



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Fairley, JL;O'Rourke, R;Puranik, R;Nikpour, M

Title:

Cardiac magnetic resonance imaging in systemic sclerosis: Heart involvement in high-resolution

Date:

2024-06-01

Citation:

Fairley, J. L., O'Rourke, R., Puranik, R. & Nikpour, M. (2024). Cardiac magnetic resonance imaging in systemic sclerosis: Heart involvement in high-resolution. *Rheumatology and Immunology Research*, 5 (2), pp.83-92. <https://doi.org/10.1515/rir-2024-0011>.

Persistent Link:

<https://hdl.handle.net/11343/348123>

License:

CC BY

Cardiac magnetic resonance imaging in systemic sclerosis: Heart involvement in high-resolution

Jessica L Fairley^{1,2,*}, Rachael O'Rourke^{3,4}, Rajesh Puranik^{5,6}, Mandana Nikpour^{1,2,5,6}

¹The University of Melbourne, Melbourne, Victoria, Australia

²St. Vincent's Hospital Melbourne, Melbourne, Victoria, Australia

³The Prince Charles Hospital, Brisbane, Queensland, Australia

⁴The University of Queensland, Brisbane, Queensland, Australia

⁵The University of Sydney, Sydney, New South Wales, Australia

⁶Royal Prince Alfred Hospital Sydney, New South Wales, Australia

Received Mar 28, 2024 accepted Jun 12, 2024

Abstract

Cardiac magnetic resonance imaging (CMR) is the gold-standard non-invasive method of assessing cardiac structure and function, including tissue characterisation. In systemic sclerosis (SSc), heart involvement (SHI) is a leading cause of mortality yet remains poorly understood. SHI is underestimated by conventional echocardiography, and CMR provides an important opportunity to better identify and quantify subtle myocardial changes including oedema and fibrosis. This review summarises current CMR techniques, the role of CMR in SSc and SHI, and the opportunities to further our understanding of its pathogenesis and management.

Keywords

systemic sclerosis • cardiac magnetic resonance imaging • scleroderma heart involvement

Introduction

Systemic sclerosis (SSc) is an autoimmune disorder characterised by multiorgan involvement, fibrosis and tightening of the skin, as well as fibrosis of internal organs.^[1] SSc has the highest case-based mortality of all rheumatic diseases, and significantly reduced life expectancy.^[2] SSc Heart Involvement (SHI) is associated with a poor prognosis,^[3,4] but remains a poorly understood and under-recognised complication of SSc.

Autopsy studies have shown inflammatory, fibrotic and vascular changes within the myocardium, even among those without cardiac symptoms in life.^[5] Myocardial fibrosis can be identified in up to 80% of autopsy studies,^[5] suggesting a large 'subclinical' burden of SHI. Furthermore, echocardiography alone is inadequate to detect this myocardial fibrosis, with over 90% of patients with normal transthoracic echocardiography (TTE) having a pathological burden of myocardial fibrosis on cardiac magnetic resonance imaging (CMR).^[6]

This discrepancy highlights the needM for advanced imaging techniques, particularly CMR, to help understand and identify SHI given its prognostic impact. This review provides an overview of CMR techniques, and explores its role in understanding and managing SHI.

What is CMR?

CMR provides gold-standard non-invasive structural and functional imaging of the myocardium including tissue characterisation. CMR utilises either 1.5 Tesla (T) or 3T scanners with vector (VCG)-gating and dedicated software to provide detailed images of the myocardium.^[7,8] Different parameters are assessed utilising different CMR sequences (Table 1).

Structure and Functional Imaging

The initial portion of a CMR scan is dedicated to structural imaging, including cardiac size, wall thickness, morphology and function.^[9,10] This involves a combination of cine images to capture motion of both the right and left ventricles, and measurements (e.g., left ventricular [LV] ejection fraction [LVEF]). These measurements performed using CMR are generally more reproducible and accurate than those done with TTE, allowing detection of more subtle phenotypes.^[10] Specific anatomical regions may be better visualised with CMR than

Address for correspondence:

*Dr Jessica L Fairley, Research Fellow, Department of Medicine, The University of Melbourne at St Vincent's Hospital Melbourne, 41 Victoria Parade Fitzroy, Victoria, Australia. E-mail: Jessica.fairley@svha.org.au



 Open Access. © 2024 The author(s), published by De Gruyter on behalf of NCRD-DID.  This work is licensed under the Creative Commons Attribution 4.0 International License.

Table 1: Myocardial tissue characterisation using CMR.

