The role of cardiovascular magnetic resonance imaging in rheumatic heart disease

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ABSTRACT

Cardiovascular involvement is a well-known feature of inflammatory rheumatic diseases, although often clinically silent, so early cardiovascular involvement may remain unrecognised. Thus, increased awareness and improved insights into the pathomechanisms of heart disease in the context of inflammatory rheumatic disease has led to an emerging role of cardiovascular magnetic resonance (CMR) as an accurate and non-invasive diagnostic test for detection of early (as well as late) cardiovascular involvement in inflammatory rheumatic disease. The present article will review the current potential as well as the limitations of established and emerging, qualitative and quantitative CMR techniques in the setting of inflammatory rheumatic disease and shed some light onto current developments in the field.

Introduction

A wide range of inflammatory rheumatic diseases with potential cardiovascular involvement exists, including systemic lupus erythematosus, rheumatoid arthritis and seronegative arthritis, systemic sclerosis, mixed connective tissue disease (including dermatomyositis, polymyositis, and inclusion body myositis), vasculitis, and sarcoidosis (1). A common endpoint of the various underlying pathophysiological processes in inflammatory rheumatic disease is cardiovascular disease. Despite pathophysiologically different mechanisms, patterns of cardiovascular involvement are somewhat similar, either resulting from direct inflammatory myocardial injury (2-8) or mediated via vasculitic coronary or aortic involvement, endothelial dysfunction or microvascular disease (9-13).

Cardiac involvement in inflammatory rheumatic disease is mostly subclinical, especially in younger patients, as acute symptoms in other organ systems are predominant. Symptoms of cardiovascular involvement most commonly occur late during disease, while silent cardiac involvement is usually present during the first decade following diagnosis (14) (Fig. 1). In general, cardiac involvement in inflammatory rheumatic disease is known to be associated with adverse outcomes (15-17), highlighting the need for sensitive diagnostic tools to recognise and characterise cardiovascular tissue before the onset of overt cardiovascular dysfunction.

Routine cardiovascular imaging modalities in clinical cardiology, such as echocardiography, nuclear imaging, and invasive coronary angiography are limited in the early diagnosis of cardiovascular disease in patients with inflammatory rheumatic disease. Endomyocardial biopsy (EMB) is considered to be the "gold standard" for suspected myocarditis with or without concomitant presence of inflammatory rheumatic disease, according to the latest position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease (18). Nevertheless, performing EMB in the setting of known inflammatory rheumatic disease, but absence of any symptoms of cardiac involvement would raise considerable ethical concerns due to the invasive nature of the procedure and its associated risks. By contrast, cardiovascular magnetic resonance (CMR) with its unique capacity for non-invasive, radiation-free tissue characterisation, not only represents a gold standard for the analysis of cardiac function, but also has been proposed as a promising tool to detect cardiovascular inflammation, fibrosis, and microvascular disease in preclinical disease stages (19). This article summarises the main applications of CMR in inflammatory rheumatic disease and allow some (not uncritical) insights into novel developments in the field of quantitative CMR.

