Journal of Inflammation Research

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REVIEW

Cardiovascular magnetic resonance imaging: clinical implications in the evaluation of connective tissue diseases

This article was published in the following Dove Press journal:
Journal of Inflammation Research
11 May 2017
Number of times this article has been viewed

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Abstract: Cardiovascular magnetic resonance imaging is a recently developed noninvasive, nonradiating, operator-independent technique that has been successfully used for the evaluation of congenital heart disease, valvular and pericardial diseases, iron overload, cardiomyopathies, great and coronary vessel diseases, cardiac inflammation, stress–rest myocardial perfusion, and fibrosis. Rheumatoid arthritis and other spondyloarthropathies, systemic lupus erythematosus, inflammatory myopathies, mixed connective tissue diseases (CTDs), systemic sclerosis, vasculitis, and sarcoidosis are among CTDs with serious cardiovascular involvement; this is due to multiple causative factors such as myopericarditis, micro/macrovascular disease, coronary artery disease, myocardial fibrosis, pulmonary hypertension, and finally heart failure. The complicated pathophysiology and the high cardiovascular morbidity and mortality of CTDs demand a versatile, noninvasive, nonradiative diagnostic tool for early cardiovascular diagnosis, risk stratification, and treatment follow-up. Cardiovascular magnetic resonance imaging can detect early silent cardiovascular lesions, assess disease acuteness, and reliably evaluate the effect of both cardiac and rheumatic medication in the cardiovascular system, due to its capability to perform tissue characterization and its high spatial resolution. However, until now, high cost; lack of interaction between cardiologists, radiologists, and rheumatologists; lack of availability; and lack of experts in the field have limited its wider adoption in the clinical practice.

Keywords: connective tissue diseases, cardiovascular magnetic resonance imaging

Introduction

Cardiology has various noninvasive imaging modalities at its disposal, such as the rest–stress electrocardiogram, rest–stress echocardiography, nuclear imaging, and, more recently, cardiovascular magnetic resonance (CMR) imaging to detect cardiac involvement in connective tissue diseases (CTDs). Exercise electrocardiogram is an important predictive test to select patients either very unlikely or very likely to present cardiac events. However, it is plagued by a low predictive value for intermediate-risk patients. Stress echocardiography, an operator-dependent technique, is based on the induction of a transient worsening in regional function by means of dobutamine pharmacological stress. It has equal diagnostic and prognostic value as radionuclide stress perfusion, but without radiation exposure and with a significantly lower cost. Although being an important imaging modality for patients with suspected coronary artery disease (CAD), stress myocardial perfusion scintigraphy has serious limitations including radiation exposure, imaging artifacts, and low spatial resolution that precludes detection of small myocardial lesions that commonly occur in patients with CTDs.[1]

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CMR is a recently developed noninvasive, nonradiating, operator-independent technique. Until now it has been successfully used for the evaluation of a number of cardiac diseases including congenital heart diseases, iron overload, valvular and pericardial diseases, cardiomyopathies, and great and coronary vessel diseases.[2–13] Recently, its diagnostic capabilities have also been extended to the evaluation of cardiac inflammation and to stress–rest myocardial perfusion.[14,15] CMR has the important advantage of being able to reveal the pathophysiologic background of cardiovascular lesions in patients with CTDs, even in those with silent disease. However, until now, high cost; lack of interaction between cardiologists, radiologists, and rheumatologists; as well as lack of availability and expertise have limited its wider adoption in clinical practice.[16]

How does it work?

CMR images are derived from radio-wavelength photons, thus precluding the need for ionizing radiation as in other imaging modalities. These photons are produced by protons (hydrogen nuclei), which are present in abundance in the human body as part of water and lipid molecules. All subatomic particles inherently rotate around their axes. The total angular momentum of a nucleus is called the spin. However, since protons are charged particles, they generate a magnetic field as they rotate around their axes; the vector of this magnetic field is called the magnetic moment, and its direction is perpendicular to the rotational plane of the spin. In nature, the direction of each magnetic moment is random. During a CMR investigation, the patient is subjected to a powerful exogenous magnetic field generated by the main magnetic coil of the scanner. The randomly spinning protons are forced to orient their magnetic moments in a specific direction, facing either parallel or antiparallel to the vector of the exogenous magnetic field, although the majority align themselves parallel to the field vector as this state is preferable (due to lower energy). The protons are then excited by a radiowave frequency electromagnetic radiation pulse. This radiowave frequency pulse disturbs the alignment of the protons, and by providing additional energy, it causes a certain proportion of them to change the direction of their magnetic moments to the antiparallel direction, a higher energy state. After reaching this higher energy state, the protons begin reverting to the lower energy state of parallel direction. As this occurs, the magnetic moments begin to realign to their original, low-energy orientation in the exogenous magnetic field, while the excess energy is re-emitted as radio-wavelength photons. This process is called relaxation, and the relaxation of the net vector of protons is attributable to two distinct but simultaneous processes, referred to as longitudinal (T1) and transverse (T2) relaxation times. The absorbed radiowaves emitted during relaxation are digitized and can be used to provide important information about human tissues. By using smaller magnetic fields generated by three sets of gradient coils (one for each of the *x*, *y*, and *z* axes), the main magnetic field can be manipulated so that high-quality images of specific sections of the human body can be generated. This last possibility makes CMR a far more versatile and robust technique than other imaging modalities, which are limited to axial sections of the body.