Technique	Utility	Pitfalls
LGE	<ul style="list-style-type: none"> Gadolinium highlights areas of increased extracellular volume Identifies areas of focal myocardial fibrosis, necrosis, oedema or inflammation 	<ul style="list-style-type: none"> More difficult to identify subtle diffuse processes
T1 mapping	<p>Native T1</p> <ul style="list-style-type: none"> Abnormalities of both intra- and extra-cellular space (e.g., hypertrophy, oedema, fibrosis or infiltrative processes) Doesn't require gadolinium contrast <p>Postcontrast T1</p> <ul style="list-style-type: none"> Allows calculation of volume of extracellular space alone 	<ul style="list-style-type: none"> Less sensitive to abnormalities of only extracellular space Depends on exact local set-up; values not generalisable Abnormal values have significant overlap with normal patients. Requires gadolinium contrast Prone to artefact in setting of arrhythmia and breathing movement.
ECV fraction	<ul style="list-style-type: none"> Based on pre- and post-contrast T1 mapping Quantifies the proportion of myocardium that is extracellular to identify processes that expand the extracellular space Particularly good in detecting diffuse sub-clinical fibrosis and infiltrates 	<ul style="list-style-type: none"> Requires gadolinium contrast Removes issue of overlap with normal patients with high T1 native values.
T2 mapping	<ul style="list-style-type: none"> More sensitive to oedema than T1 mapping and T2 DIR sequences alone Particularly good at detecting global inflammation which can occur in CTD 	<ul style="list-style-type: none"> Can help overcome false-negative results of LGE and T2 DIR visual assessment in those with myositis

CMR, cardiac magnetic resonance imaging; CTD, connective tissue disease; ECV, extracellular volume; LGE, late gadolinium enhancement.

TTE, including the LV apex, lateral wall, basal septum and right ventricle.^[10] CMR can also overcome specific limitations to the quality of TTE images e.g., obesity or respiratory disease,^[11] and has higher spatial resolution and can image larger, unrestricted fields of view.

Late Gadolinium Enhancement (LGE)

Post-contrast imaging utilising LGE is key in identifying myocardial fibrosis. While fibrosis can result from many pathologies, its pattern and distribution can help to identify disease aetiology, while its extent may assist in predicting heart failure and malignant arrhythmia^[10] (Figure 1). Gadolinium contrast is administered and accumulates in the extracellular space on delayed phase imaging, thus highlighting this space. The signal from normal myocardium is balanced by identifying and nullifying the approximate T1 value of normal tissue.^[12] The concentration of gadolinium becomes higher in areas with expansion of ECV, including those of necrosis and both macro- and micro-fibrosis.^[10,12] LGE can be reported visually or quantitatively. Diffuse and/or mild delayed enhancement can be difficult to detect qualitatively. For this reason, tissue mapping is important. Different acquisition techniques and contrast agents can provide variable accuracy for LGE, although guidelines now exist for standardised protocols, reporting, interpretation and post-processing.^[8,13,14] The skill and experience of the radiographer and imaging physician is also crucial as undertraining and limited experience greatly affects image quality, and the sensitivity and specificity of the scan.

Tissue Mapping & Characterisation

Mapping and quantitative analysis are more recent techniques

that improve sensitivity and specificity, especially in cases of diffuse homogenous changes or with sub-clinical involvement that can be difficult to otherwise detect. T1, T2 and T2* are fundamental tissue magnetic relaxation times; measurement of these properties can be used to create a quantitative map of these values.^[10,15] Accurate measurements are however difficult to obtain due to artefact when the patient has implanted devices, arrhythmia or very thin myocardium.

T1 Mapping & ECV

In T1 mapping, a map of the measured T1 relaxation times of each pixel of myocardium is created.^[10] Native (pre-contrast) T1 relaxation times depend on the exact magnet and sequence used, cardiac phase and region of measurement.^[15,16] Accordingly, there are both measurement and biological factors implicated in variation in T1 values, which are specific to the local set-up including the exact magnet used in its local environment.^[15]

Native T1 values are a composite signal of both the intracellular and extracellular space, and therefore can reflect abnormalities of both regions.^[15] Helpfully, native T1 mapping can be performed without contrast if gadolinium is contraindicated. High native T1 values can occur due to oedema (e.g., inflammation or infarction), increased interstitial/extracellular space (e.g., fibrosis), increased intracellular space (e.g., hypertrophy).^[10,15] They also overlap with normal myocardium. Reduced T1 values can occur due to lipid overload (e.g., lipomatous metaplasia or glycoposphingolipid accumulation) or iron overload.^[15]

Postcontrast T1 mapping with extracellular volume calculations reflects the size and composition of the extracellular

space alone.^[12,15] Pre- and post-contrast T1 mapping can be used to calculate and map the distribution of the myocardial extracellular volume (ECV) fraction (Figure 2). This represents the proportion of the myocardium that is extracellular, as multiple pathological processes can increase the extracellular space (e.g., fibrosis, amyloid or oedema).^[12] This provides a more sensitive and specific measure of myocardial fibrosis than precontrast T1 mapping alone and can more accurately agree with histological extent of fibrosis than postcontrast T1.^[15] Increased ECV can also occur in amyloidosis, oedema and infiltrates, with the extent of increase in ECV more indicative of certain pathological processes.

