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MINI-REVIEW ARTICLE

Cardiac MRI in Autoimmune Diseases: Where Are We Now?

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Abstract: Cardiovascular magnetic resonance imaging (CMR) allows the early diagnosis of various cardiovascular pathophysiologic phenomena in autoimmune diseases. Preliminary studies suggest that CMR holds a promising role in initiating the necessary changes in anti-rheumatic and cardiac treatment among patients with autoimmune diseases and cardiovascular diseases (CVD). It is widely known that the presence of late gadolinium enhancement (LGE) has been related to a worse cardiovascular prognosis. CMR has been documented to be the most valuable tool for diagnosis and risk prediction of cardiac involvement in a sarcoidosis population, while in SLE, the gap between clinical and autopsy diagnosis of the myocardial disease could be narrowed with the implementation of CMR. In different connective tissue diseases, including SLE, LGE has been demonstrated to be present early after the initial diagnosis of SLE. Considering that CMR, including LGE identifies more patients with silent myocardial disease in SLE and other connective tissue diseases than echocardiography, CMR should be the preferred imaging modality, especially in the era of modern techniques with broader availability and expertise. In this review, we summarize the major indications, advantages and limitations of the use of CMR among patients with autoimmune disorders.

Keywords: Autoimmune disorders, cardiac magnetic resonance (CMR), late gadolinium enhancement (LGE), early gadolinium enhancement (EGE), cardiac MRI, EGPA.

1. INTRODUCTION

Autoimmune rheumatic diseases are associated with a high incidence of cardiovascular diseases (CVD) [1]. Until today, CVD is often underestimated in patients with rheumatic diseases because usually, rheumatologists focus on the signs and symptoms of the systemic disease. Although the various treatment modalities have resulted in reducing disease-related mortality, life expectancy in people with autoimmune diseases remains lower compared to the general population, and cardiovascular involvement mainly accounts for this fact [2-7]. CVD in rheumatic diseases is the result of various pathophysiologic mechanisms, including myocardial, inflammatory, ischemic, and fibrotic changes [8, 9]. No matter the pathophysiologic background, the symptoms of heart involvement are usually subtle and indolent; thus, they are usually underestimated. In general, the development of clinically overt cardiac signs is equal to advanced cardiac disease and carries a poor prognosis [10].

Cardiovascular magnetic resonance imaging (CMR) allows the early diagnosis of various cardiovascular pathophysiologic phenomena in autoimmune diseases [11, 12]. Preliminary studies suggest that CMR holds a promising role in initiating the necessary changes in anti-rheumatic and cardiac treatment among patients with autoimmune diseases and CVD [13, 14].

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2. DIAGNOSTIC ROLE OF CMR

EGPA (Eosinophilic Granulomatosis with Polyangiitis, formerly known as Churg-Strauss syndrome) and GPA (Granulomatosis with Polyangiitis, formerly known as Wegener's granulomatosis) are both subtypes of ANCA-associated vasculitides. The prevalence of myocardial involvement varies, ranging from 16 to 92% in EGPA and 6 to 86% in GPA patients, depending on different diagnostic methods and disease activity [15]. Patients with myocardial involvement may have no or nonspecific symptoms, normal ECG, and preserved left-ventricular ejection fraction (LV-EF); yet, they may nevertheless face life-threatening arrhythmia or end-stage heart failure during the course of the disease [16, 17]. EGPA patients frequently show myocardial granulomas and severe tissue alterations on histopathology, and up to 50% of patients die of cardiac causes [18, 19]. This is also true in GPA patients [20]. Since myocardial involvement might be reversible if prompt, adequate treatment is initiated, a reliable tool for the early detection of myocardial involvement is warranted [21]. Cardiovascular magnetic resonance (CMR) offers not only functional assessment but also excellent tissue characterization by the use of late gadolinium enhancement (LGE) [22]. However, LGE is known to perform best in the detection of focal myocardial processes rather than diffuse fibrotic or inflammatory processes [23].

CMR contributes to the diagnosis of myocarditis by mainly using three types of images: T2-weighted (T2-W), early T1- weighted: early gadolinium enhancement (EGE) images taken 1 min and late gadolinium enhancement (L-

GE) images taken 15 minutes after the injection of the contrast agent. T2-W is an indicator of tissue water content, which is increased in inflammation or necrosis, *i.e.* is depicting edema imaging. However, it is not possible to differentiate between necrosis and inflammation only by the use of T2-W images [24-30]. To have a more accurate tissue characterization by CMR, images early and late after gadolinium injection should be obtained. Higher levels of EGE after contrast agent administration are due to increased membrane permeability or capillary blood flow. Herein, membrane permeability plays a key role as inflammation damages myocardial cell membranes through both T-cell perforin and B-cell antibody/complement-mediated processes. The third parameter, LGE, is the result of the contrast agent deposition in the delayed images due to myocardial necrosis in the acute phase, which increases the gadolinium distribution [25-30]. A combined CMR approach using T2-W, EGE and LGE have a sensitivity of 76%, a specificity of 95.5% and a diagnostic accuracy of 85% for the detection of myocarditis [29]. The detection of small vessel vasculitides in the myocardium is based on the sub-endocardial pattern of myocardial involvement that can be easily detected by LGE, but not by echocardiography [30-34]. Existing data support the use of LGE and T2-W myocardial imaging in defining the presence, acuity, and extent of cardiac involvement during the course of vasculitides [30-34].