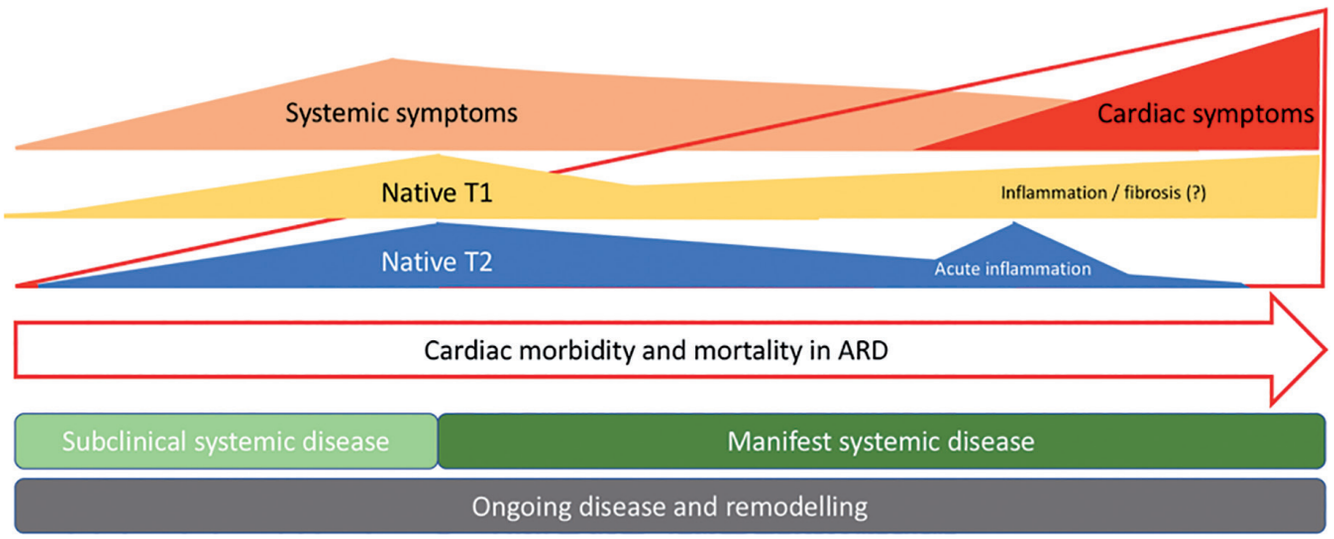

Fig. 1. Cardiac involvement in inflammatory rheumatic disease [adapted from (14)]. Schematic representation of development of cardiac involvement including potential alterations of native myocardial T1 and T2 relaxation times as quantitative CMR imaging biomarkers during the course of disease.

Myocardial inflammation

Many if not all inflammatory rheumatic diseases may include with signs of myocardial inflammation, either in a subclinical, acute, subacute or chronic stage. Myocardial inflammation may result not only from an autoimmune response in the myocardium itself but also from an inflammatory response triggered by an underlying vasculitis or by disease-modifying drugs.

In recent years, recommendations of the so-called Lake Louise criteria (20) have become an integral part of the standard CMR assessment of myocardial information and are widely used in clinical routine at specialised centers (Fig. 2). The Lake Louise criteria are considered to reflect the three hallmarks of myocardial inflammation, *i.e.* myocardial oedema, myocardial hyperemia/capillary leak, and myocardial fibrosis/necrosis. Lake Louise criteria are "positive" when two out of three diagnostic criteria are present (20): 1) a regional or global myocardial signal intensity increase on T2-weighted (T2w) images, 2) an increased global myocardial early gadolinium enhancement ratio (EGEr) between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images, and 3) at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement, LGE).

Unfortunately, the Lake Louise criteria have been found to exhibit an insufficient diagnostic accuracy especially in patients with subacute or chronic myocardial inflammation with many false positive and false negative findings (21-25). Initially, an increase of signal intensity on T2w images might be the only abnormal CMR finding without any other abnormality (25). However, T2w imaging is known to be limited by high sensitivity to motion artifacts and/or problems caused by an incomplete suppression of the blood pool signal in black blood imaging (26, 27). Measurement of the EGEr may not be feasible in inflammatory rheumatic diseases due to frequent concurrent skeletal muscle inflammation, leading to false negative results (28-31). The third Lake Louise criteria, LGE, represents a robust technique for imaging of myocardial necrosis and fibrosis, resulting in a predominant subepicardial or intramural (sometimes also transmural) location of delayed contrast accumulation. Since LGE requires the presence of normal myocardium serving as a reference region to detect areas of contrast enhancement, diffuse fibrotic patterns, which are commonly encountered in inflammatory rheumatic diseases, represent a significant hurdle for LGE imaging in this specific setting. Finally, Lake Louise criteria may remain abnormal even if the underlying disease is quiescent in patients who are asymptomatic and optimally treated (32).