T2 Mapping

T2 Double inversion recovery (DIR) images (also called “black” or “dark” blood imaging) has historically been used to detect myocardial oedema but is also useful for detection of haemorrhage and fatty infiltration. This technique can yield a false negative result for oedema detection however, as it is prone to artefact and has low sensitivity when the changes are diffuse. T2 mapping has therefore been developed to create a map of myocardial T2 relaxation times in a similar process to T1 mapping.^[10] T2 signal is particularly sensitive to oedema, fat and paramagnetic substances such as iron in haemoglobin.^[10] Global inflammation occurring in connective tissue diseases are more readily detectable by T2 mapping than by LGE^[17] as delayed enhancement due to oedema can be subtle.^[10] T2* mapping can also be used to detect and quantify iron deposition^[18] and haemorrhage.^[19]

Diagnosis of Myocarditis

Myocarditis is diagnosed according to the Lake Louise Criteria^[20] (Figure 1). These consensus criteria require both evidence of myocardial oedema (using a T2-based image acquisition) and a marker of associated non-ischaemic myocardial injury (abnormal native T1, ECV or LGE).^[20] Other supportive features include the presence of pericarditis (effusion in cine images, or abnormal LGE, T2 or T1) or systolic LV dysfunction (regional or global wall motion abnormality).^[20] These changes may be regional or global (Figure 3).

Strain Imaging

CMR assessment of myocardial strain can detect early abnormalities of myocardial deformation prior to overt myocardial dysfunction.^[21] Strain measures the percentage change in myocardial length as a marker of contractile function;^[21] this may be longitudinal, circumferential or radial, as well as global or regional.^[21] Measurement of longitudinal strain may identify early LV or RV dysfunction prior to deterioration of ejection fraction.^[22] This can be done via CMR tagging (acquiring specific sequences), or post-processing technologies applied to standard CMR techniques.^[21] However, different techniques may introduce variability in strain results, and further validation studies are required.^[21]

CMR Findings & Their Implications in SSc

The advent of CMR has identified a significantly greater burden of both myocardial fibrosis and inflammation than TTE or symptomatic assessment alone,^[6,17,23] in keeping with the frequency detected in historical autopsy studies.^[5] It must be acknowledged that as a relatively new imaging technology, our understanding of the implications of specific CMR abnormalities in SSc is evolving. However, emerging data suggest that CMR abnormalities are important prognostic indicators and potential therapeutic targets in SSc.

Myocardial Inflammation/oedema

Chronic inflammation and myocarditis are also detected more frequently with the advent of CMR.^[6,17,23,24] Left ventricular myocardial thickening diastolic dysfunction and diffuse myocardial oedema detected via T2 mapping in SSc is highly concerning for an active inflammatory myocardial lesion (e.g., myocarditis)^[20] (Figures 1, 3). This change is not identified via LGE or T1 mapping and may be missed on echocardiography. In particular, T2 mapping can help overcome the risk of false-negative results due to diffuse, subtle change not detected by readers and in those with myositis,^[24] because of the use of muscle signal intensity as a reference in those with skeletal myositis. This is one of the more reliable and significant markers of left heart disease in the context of SSc and provides an important opportunity for early detection and thus treatment which may prevent progression to fibrosis. In some individuals with asymptomatic early diffuse SSc (dcSSc), CMR has been able to identify T2 mapping abnormalities that progressed to florid myocarditis,^[23] although this is not always the case.^[6] Accordingly, all patients undergoing CMR with SSc should have T2 mapping performed in the short-axis view and 4-chamber planes. Resolution of T2 mapping abnormalities may also be a marker of treatment response in myocarditis (Figure 2).

Myocardial Fibrosis

Both focal and diffuse myocardial fibrosis has been identified in asymptomatic SSc cohorts.^[17] T1 mapping as a marker of diffuse myocardial fibrosis in SSc can identify more abnormalities than LGE alone.^[25] Importantly, native T1 mapping has been proven to directly correlate with the degree of myocardial fibrosis on endomyocardial biopsy in SHI.^[24] Native T1 and ECV, reflecting myocardial fibrosis, have been shown to be significantly elevated in SSc compared to controls, and correlate with SSc disease activity.^[17] ECV quantification may also help to identify early LV disease^[26] (Figure 2).

Myocardial Fibrosis & Adverse Cardiovascular Outcomes

Recent data suggest that CMR markers of myocardial fibrosis (LGE, native T1 and ECV) are predictive of adverse