In MR examinations, a pulse sequence is defined as a combination of sets of radiowave frequency pulses with the application of magnetic fields through the main and gradient magnetic coils, with the goal of imaging specific tissue types. Basic pulse sequences used in CMR are gradient-echo, which can generate a cine loop (Figure 1), T1 images, usually used for anatomic evaluation and for perfusion-fibrosis assessment (Figure 2), and T2 images (Figure 3), commonly used for the evaluation of myocardial edema and assessment of disease acuteness. Late gadolinium-enhanced images are T1 images taken 15 min after intravenous administration of the paramagnetic contrast agent gadolinium and allow the detection of myocardial fibrotic tissue (scar), which appears as a bright area in a background of nulled, black myocardium – "bright is dead" (Figures 4 and 5). However, diffuse myocardial fibrosis could be missed by traditional late gadolinium-enhanced imaging in cases where the entire myocardium is affected, as occurs with systemic sclerosis (SSc). In these cases, T1 mapping and extracellular volume

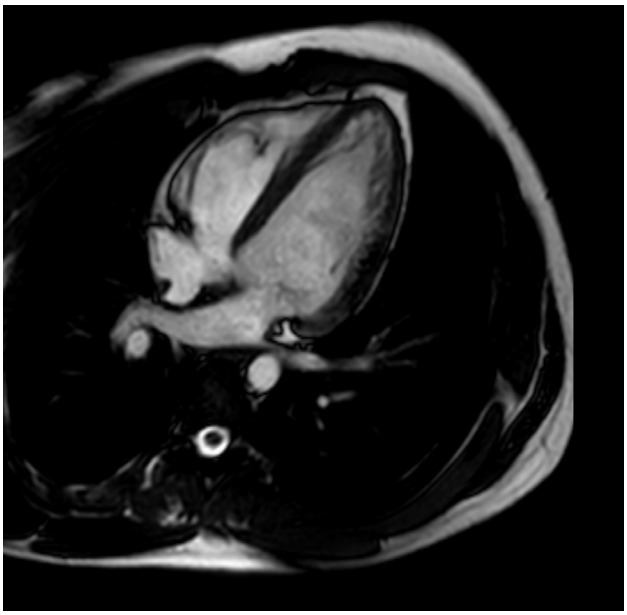

Figure 1 Four-chamber gradient echo image used for function assessment.

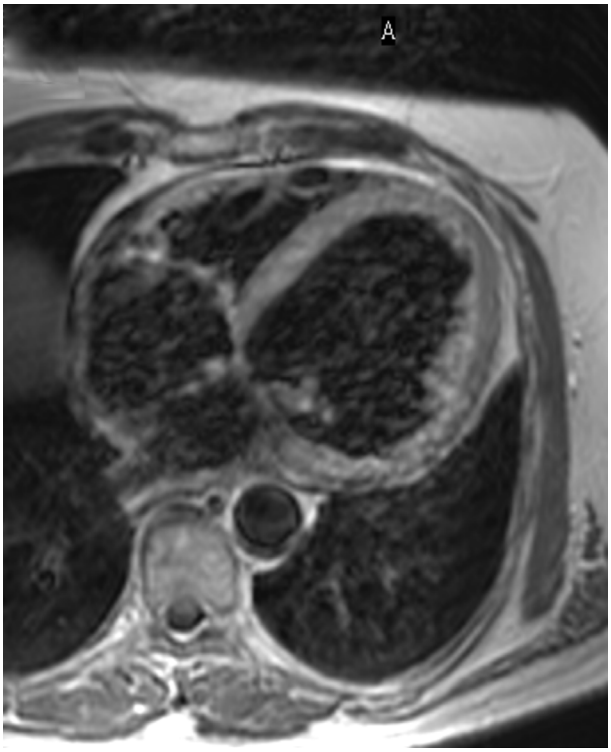

Figure 2 Four-chamber T1 imaging used for anatomical assessment.