Thus, in order to overcome the limitations of the Lake Louise criteria and of a pure visual image interpretation, quantitative mapping techniques (*i.e.* T1, T2, and extracellular volume (ECV) mapping) have been introduced recently for a more reliable and objective detection and monitoring of myocardial oedema and / or diffuse fibrosis in the setting of myocardial inflammation (Figs. 2-3). T2 parametric maps thereby display T2 relaxation times pixel by pixel and are generated after the acquisition of a series of images with various echo times, from which a T2 decay curve is derived (27, 31). T1 mapping is technically equivalent to T2 mapping, with a T1 relaxation curve being derived from a series of images acquired with various inversion times. Native T1 and T2 mapping do not require administration of contrast agent, unlike ECV mapping, which is calculated from the change in the T1 relaxation rate in the blood pool and myocardium between pre- and post-contrast imaging, calibrated according to the patient's haematocrit (33).

The three mapping methods are thought to deliver complementary information on the type of cardiac involvement in inflammatory rheumatic disease (14). Native T1 and ECV are considered to be sensitive indicators of myocardial inflammation, sarcoid, amyloid, fatty infiltration, as well as diffuse or replacement fibrosis (5, 7, 34, 35). Native T2 is considered a specific marker for

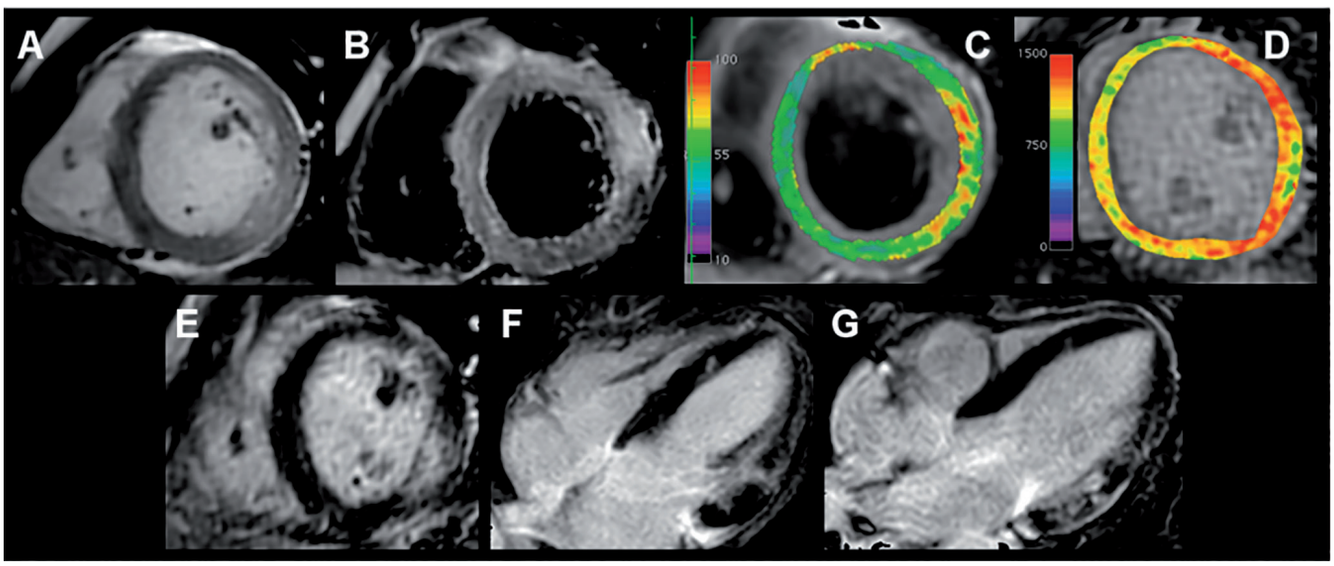

Fig. 2. A 34-year-old female with systemic lupus erythematosus (8 years since diagnosis) and acute chest pain, raised troponins but negative invasive coronary angiography. CMR with cine (**A**) and T2-weighted black blood imaging (**B**) shows acute, focal oedema mainly in the basolateral left ventricular wall with increased signal intensity and correspondingly elevated T2 relaxation times on T2 mapping (**C**) up to >100 ms. The corresponding T1 map (**D**) shows highly elevated T1 relaxation times >1500 ms in the entire lateral wall but also a diffuse pattern of mildly elevated T1 relaxation times in the remaining myocardium. LGE imaging (**E-G**) shows patchy, focal intra- to transmural enhancement in the lateral wall and smaller spots of intramural enhancement in the midventricular septum (**F** and **G**). CMR is consistent with acute myocardial inflammation and Lake Louise criteria are fulfilled. Moreover, the diffusely elevated T1 relaxation times without correspondingly (diffusely) elevated T2 relaxation times speak in favour of an additional subtle component of diffuse myocardial fibrosis in the setting of a long-standing systemic lupus erythematosus.

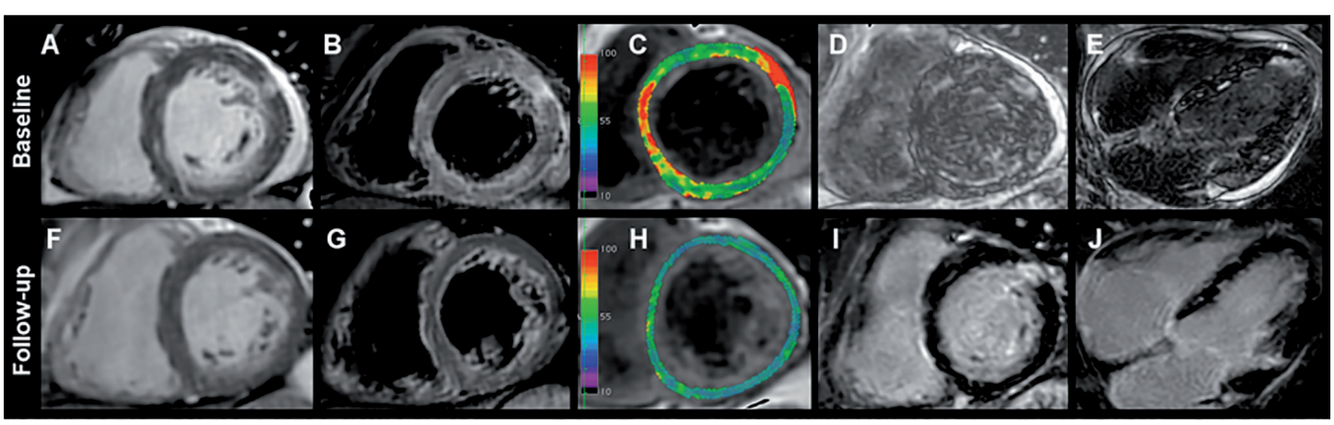

Fig. 3. A 53-year-old male with recently diagnosed Churg-Strauss vasculitis and known eosinophilic pericarditis. Repeated echocardiography showed an increasing left ventricular wall thickness, so the patient was referred to CMR to rule out myocardial inflammatory involvement. In the initial CMR (upper row, baseline examination), cine images (**A**) and T2-weighted images (**B**) demonstrate focal oedema in the anterolateral left ventricular wall with correspondingly highly elevated T2 relaxation times >100 ms on T2 mapping (**C**). Besides, diffusely elevated T2 times are displayed in the remaining myocardium with a focus in the septum. Besides, the mild pericardial effusion is noted (A-E). LGE imaging (**D** and **E**) shows alternated gadolinium kinetics (a black blood pool without adequate contrast between myocardium and blood pool due to lack of contrast inversion and insufficient inversion time selection on the Look-Locker sequence) due to massive concomitant systemic inflammation as reported previously (66) which can also be a typical sign of amyloidosis. Besides the resulting insufficient image quality, strong contrast enhancement in the pericardium and small areas of focal subendocardial and intramural contrast enhancement are suspected. CMR results are consistent with eosinophilic inflammatory peri-myocarditis. After the relief of acute symptoms, the follow-up examination after six months (bottom row) shows complete resolution of focal and diffuse myocardial oedema as well as of pericardial effusion on cine and T2-weighted imaging as well as on T2 mapping (**F**-**H**). Patchy, focal myocardial scars can be detected in the basal anterolateral left ventricular wall and the septum on LGE imaging (**I** and **J**), now showing utterly normalised gadolinium kinetics indicative of a resolved systemic inflammation (66).