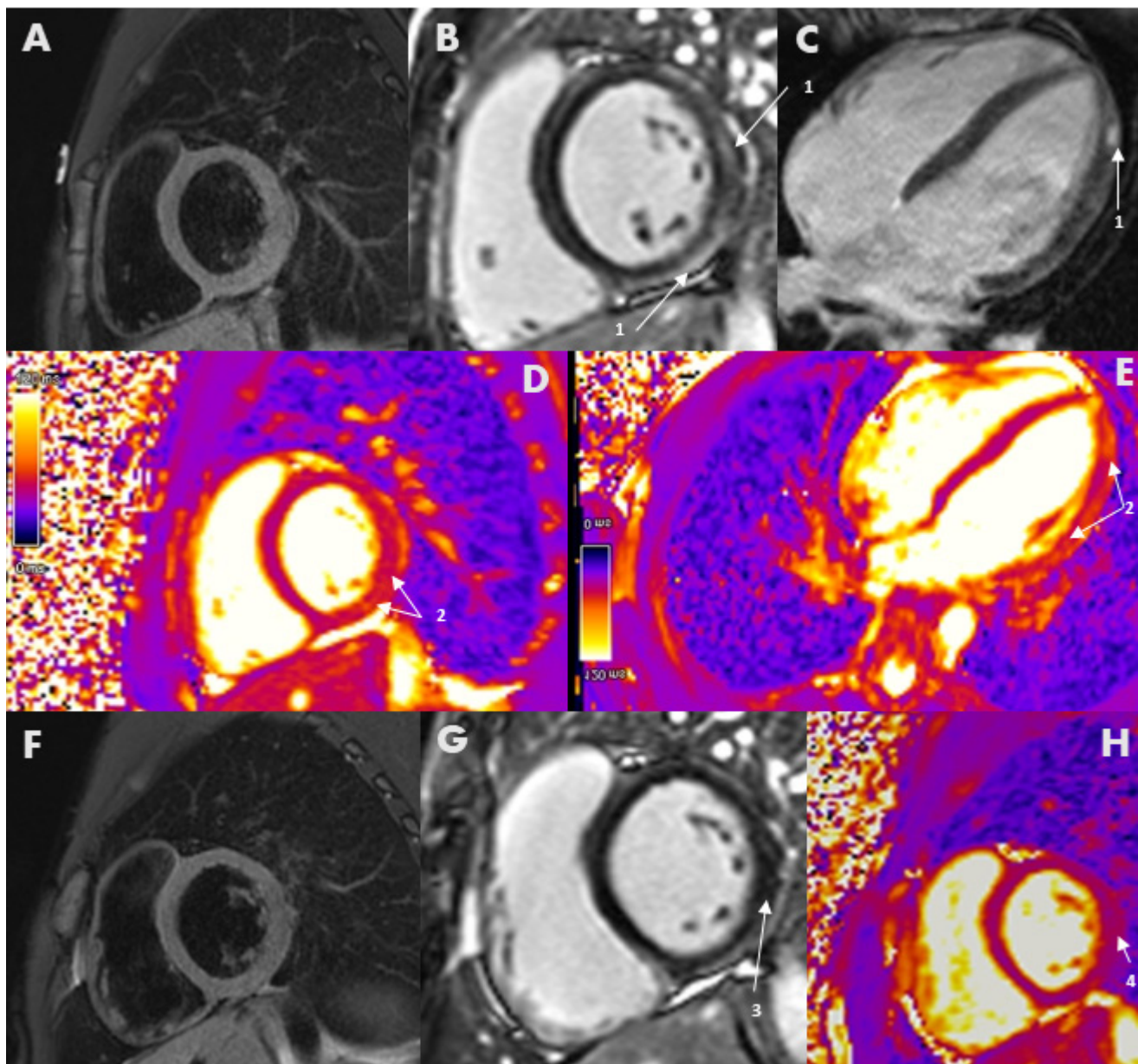


Figure 1. Acute Myocarditis. **A** Short-axis view of subtle T2 double-inversion recovery changes. **B** short & **C** long-axis view of epicardial late gadolinium enhancement (LGE) within the lateral segments of the left ventricle (1). **D** short & **E** long axis T2 colour maps confirm abnormal T2 signal within the left ventricular lateral segments (2), meeting Lake Louise criteria for myocarditis. The scale for the T2 colour maps is shown on the left, with purple representing myocardium with normal T2 relaxation times and orange representing myocardium with prolonged T2 relaxation times. **F** & **G** Follow up imaging post-resolution of myocarditis, showing mild residual LGE indicating post-inflammatory fibrosis (3). **H** Follow-up T2 mapping showing resolution of T2 abnormalities (4).

cardiovascular outcomes (death, severe arrhythmia and heart failure hospitalisation) in SSc.^[27] In multivariable analysis, LGE appears to have a prognostic value that is incremental to elevated native T1 or ECV values, suggesting a role of both diffuse and focal myocardial fibrosis.^[27] In SSc patients with acute cardiac events and normal echocardiography, CMR parameters of fibrosis (LGE and T1 mapping) and oedema (T2 mapping) have been shown to predict a combined end-point of arrhythmia, angina, dyspnoea or cardiac mortality.^[28] Overall,

these studies suggest that abnormalities on CMR indicating SHI do portend an adverse prognosis.

