturbances of any type have been detected.
- The clinical picture requires modification of treatment with immunomodulatory agents.
- There is an increase in cardiac troponins, brain-type natriuretic peptide, N-terminal pro-brain-natriuretic peptide, or D-dimers, even if symptoms are only subtle.
- The patient mentions any kind of typical or atypical cardiac symptoms, and the routine cardiac evaluation is normal.

Recently, our team proposed a combined brain/heart MRI evaluation for the detection of silent brain lesions that are usually detected in ARD patients with CVD [29]. We believe that this combined approach will open a new avenue in the evaluation of ARDs and will facilitate early brain/heart treatment. However, there is currently insufficient information to recommend a combined brain/heart approach for all ARD patients. Identifying which patients to prioritize should be the focus of future studies.

## Translating the Greek experience to the international arena

Greece is one of the first countries where the idea of cardio-rheumatology was conceived and developed, with CMR figuring prominently as a diagnostic tool [30]. This was the result of a collaboration between two professors of rheumatology (P. P. Sfikakis and G. D. Kitas) and a cardiologist and professor of CMR with extensive experience at the interface between cardiology and rheumatology (S. I. Mavrogeni, co-author of this paper). Since this collaboration began, cardio-rheumatology has attracted a great deal of interest and has found broad acceptance among the international rheumatology and cardiology community [31]. In recognition of this, the Society for Cardiovascular Magnetic Resonance (SCMR) created a targeted working group for cardio-rheumatology chaired by S. I. Mavrogeni. It was tasked with promoting collaborations for multicenter studies, with the goal of using CMR to evaluate the cardiovascular system in ARD patients. Currently, two such multicenter studies are underway in patients with systemic sclerosis and systemic lupus erythematosus. These are expected to increase our knowledge of the pathophysiology and management of CVD in these patients, and show us how to better identify high-risk patients that could benefit from therapeutic interventions. Although the journey of cardio-rheumatology is only just beginning, it is important that CMR has been the common denominator that has brought these different specialties together and provided them with a shared goal: to optimally identify ARD patients with CVD and initiate appropriate treatment.