The most important information that CMR can give in ANCA-associated vasculitides is the evaluation of disease acuity using the combination of edema and fibrosis imaging. If both parameters are increased, there is evidence of acute myocardial lesion [35-37]. If T2-W is normal and only LGE is identified, then the cardiac lesion is chronic [38, 39]. This information is of great diagnostic value because cardiac involvement in ANCA-associated vasculitis is usually indolent [40, 41]. Furthermore, CMR using the combination of T2-W images, EGE and LGE can distinguish acute from chronic myocardial inflammation [40-42].

Relatively newer sequences, such as T1 and T2 mapping, could already prove their diagnostic value in the detection of both focal and diffuse myocardial alterations in various cardiomyopathies, including cardiac involvement in rheumatic disorders or inflammatory cardiomyopathies, and therefore might be appropriate tools to complement LGE-CMR [43-45]. Data demonstrate that patients with EGPA and GPA show several abnormalities detected by CMR mapping techniques. Interestingly, most patients were non- or oligosymptomatic, had normal ECG, and a preserved LV-EF, suggesting an incremental value of mapping techniques in the assessment of subclinical myocardial involvement in early, potentially reversible stages of ANCA-associated vasculitides, which might have been missed otherwise [46, 47]. Since native T1, ECV, and T2 values were independent of the presence of LGE, these parameters seem to provide complementary information about diffuse myocardial involvement compared to LGE alone. Most significant differences (beyond the 95% percentile of controls) were observed for native T1 and T2, suggesting a combination of both chronic (fibrosis) and acute (inflammation) stages in ANCA-Associated Vasculitides (AAV) patients. Recent T1 and T2 mapping techniques might play a role in patients with AAV for: 1) detection of even subtle myocardial involvement, 2) assessment of different stages of the disease (acute *vs.* chronic), 3) decision-making about subsequent medical therapy, preventing progression of further cardiac damage, and 4) the evaluation of response to treatment during follow-up [46, 47]. However, there are several limitations regarding the recent T1 and T2 mapping, such as the lack of specificity, the lack of cut-off values as well as the interlab variability too.

Endomyocardial biopsy (EMB) has not been routinely performed. However, it is known that EMB has several limitations, lowering its diagnostic benefit. Furthermore, in asymptomatic to oligo-symptomatic patients with preserved LV-EF and negative LGE-CMR, the risk-to-benefit ratio of EMB is questionable. Whether abnormalities by T1 and T2 mapping in patients with ANCA-associated vasculitides represent myocardial involvement should be evaluated by further studies, including EMB [48-50]. However, T1 and T2 mapping seem to be appropriate techniques since a combination of both inflammation and fibrosis could be detected by histology in other studies with AAV patients [3, 25].

Currently, the most commonly employed noninvasive imaging modality used in cardiovascular imaging is echocardiography, due to its high availability, portability, low cost, lack of ionizing radiation exposure, and high expertise among cardiologists [40-44]. It can reliably identify morphological, functional, and valvular alterations both at restand stress; however, image quality is strongly dependent on the acoustic window of the patient and the expertise of the operator. Furthermore, classic echocardiographic indexes do not address the aforementioned necessity for cardiac tissue characterization [44, 45]. Transthoracic echocardiography using classical and novel ultrasound techniques such as tissue Doppler imaging and speckle tracking in an SLE population documented that systolic longitudinal and diastolic performance impairments were frequent findings in SLE patients without overt CVD [46, 47]. Although these advanced echocardiographic techniques provided more details about the cardiovascular background in auto-immune rheumatic diseases (ARDs), they could not define the exact nature of myocardial lesions in patients with preserved diastolic or systolic function, as is often the case in ARDs patients [48, 49]. Their role is thus restricted to the detection of changes based on serial evaluations of the same patient; however, clear documentation of edema, fibrosis, perfusion defects, or necrosis is of paramount importance for risk stratification of ARDs patients, cannot be obtained [49-51].