Data are somewhat conflicting about the role of CMR parameters in predicting the risk of arrhythmias in SSc. In SSc without overt cardiovascular disease or pulmonary arterial hypertension (PAH), no association was found between CMR-markers of focal or diffuse myocardial disease and arrhythmias.^[6] However, a further study showed that increased

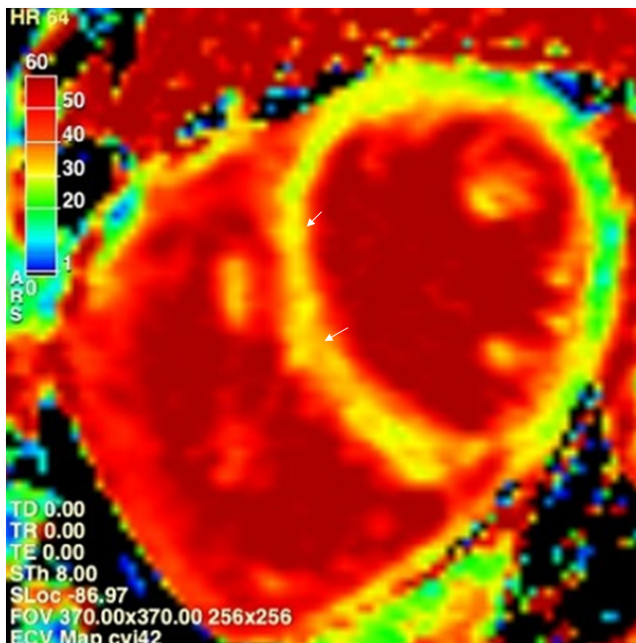


Figure 2. Myocardial Fibrosis. Extracellular volume (ECV) colour map showing diffuse interstitial fibrosis, more pronounced within the septum. The left-hand scale shows that a normal ECV of 25% should be in the green range. Yellow and orange myocardium indicates abnormal ECV (arrows).

numbers of LGE-enhancing segments were associated with abnormalities on Holter monitoring in a cohort without cardiovascular risk factors but with a high proportion of PAH.^[29] In cohorts of those with SSc and arrhythmia, CMR parameters including LGE and T2 mapping times were shown to predict recurrence of future ventricular arrhythmia.^[30] It should also be noted that the burden of myocardial fibrosis in other conditions such as hypertrophic cardiomyopathy, mitral valve prolapse and arrhythmogenic cardiomyopathy is a known predictor of arrhythmia risk. It is unknown whether there is a “threshold” of LGE or fibrosis that confers risk of arrhythmia/adverse outcome in SSc. Accordingly, further data are required in asymptomatic SSc cohorts to determine the predictive value of CMR for arrhythmic events, particularly in the absence of PAH. However, CMR may be a useful tool in determining likelihood of arrhythmia recurrence.

Myocardial Fibrosis & Impaired LV Function

CMR abnormalities may predict decline in cardiac function. Both T1 mapping and ECV have been shown to correlate with N-Terminal-pro-Brain Natriuretic Peptide (NT-pro-BNP) levels.^[24] Subtle functional impairment may occur later in the disease course in those with early markers of fibrosis identified.^[31] Myocardial abnormalities may also be associated with impaired strain parameters,^[17] and those with myocardial fibrosis may have a lower LVEF.^[32] This suggests that myocardial fibrosis may have functional implications, even though relatively small regions of myocardium may be affected.^[32] In

keeping with this idea that subtle systolic dysfunction correlates with CMR-markers of fibrosis, global longitudinal strain on echocardiography has also been shown to negatively correlate with native T1, ECV and novel cardiac biomarkers.^[33] This highlights the potential pathogenesis of SHI, with an early subclinical phase characterised by subtle T1/ECV changes indicative of global fibrosis causing impaired diastolic function, which may progress to more severe focal fibrosis characterised by LGE and systolic dysfunction.

Pericardial Pathology

CMR can provide detailed assessment of the pericardium and associated pathology, common in SSc,^[34] including effusion, inflammation and constrictive physiology^[35] (Figure 4). Pericardial thickness can be readily detected via CMR, and pericardial LGE together with T2 hyperintensity indicates active inflammation as a therapeutic target.^[35] Constriction physiology can be identified as abnormal ventricular interdependent on real-time cine imaging.

Microvascular Dysfunction

Considerable interest exists as to whether microvascular dysfunction may underpin myocardial fibrosis in SHI. Historical nuclear medicine studies have identified reversible myocardial perfusion defects in those with SSc.^[36] Furthermore, lower LVEFs have been identified in SSc in those with greater perfusion defects on nuclear medicine imaging.^[37] Novel CMR techniques provide the opportunity to explore microvascular function. Dynamic CMR can assess microvascular myocardial perfusion both qualitatively and quantitatively.^[38] However, these are currently limited to a research setting.

Progression over Time

Further data are required to understand the progression of CMR abnormalities over time in SSc. In one cohort ($n = 31$), CMR identified myocarditis in one participant, and new/worsening LGE in 4/31 participants with SSc without cardiovascular disease undergoing serial CMR over 33 months' follow-up.^[39] All participants with new/worsening LGE or myocarditis had recent-onset dcSSc and interstitial lung disease (ILD), suggesting that while serial CMR was not particularly useful in unselected participants, it did identify new abnormalities in this high-risk group.

