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-
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.

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. Sifakis 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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