Figure 3 Short-axis T2 imaging from a patient with SLE and myocardial edema.
Note: The arrows show areas of myocardial edema in a patient with SLE.
Abbreviation: SLE, systemic lupus erythematosus.

quantification can provide a more reliable surrogate estimation of diffuse fibrosis. Finally, noninvasive angiography of vessels can also be performed with the use of a bolus injection of gadolinium (Figure 4).[16] The use of these

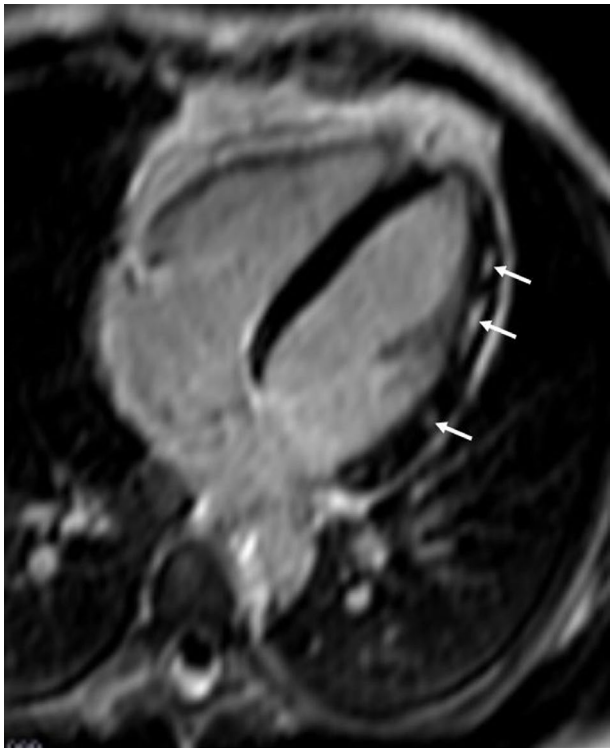

Figure 4 Patchy fibrosis due to myocardial inflammation in a patient with polymyositis.
Note: The arrows show areas of patchy fibrosis in the lateral wall of LV, due to myocardial inflammation in a patient with polymyositis.
Abbreviation: LV, left ventricle.

Figure 5 Transmural myocardial infarction in a SLE patient.
Note: The arrows show area of transmural myocardial infarction in a patient with SLE.
Abbreviation: SLE, systemic lupus erythematosus.

sequences allows for reliable assessment of both right and left ventricular volumes and ejection fractions; early detection of myocardial inflammation, which is notably an ability unique to CMR; early detection of perfusion defects due to either macro/microvascular disease; and early assessment of localized or diffuse myocardial fibrosis.[16]

Patients with CTDs presenting with cardiovascular involvement

Rheumatoid arthritis and the spondyloarthropathies

Accelerated atherosclerosis leads to a twofold higher incidence of CAD, stroke, heart failure, and peripheral arterial disease.[17,18] However, the high incidence of heart failure cannot be explained only by CAD.[19,20] Other prevalent pathologic entities in rheumatoid arthritis include pericarditis, myocarditis, and vasculitis.[17,18] Similar problems may occur in the spondyloarthrotopathies.[21]

Systemic lupus erythematosus (SLE)

Cardiovascular disease is a major cause of morbidity and mortality in SLE and is due to CAD, vasculitis, and myocarditis.[22–24] The prevalence of CAD is 6%–10%, and the risk of developing CAD is 4–8 times higher in SLE compared with controls. Clinically overt myocarditis appears in 3%–15% of SLE, usually in association with pericarditis; however, it is more common at autopsy, suggesting subclinical presentation.[22–24]

Systemic vasculitides

The typical lesions in vasculitis include inflammation and fibrinoid necrosis of the blood vessel wall. The classification of systemic necrotizing vasculitides depends on the predominant type of vessels affected.[25] Large-vessel vasculitides includes giant cell and Takayasu arteritis and involves the aorta and its major branches. Medium-vessel vasculitides includes polyarteritis nodosa and Kawasaki disease, while small-vessel vasculitides includes Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome, and mixed cryoglobulinemic vasculitis. Based on biopsy findings, inflammation in the myocardium and small vessels may contribute to cardiac ischemia and heart failure.[26] Vasculitis in SLE, SSc, rheumatoid arthritis, and Sjögren's syndrome affects small-sized vessels, and despite not being clinically predominant, they can be life-threatening.[27]

Inflammatory myopathies

Heart involvement in polymyositis/dermatomyositis varies between 6% and 75% and may be clinically overt at diagnosis, after initiation of treatment, or even during remission; it is usually clinically silent and may lead to fatal arrhythmias or heart failure.[28]

SSc

SSc is also called scleroderma and is characterized by involvement of small vessels, resulting in fibrosis of various organs, including the heart.[29] Cardiac mortality is responsible for 15% of all scleroderma deaths and is either primary, due to myocardial inflammation-fibrosis, or secondary, due to pulmonary arterial hypertension.[30,31]