CMR & Clues About the Aetiology of SHI

CMR data have provided clues about the aetiology of SHI. CMR measures of myocardial fibrosis appear more common in more severe SSc,^[17,24] and in dcSSc compared to limited SSc (lcSSc).^[32] Other data suggest that T1 mapping parameters may correlate with modified Rodnan skin score.^[24,40] Those with

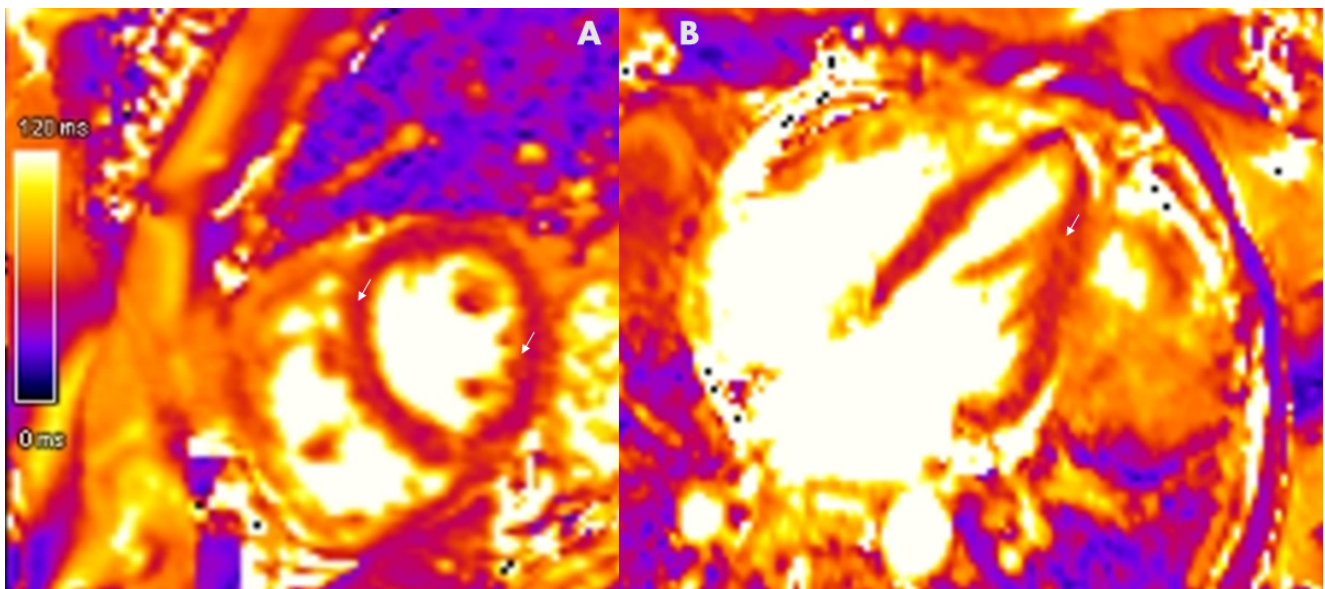


Figure 3. Diffuse myocardial oedema as a hallmark of connective-tissue disease associated myocarditis. A Short-axis view & B Long-axis view, T2 colour maps showing diffuse prolonged T2 relaxation times displayed as orange, confirming diffuse oedema (arrows).

dcSSc may also have a greater extent of affected myocardium on CMR^[17] in keeping with findings from historic autopsy studies.^[5] Furthermore, myocardial fibrosis does not appear to be associated with markers of atherosclerosis.^[32] No difference in frequency of ischaemic heart disease or its risk factors has been noted in SSc cohorts with and without elevated T1 relaxation times.^[25] CMR has also helped to confirm that electrocardiographic abnormalities in SSc are more likely to be associated with SSc disease than coronary artery disease (CAD).^[41] Perfusion abnormalities may be more common in those with recent-onset SSc, compared to myocardial fibrosis in those with longer-standing disease,^[42] in keeping with the hypothesis that microvascular perfusion abnormalities lead to myocardial fibrosis in SSc.^[43] Serum inflammatory markers may also be associated with T1 mapping^[24] and CMR perfusion defects,^[32] supporting a potential role of biochemical inflammation in myocardial disease.

CMR & Treatment of Myocardial Disease in SSc

No consensus guidelines exist for how CMR should be used to guide management in SSc. Given that CMR markers of myocardial oedema may be associated with tissue inflammation and myocarditis, close observation and/or commencement/intensification of disease-modifying therapy should be considered depending on the severity of these changes and associated symptoms.^[24,44] Management of CMR markers of myocardial fibrosis is less clear. The available data suggest that CMR markers of myocardial fibrosis are an important prognostic indicator in SSc and arguably warrant at least careful observation. The advent of antifibrotic therapies has

raised the possibility of their use in myocardial fibrosis. In a small pilot study of patients treated with nintedanib for SSc-ILD, compared to a control group, myocardial ECV and RV ejection fraction were shown to stabilise in the nintedanib-treated participants and deteriorate in untreated participants.^[45] If changes are identified in a coronary artery distribution, then investigation and treatment of CAD should be considered. Some authors argue that the identification of diffuse myocardial fibrosis warrants consideration of vasodilatory treatment (e.g., calcium channel blockade), to address potential occult microvascular disease.^[46] Furthermore, given that CMR abnormalities are indicative of myocardial pathology, other cardioprotective medications may be beneficial, including angiotensin converting enzyme (ACE) inhibitors with a potential anti-inflammatory effect.^[47] This is particularly relevant in cases with borderline LV function. However, this remains unproven in SSc and accordingly should be assessed on a case-by-case basis.