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**References**


1 Pohl D, Benseler S . Systemic inflammatory and autoimmune disorders. Handb Clin Neurol. 2013;112:1243–52.
2 Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59(12):1690–7.
3 Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol. 2006;2(2):99–106.
4 Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann. Rheum. Dis. 2011;70(1):8–14.
5 Hollan I, Meroni PL, Ahearn JM, Cohen Tervaert JW, Curran S, Goodyear CS, et al. Cardiovascular disease in autoimmune rheumatic diseases. Autoimmun Rev. 2013;12(10):1004–15.
6 Björnådal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. J Rheumatol. 2004;31(4):713–9.
7 Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol. 2011;7(7):399–408.
8 Gasparyan AY. Cardiovascular risk and inflammation: pathophysiological mechanisms, drug design, and targets. Curr Pharm Des. 2012;18(11):1447–9.
9 Dimitroulas T, Giannakoulas G, Karvounis H, Garyfallos A, Settas L, Kitas GD. Micro- and macrovascular treatment targets in scleroderma heart disease. Curr Pharm Des. 2014; 20(4):536–44.
10 Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum. 2010;39(4):269–77.
11 Hansildaar R, Vedder D, Baniaamam M, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. Lancet Rheumatol. 2020;doi: 10.1016/S2665-9913(20)30221-6 [Epub ahead of print].
12 Mavrogeni SI, Kitas GD, Dimitroulas T, Sfikakis PP, Seo P, Gabriel S, et al. Cardiovascular magnetic resonance in rheumatology: Current status and recommendations for use. Int J Cardiol. 2016;217:135–48.
13 Mavrogeni S, Sfikakis PP, Gialafos E, Bratis K, Karabela G, Stavropoulos E, et al. Cardiac tissue characterization and the diagnostic value of cardiovascular magnetic resonance in systemic connective tissue diseases. Arthritis Care Res (Hoboken). 2014;66(1):104–12.
14 Mavrogeni S, Spargias K, Markussis V, Kolovou G, Demerouti E, Papadopoulou E, et al. Myocardial inflammation in autoimmune diseases: investigation by cardiovascular magnetic resonance and endomyocardial biopsy. Inflamm Allergy Drug Targets. 2009;8(5):390–7.
15 Mavrogeni S, Manoussakis MN. Myocarditis and subclavian stenosis in Takayasu arteritis. Int J Cardiol. 2011;148(2):223–4.
16 Mavrogeni S, Sfikakis PP, Gialafos E, Karabela G, Stavropoulos E, Sfendouraki E, et al. Diffuse, subendocardial vasculitis. A new entity identified by cardiovascular magnetic resonance and its clinical implications. Int J Cardiol. 2013;168(3):2971–2.
17 Raman SV, Aneja A, Jarjour WN. CMR in inflammatory vasculitis. J Cardiovasc Magn Reson. 2012;14(1):82.
18 Mavrogeni S, Sfikakis PP, Gialafos E, Bratis K, Karabela G, Stavropoulos E, et al. Cardiac tissue characterization and the diagnostic value of cardiovascular magnetic resonance in systemic connective tissue diseases. Arthritis Care Res (Hoboken). 2014;66(1):104–12.
19 Mavrogeni S, Markousis-Mavrogenis G, Koutsogeorgopoulou L, Dimitroulas T, Bratis K, Kitas GD, et al. Cardiovascular magnetic resonance imaging pattern at the time of diagnosis of treatment naïve patients with connective tissue diseases. Int J Cardiol. 2017; 236:151–156.
20 Mavrogeni SI, Sfikakis PP, Dimitroulas T, Koutsogeorgopoulou L, Markousis-Mavrogenis G, et al. Prospects of using cardiovascular magnetic resonance in the identification of arrhythmogenic substrate in autoimmune rheumatic diseases. Rheumatol Int. 2018;38(9):1615–1621.
21 Mavrogeni S, Gargani L, Pepe A, Monti L, Markousis-Mavrogenis G, De Santis M, et al. Cardiac magnetic resonance predicts ventricular arrhythmias in scleroderma: the Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS). Rheumatology (Oxford). 2020;59(8):1938–1948.
22 Ntusi NAB, Francis JM, Gumedze F, Karvounis H, Matthews PM, Wordsworth PB, et al. Cardiovascular magnetic resonance characterization of myocardial and vascular function in rheumatoid arthritis patients. Hellenic J Cardiol. 2019;60(1):28–35.
23 Ntusi NAB, Francis JM, Sever E, Liu A, Piechnik SK, Ferreira VM, et al. Anti-TNF modulation reduces myocardial inflammation and improves cardiovascular function in systemic rheumatic diseases. Int J Cardiol. 2018;270:253–259.
24 Greulich S, Mayr A, Kitterer D, Latus J, Henes J, Steubing H, et al. T1 and T2 mapping for evaluation of myocardial involvement in patients with ANCA-associated vasculitides. J Cardiovasc Magn Reson. 2017;19(1):6.
25 Hinojar R, Foote L, Sangle S, Marber M, Mayr M, Carr-White G, et al. Native T1 and T2 mapping by CMR in lupus myocarditis: disease recognition and response to treatment. Int J Cardiol. 2016;222:717–726.
26 Winau L, Hinojar Baydes R, Braner A, Drott U, Burkhardt H, Sangle S, et al. High-sensitive troponin is associated with subclinical imaging biosignature of inflammatory cardiovascular involvement in systemic lupus erythematosus. Ann Rheum Dis. 2018;77(11):1590–1598.
27 Myerburg RJ, Reddy V, Castellanos A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Coll Cardiol. 2009;54(9):747–63.
28 Pieroni M, De Santis M, Zizzo G, Bosello S, Smaldone C, Campioni M, et al. Recognizing and treating myocarditis in recent-onset systemic sclerosis heart disease: potential utility of immunosuppressive therapy in cardiac damage progression. Semin Arthritis Rheum. 2014;43(4):526–35.
29 Markousis-Mavrogenis G, Mitsikostas DD, Koutsogeorgopoulou L, Dimitroulas T, Katsifis G, Argyriou P, et al. Combined brain-heart magnetic resonance imaging in autoimmune rheumatic disease patients with cardiac symptoms: hypothesis generating insights from a cross-sectional study. J Clin Med. 2020;9(2):447.
30 Mavrogeni S, Papadopoulos G, Douskou M, Kaklis S, Seimenis I, Baras P, et al. Magnetic resonance angiography is equivalent to X-ray coronary angiography for the evaluation of coronary arteries in Kawasaki disease. J Am Coll Cardiol. 2004;43(4):649–652.
31 Ruparelia N, Chai JT, Fisher EA, Choudhury RP. Inflammatory processes in cardiovascular disease: a route to targeted therapies. Nat Rev Cardiol. 2017; 14(3):133–144.


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