Mixed CTDs

Raynaud's phenomenon of the small vessels of the heart, similar to that observed in the fingers, and development of pulmonary arterial hypertension are included among the most important cardiac lesions in mixed CTDs.[32]

Sarcoidosis

Cardiac involvement occurs in 20%–30% of sarcoidosis (SRC) patients and conveys a poor prognosis.[33] Autopsy findings confirmed that granulomas may occur in the myocardium in up to 50% of fatal SRC and cardiac dysfunction, with sudden death in up to 67% of cardiac SRC.[33] Despite characteristic autopsy findings, only 5% of SRC patients present with clinically overt cardiac disease and only 40%–50% of them are correctly diagnosed during lifetime.[21] CMR can detect early cardiac involvement in SRC, including both inflammation and fibrosis as well as perfusion defects.[34]

Clinical implications of CMR in CTDs

Although considerable improvement has been achieved in both the diagnosis and treatment of CTDs, premature mortality remains a serious, unresolved issue.[16] Cardiovascular disease in CTDs has been underdiagnosed and undertreated because of a number of contributing factors. The silent and confusing symptoms observed in these patients combined with the lack of accurate diagnostic tools capable of detecting asymptomatic cardiovascular lesions are of major concern in this regard. Additionally, the relapsing nature of CTDs poses great difficulties in the identification of underlying cardiovascular disease, as acute lesions may be superimposed on preexisting areas of fibrosis.[16]

Currently, the most commonly used noninvasive diagnostic tool for investigating cardiac involvement in CTD patients is echocardiography, due to high availability, portability, low cost, lack of radiation, and great expertise among cardiologists. However, this technique cannot distinguish between

possible etiologies of myocardial dysfunction with accuracy. Furthermore, it is operator dependent, is inherently limited by the requirement for an acoustic window, and cannot perform tissue characterization to detect early silent lesions.[35] On the other hand, nuclear techniques used in cardiology practice for the assessment of myocardial ischemia–fibrosis have the disadvantages of high cost, radiation exposure, and low spatial resolution, while not allowing the diagnosis of myocardial edema and subepicardial, intramyocardial, or subendocardial fibrotic lesions, which are frequently found in CTD patients.[16]

By means of performing tissue characterization, CMR allows early diagnosis and better understanding of CTD pathophysiology and involvement in cardiovascular disease. Particularly in SSc, where myocardial disease is the result of inflammatory, fibrotic, and microvascular lesions, CMR has a greater sensitivity (75%) in detection compared to echocardiography (48%).[36]

Clinical implications of CMR in the risk stratification of CTD patients include

1. Early cardiovascular diagnosis in CTD patients, including inflammation, perfusion defects, and diffuse or localized fibrosis, even if these patients have silent or oligosymptomatic presentation.[12,14]
2. Detection of cardiovascular disease acuteness that cannot be achieved with echocardiography or by nuclear techniques.[37,38]
3. Large-vessel angiography with simultaneous assessment of arterial wall inflammation that can neither be performed with echocardiography nor with nuclear techniques.[37]
4. Tissue characterization that cannot be obtained in an accurate way with echocardiography, nuclear techniques, and cardiac computed tomography.[37,38] These techniques may suggest the presence of potential lesions, but offer no definitive information.
5. Pharmacologic stress CMR, a noninvasive, nonradiating alternative for stress echocardiography. As not constrained by the limitations of the requirement for an acoustic window and/or the occurrence of breast artifacts, CMR is the technique of choice for coronary artery and cardiac microvascular disease assessment. This is especially the case in females, who constitute the majority of CTD patients and are commonly unable to perform exercise at an adequate level due to arthritis or muscular discomfort.[39]
6. Vigilant long-term cardiovascular monitoring is required in CTD patients due to both the effects of the systemic disease on the cardiovascular system and the cardiovascular burden of medications used for the management of systemic inflammation. CMR can identify high-risk patients and evaluate treatment efficacy and toxicity-related side effects on the heart.[40,41]
7. Cardiac lesions detected by CMR in patients with CTDs can motivate the early commencement of protective cardiac medication according to American College of Cardiology/American Heart Association Guidelines and the modification of rheumatic medication if myocardial inflammation is observed although the systemic disease seems quiescent.[42–44]

Conclusion

The complicated pathophysiology of CTDs calls for a versatile, noninvasive, nonradiative diagnostic tool suitable for early cardiovascular diagnosis, risk stratification, and treatment follow-up. CMR can detect silent cardiovascular lesions early, assess disease acuteness, and reliably evaluate the effect of both cardiac and rheumatic medication on the cardiovascular system due to its capability to perform tissue characterization and its high spatial resolution. Therefore, its clinical use is strongly recommended in patients with CTDs.

Disclosure

The authors report no conflicts of interests in this work.

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