Limitations of CMR

While CMR presents a new and innovative way to characterise SHI, it has several limitations. Firstly, patient factors can limit image quality. Arrhythmia or ectopic beats can significantly degrade image quality and impinge on the accuracy of measurements. This can limit the utility of CMR in those with chronic arrhythmia or frequent ectopy. Patients are also required to perform a prolonged breath-hold to obtain diagnostic images, although modern platforms are now overcoming this with compressed sense algorithms and real time imaging. In those with significant underlying lung disease,

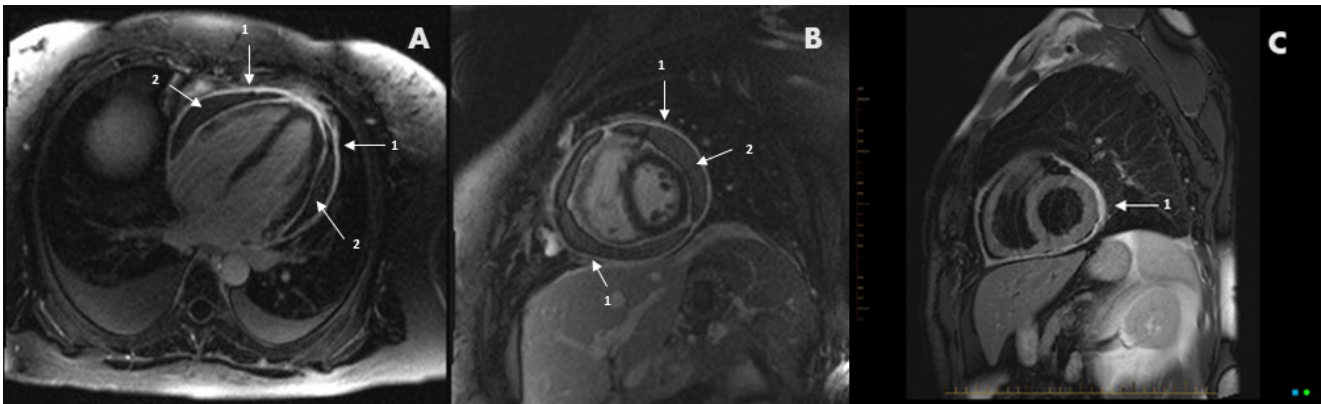


Figure 4. Pericarditis A long- & B short-axis views of constrictive pericarditis with overtly thickened pericardium (1) moderate volume effusion (2) and intense delayed enhancement involving both visceral and parietal pericardial layers. C Left ventricular short-axis plane T2 double inversion recovery sequence showing diffuse pericardial thickening (1) and high signal representing oedema.

including interstitial lung disease and PAH, as is common in SSc, patients may struggle to hold their breath long enough to obtain diagnostic images.

Additionally, CMR takes longer than average magnetic resonance imaging (MRI) scans and requires the whole head and torso of the patient to be within the magnet. Claustrophobia can thus be more problematic in patients undergoing CMR, particularly with concomitant obesity. As CMR scans take longer to perform than non-cardiac MRI, fewer patients can be imaged in the same timeframe. The level of expertise required to accurately perform and read diagnostic CMR requires subspecialty training and experience for both radiographers and imaging physicians, meaning that fewer centres offer this service and that CMR is expensive. Access to CMR is thus limited across, and SSc may not be a funded indication for CMR in many countries and institutions. As noted above, normal values for some measurements (e.g., T1 values) are dependent on the local infrastructure and sequencing and are not transferrable between set-ups. Other measures may be less reproducible and therefore harder to standardise.

MRI can be contraindicated in the presence of magnetic implants or injuries. While many implanted devices are now 'compatible' with MRI scanners, these devices, as well as prior surgery or other intervention where metal persists in the body, may still cause artefact which precludes accurate MRI of the chest. This artefact can particularly affect tissue characterisation and mapping techniques which are essential in assessment of SHI.

Finally, gadolinium contrast is required to achieve optimal tissue characterisation. This is contraindicated in those with severe renal impairment due to the risk of nephrogenic systemic fibrosis, or a history of anaphylaxis to similar contrast agents. Repeated doses of gadolinium-based contrast agents are also not recommended in young patients, as there is potential

buildup of these agents in the brain and other parts of the body. While this is less problematic with newer agents, and the clinical significance is uncertain, limiting exposure seems prudent.