3. PROGNOSTIC ROLE OF CMR

3.1. The Potential of LGE in Risk Stratification of Rheumatic Diseases

LGE has a low prevalence in a middle-aged population at low- or intermediate risk, estimated to be around 0.7% [52]. It is widely known that the presence of LGE has been related to a worse cardiovascular prognosis [53-55]. For ex-

ample, in sarcoidosis, the presence of LGE has been related to a significantly increased risk of cardiovascular morbidity and mortality [56, 57]. CMR has been documented to be the most valuable tool for diagnosis and risk prediction of cardiac involvement in a sarcoidosis population (Fig. **1**) [57]. In SLE, the gap between clinical and autopsy diagnosis of the myocardial disease could be narrowed with the implementation of CMR, when comparing 30% of LGE in a recently published cohort by Burkardt *et al.*, with an approximately 40% myocardial involvement observed in autopsy studies [58, 59]. In different connective tissue diseases, including SLE, LGE has been demonstrated to be present early after the initial diagnosis of SLE (Figs. **2** and **3**) [58]. Considering that CMR, including LGE identifies more patients with silent myocardial disease in SLE and other connective tissue diseases than echocardiography, CMR should be the preferred imaging modality, especially in the era of modern techniques with broader availability and expertise [58, 59]. Since there have not been any good clinical parameters to predict myocardial disease in SLE patients yet, LGE in CMR might provide this potential. The increasing extend of LGE is related to poorer outcomes among patients with cardiomyopathies of another origin. However, data comparing SLE patients with and without LGE are scarce [58, 59].

Regarding rheumatoid arthritis patients, subclinical CVD has been documented, with focal and diffuse myocardial fibrosis and inflammation, findings which have been related to myocardial strain and rheumatoid arthritis disease activity [25].

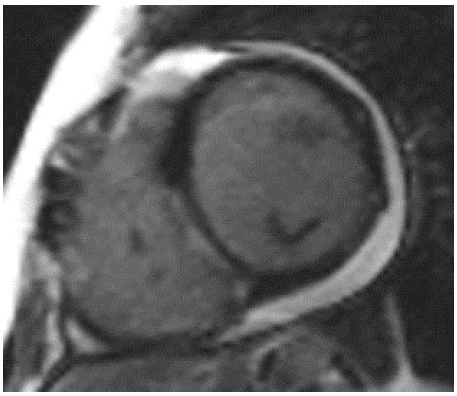

Fig. (2). A short axis Late Gadolinium Enhancement (LGE) image of a female patient with dermatomyositis shows enhancement of the interventricular septum (at the RV side). Also, note the presence of pericardial effusion.

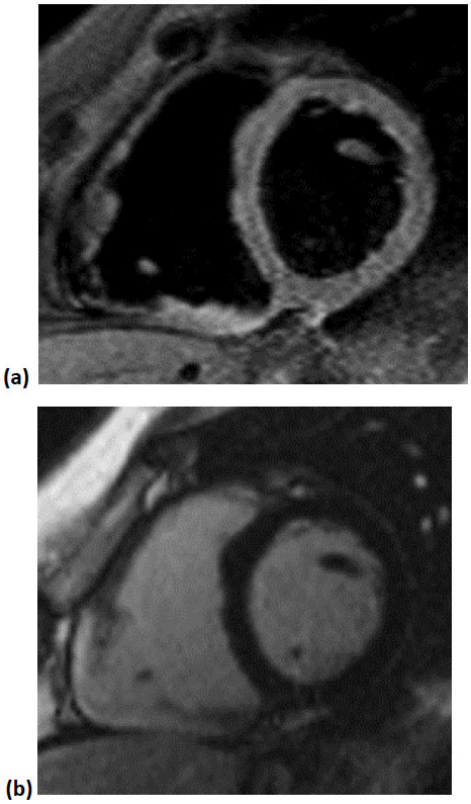

Fig. (1). Cardiac sarcoidosis in a 38-year-old man. Short axis T2W STIR (**a**) and LGE (**b**) images. Thickening of the RV free and inferior wall showing an increased signal intensity representing cardiac inflammation. Late imaging shows enhancement of the same areas.

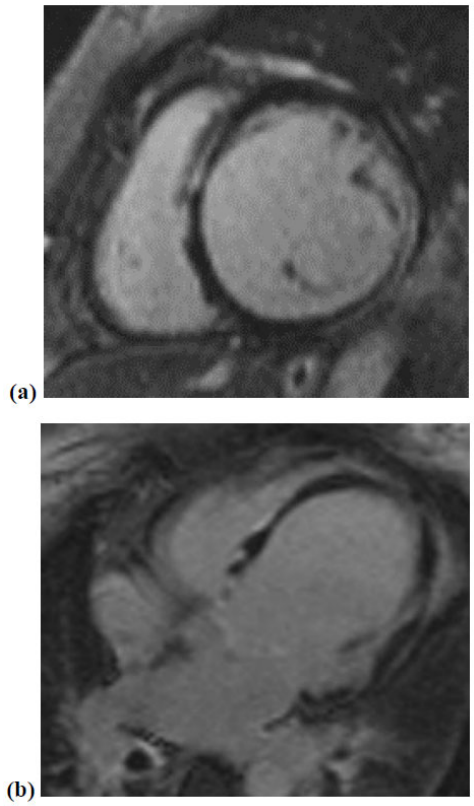

Fig. (3). Short (**a**) and horizontal long (**b**) axis Late Gadolinium Enhancement (LGE) images of a female patient with lupus show enhancement involving the interventricular septum (at the RV side), the inferior and the lateral wall (mostly at the sub-epicardium).