myocardial oedema. Both T1 and T2 are elevated in the presence of active myocardial inflammation (27, 34, 36) (Figs. 2-3), reflecting disease severity and tracking the response to anti-inflammatory treatment (3, 37) (Fig. 3). Finally, T1 mapping has been shown to relate to prognosis, outperforming traditional risk measures such as left ventricular ejection fraction or the presence of LGE (38).

As is the case with all clinical measures, including imaging measures, some skepticism is advisable despite these encouraging results, especially when encountering the broad spectrum of the disease. Native T1 alone appears not suitable to differentiate between myocardial inflammation and diffuse fibrosis, since native T1 is elevated in both entities, which are likely to coex-

ist in inflammatory rheumatic disease (Fig. 2). The problem of T1 mapping being not specific for any substrate of cardiovascular disease – neither oedema nor fibrosis (34) – is increasingly recognised and subject to considerable debate. Similarly, ECV is not specific for diffuse fibrosis when joint inflammation/oedema is present (39). Finally, T2 mapping – although considered to be more specific for myocardial oedema – appears limited by considerable inter-individual variability of T2 relaxation times, which does not allow for the definition of a clear cut-off between health and disease (36, 40-42). More sophisticated methods for analysing T2 maps in the setting of myocardial inflammation have been reported (36, 43, 44), *e.g.* proposing an analysis of the inflammation-induced inhomogeneity of myocardial T2 relaxation times and should be further elucidated in the setting of inflammatory rheumatic disease. Although CMR faces the abovementioned hurdles, the potential for non-invasive assessment of early subclinical up to overt cardiac involvement in inflammatory rheumatic disease is extremely promising and thus offers the possibility for novel treatment options applied early during disease. Future larger prospective studies should aim at elucidating solutions for the current limitations of conventional as well as novel quantitative CMR techniques in the setting of myocardial inflammation with and without inflammatory rheumatic disease in order to avoid a need for invasive procedures such as EMB.

Microvascular coronary disease

Microvascular coronary disease (MCD) is highly prevalent in inflammatory rheumatic diseases (12, 45, 46). MCD leads to pathologic microvascular resistance, which can cause myocardial ischaemia even in the absence of macrovascular coronary artery disease (47). MCD has been shown to be one of the events first occurring during the progression of cardiac involvement mainly in systemic sclerosis, as well as in other inflammatory rheumatic diseases (48), including systemic lupus erythematosus and sarcoidosis (45, 46, 49). Over the time, diffuse disturbance of microvasculature results in repetitive ischaemic episodes with intermittent myocardial hypoperfusion form circumscribed (patchy) mid-myocardial fibrosis (45, 49) in late disease. In order to detect these early changes in microvasculature, an accurate, fast, non-invasive, reproducible and radiation-free examination to investigate MCD is needed.

CMR with stress-perfusion-testing has capacity to detect CAD and MCD with high sensitivity and specificity (45, 50-52) and shows excellent agreement with the invasive reference standard (53). For stress-perfusion-analysis, a vasodilator (typically adenosine, dipyridamole or regadenoson) is infused, and areas of reduced vasodilator reserve are delineated by the absence of contrast enhancement (50, 54). CMR perfusion studies benefit from a high temporal and spatial resolution, which allows for the detection of even small amounts of hypoperfusion, which are frequently missed by other non-invasive imaging tests (55). In addition, CMR perfusion examinations can differentiate between classical regional ischaemia due to epicardial CAD and diffuse subendocardial hypoperfusion due to MCD (14).

Since CMR stress perfusion imaging provides accurate detection or exclusion of significant CAD or MCD, it is a gatekeeper for further interventions in the case of CAD or intensified traditional treatment for MCD (14, 51).