CMR has been proved useful in detecting cardiac involvement in patients with systemic sclerosis, even in the absence of cardiac symptoms, such as in cases of chronic myocardial inflammation and focal and diffuse myocardial fibrosis [60]. Besides, CMR has documented that the pattern of myocardial fibrosis in 105 patients with systemic sclerosis and Q waves has been due to the systemic disease and not to coronary artery disease [61].

Table 1. Proposing the performance of CMR in various autoimmune disorders, according to Mavrogeni *et al.*, [58].

When to CMR?	Why?
There is a plan to change treatment, especially if biological agents are to be administered	Use with caution in patients with heart failure due to the risk of HF or MI due to anti-TNFa treatment
Arrhythmia	Could indicate cardiomyopathy
Increases in troponin, brain natriuretic peptide or D-dimers	Could indicate cardiomyopathy or pulmonary embolism
Newly onset of heart failure	Could indicate cardiomyopathy
The patient is complaining of cardiac symptoms, and the routine cardiac evaluation is normal	Indolent cardiomyopathy could be unraveled
There is a mismatch between clinical and laboratory findings	Indolent cardiomyopathy could be unraveled
The patient is being treated with hydroxy-chloroquine or biologic agents	Hydroxychloroquine may cause cardiomyopathy, and anto-TNFa may exacerbate HF or MI

Coronary artery disease has turned out to be a major cause of morbidity and mortality among SLE patients; therefore, SLE patients with the highest risk of CVD adverse events should be identified early in the course of the disease [57-59]. In the study by Burkardt *et al.*, repolarisation abnormalities, hypertension, renal disorders together with larger left ventricular end-diastolic volumes were more common among patients with stress-perfusion deficits [59]. Since clinical symptoms were unspecific, the above-mentioned parameters, which were easy to detect, have to be particularly evaluated and valued for the presence or not of coronary artery disease in SLE patients in the future. Attention should be drawn to the various ECG abnormalities. A previous study has associated ECG abnormalities of Q-waves in the inferior leads with CMR abnormalities, representing acute myocarditis, past myocarditis or past myocardial infarction with the use of CMR, including LGE, but without stress perfusion imaging [57]. An algorithm for the CVD work-up of SLE patients has only recently been suggested by Mavrogeni *et al.*, (Table **1**) [58]. In this algorithm, echocardiography remains the cornerstone for non-invasive techniques for the assessment of CVD involvement as it is inexpensive, widely available and can guide further workup, especially in the acute clinical setting. CMR has been highlighted as a preferred imaging modality in SLE patients with no CVD symptoms or in oligo-symptomatic patients, when ECG or echocardiography was abnormal and in not acutely symptomatic patients, ie under circumstances where additional clinical or laboratory features were present *e.g.* ECG abnormalities or inflammatory biomarkers. In these situations, CMR would be a wonderful tool for further diagnostic evaluation and treatment and could, as well, reduce exposure to radiation. The Achilles' heel of CMR remains the lower availability and the higher costs [59, 60]. Nevertheless, in the asymptomatic or oligo-symptomatic SLE patient, results of the CMR could rule out structural cardiovascular disease or could prompt for the necessity of further evaluation, such as with coronary angiography [61]. Apart from coronary angiography, which has a stable place in diagnosing coronary artery disease, another imaging modality that has recently gained attention is 18-FDG-PET/CT scan, which may detect cancer among patients with autoimmune disorders. It has been demonstrated that 18-FDG-PET/CT may differentiate between cancer and inflammation in patients with systemic immune diseases [62]. Its value regarding cardiac imaging has to be further elucidated in future large-scale studies.

CONCLUSION

In conclusion, echocardiography is an inexpensive, bedside, and widely available tool that can help the diagnosis in the appropriate clinical setting. However, its sensitivity is questionable for the diagnosis of subtle disease among patients with autoimmune rheumatic diseases. Currently, CMR seems to be a valuable solution in finding answers regarding tissue characterization, disease acuity, and prediction in these patients. MRI is surely a very useful tool in rheumatic disease, but most data are observational and there is not much evidence yet that MRI can help to guide treatment and management. Nevertheless, it could define the timely initiation of prompt treatment in patients with autoimmune diseases and could help to change their prognosis.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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