Irreversible myocardial injury

In early cardiovascular involvement in inflammatory rheumatic disease, basic cardiac parameters like ventricular volumes and function remain relatively stable for a long time, as myocardial injury from inflammatory rheumatic disease is more likely to affect diastolic than systolic function (7, 29, 56). Relevant changes in systolic function only occur late during disease with small or no chance of recovery. At the clinical end stage of cardiac involvement in inflammatory rheumatic disease, patients usually present with symptoms of heart failure or potential life-threatening arrhythmias (4).

The critical imaging finding in end-stage disease is the existence and the degree of myocardial necrosis/fibrosis, both recognised as an enlargement of the extracellular space. CMR has the unique feature to visualise the extracellular space by use of the LGE technique. The contrast agent (gadolinium) is retained in the enlarged extracellular space after a time lag of 5–15 min, while the contrast agent in the healthy myocardium is washed out. Therefore, the enlarged extracellular space appears bright – independently of the histopathological substrate as a regional scar, fibrosis or extracellular oedema (14). It is possible to visualise even small scars with LGE ($1cm^3$; Fig. 3), which would be missed by other imaging techniques (12, 57).

Furthermore, the pattern of LGE can be used to determine the underlying etiology of the disease and provide a specific diagnosis (58). In general, CMR can discriminate between ischaemic and non-ischaemic LGE patterns. The ischaemic type usually is localised subendocardial, possibly extends to transmural and follows the territory of a coronary artery. MCD as described above leads to patchy LGE or diffuse subendocardial fibrosis, which is not related to the region perfused by a coronary artery. The non-ischaemic pattern of LGE is localised intramural or subepicardial (as in myocardial inflammation; Figs. 2-3).

About 30% of inflammatory rheumatic disease patients present with a non-ischaemic type of myocardial fibrosis (6, 48, 49, 59, 60). Typically, the non-ischaemic pattern is a sequela of myocardial inflammation (Fig. 3), and disease activity is correlated with the amount of LGE in patients with rheumatoid arthritis and systemic sclerosis (61). An ischaemic pattern of fibrosis is found in certain inflammatory rheumatic diseases like antiphospholipid syndrome and Churg-Strauss vasculitis. Notably, ischaemia is connected to thrombo-vasculitis of the coronary arteries instead of classical atherosclerosis (62-64). "Classical" ischaemia caused by atherosclerosis generally is found only in older patients with mild inflammatory disease (25, 65). Nevertheless, any presence of LGE has been shown to be a sign of a poor prognosis for the patient, independent of the type of fibrosis (14).

Conclusions and outlook

Cardiovascular involvement is a well-known common feature of inflammatory rheumatic disease, although early cardiovascular involvement often remains clinically silent. Thus, increased awareness and improved insights into the pathomechanisms of heart disease in the context of inflammatory rheumatic disease has led to an emerging role of CMR as an accurate and non-invasive diagnostic test for detection of early (as well as late) cardiovascular involvement in inflammatory rheumatic disease. CMR is most promising due to i) its capacity to detect myocardial inflammation via Lake Louise criteria and novel quantitative imaging parameters (*e.g.* T1 and T2 mapping), ii) its representation of the gold standard in the evaluation of cardiac function and volumes, iii) its capacity to represent a robust non-invasive diagnostic method to assess coronary microvascular dysfunction, and finally iv) its potential to non-invasively detect diffuse (and focal) myocardial oedema and fibrosis, primarily through a multiparametric imaging approach. Nevertheless, several limitations have to be considered for the Lake Louise criteria and especially for the newer mapping techniques before a robust application for detecting subclinical disease.

In the future, a systematic CMR evaluation of inflammatory rheumatic disease patients at the time of diagnosis promises precise and early detection of cardiovascular involvement. Hence, CMR guided cardiac anti-inflammatory therapies might be initiated, which potentially will improve cardiovascular driven outcomes in inflammatory rheumatic disease patients. Systematic interdisciplinary research programmes in the field of CMR-guided inflammatory therapy with large cohort sizes appear required, particularly with recognition of current limitations of CMR, as discussed in the preceding sections.

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