Targeting CMR Use in SSc

There is a large and under-appreciated burden of fibroinflammatory disease in SSc which is detectable via CMR. However, the implications of many findings in the absence of clinical features of heart disease are unclear. Therefore, routine use of CMR in asymptomatic cohorts is not currently recommended. In the presence of clinical indicators of cardiac disease (e.g., arrhythmias, chest pain, clinical cardiac failure or abnormal cardiac biomarkers), detailed structural and functional imaging and myocardial tissue characterisation is helpful in exploring a substrate for these changes. In particular, the identification of subtle myocardial oedema using T2 mapping provides an important opportunity for early disease-modifying treatment. Recognising myocardial fibrosis using T1 mapping or LGE may also help to provide important prognostic information, and with the advent of newer antifibrotic treatments, it is possible that these changes may in future be treatable. While this is unproven in SSc, it is also possible that subtle markers of myocardial dysfunction on echocardiography e.g., abnormal global longitudinal strain, can help to risk-stratify those who would benefit from advanced myocardial imaging.

Future Avenues

CMR is a rapidly expanding and developing field, with an almost 6-fold increase in the number of CMR scans performed in the United Kingdom over the last decade^[48] and an increasing number of indications where this technique can assist with clinical decision making. Advances in

software used for image acquisition and post-processing, including the advent of deep learning and artificial intelligence, provide an important opportunity for cheaper and faster scans.^[49] This in turn may help reduce the disparity in CMR access,^[49] and facilitate faster scanning.^[50] Artificial intelligence techniques may also help to improve reproducibility by avoiding processes that are subject to intra- and inter-observer variability.^[51] Furthermore, CMR could be combined with other imaging techniques e.g. positron emission tomography (PET) scanning. PET-MRI scanning may help provide additional and complementary information about inflammatory myocardial diseases,^[52,53] especially in the context of artefact, with both conventional ¹⁸fluorodeoxyglucose (FDG) scanning and other novel tracers.^[53] However, while very sensitive and specific for active oedema, this requires the addition of a considerable dose of radiation. Finally, emerging techniques may provide additional microstructural information previously only

obtainable by histological investigation, including diffusion tensor imaging.^[53] While currently limited to research settings, these techniques would be of particular interest in SSc once more widely available.

Conclusion

CMR noninvasively characterises the myocardium in a manner that correlates with both histopathological findings and important clinical outcomes in SSc. CMR provides insights into the pathophysiology of SHI and represents an important opportunity to further our understanding of the pathogenesis and management of SHI. While access to this imaging modality is currently limited due to the level of expertise and magnet time required to provide accurate results, recognition of its importance in SSc is key to making the test more readily available.

Acknowledgements

None.

Source of funding

JLF holds a NHMRC Postgraduate Scholarship (GNT2013842), an Australian Government Research Training Program Scholarship and the University of Melbourne John Hayden Research Fellowship. MN holds an NHMRC Investigator Grant (GNT1176538).

Author contributions

JF – conceptualisation, writing – original draft preparation, writing – reviewing and editing. ROR & RP – conceptualisation, writing – reviewing and editing. MN – conceptualisation, writing – reviewing and editing, supervision.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Conflicts of interest

MN has received honoraria or consultancies from Janssen, AstraZeneca, GlaxoSmithKlein, Boehringer-Ingelheim and Bristol-Myers Squibb. JF has received conference sponsorship from Pfizer and honoraria from Boehringer-Ingelheim.

Data availability statement

No additional data is available.

REFERENCES

- [1] Bhattacharyya S, Wei J, Varga J. Understanding fibrosis in systemic sclerosis: shifting paradigms, emerging opportunities. *Nat Rev Rheumatol*. 2011;8:42–54.
- [2] Hao Y, Hudson M, Baron M, *et al*. Early Mortality in a Multinational Systemic Sclerosis Inception Cohort. *Arthritis Rheumatol*. 2017;69:1067–1077.
- [3] Fairley JL, Hansen D, Proudman S, *et al*. Prognostic and functional importance of both overt and subclinical left ventricular systolic dysfunction in systemic sclerosis. *Semin Arthritis Rheum*. 2024;66:152443.
- [4] Fairley JL, Hansen D, Burns A, *et al*. Contribution of Left Ventricular Diastolic Dysfunction to Survival and Breathlessness in Systemic Sclerosis-Associated Interstitial Lung Disease. *J Rheumatol*. 2024;51:495–504.
- [5] D'Angelo WA, Fries JF, Masi AT, *et al*. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med*. 1969;46:428–440.
- [6] Ross L, Costello B, Brown Z, *et al*. Myocardial fibrosis and arrhythmic burden in systemic sclerosis. *Rheumatology (Oxford)*. 2022;61:4497–4502.
- [7] Messroghli DR, Moon JC, Ferreira VM, *et al*. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017;19:75.
- [8] Kramer CM, Barkhausen J, Bucciereilli-Ducci C, *et al*. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson*. 2020;22:17.
- [9] Russo V, Lovato L, Ligabue G. Cardiac MRI: technical basis. *Radiol Med*. 2020;125:1040-1055.
- [10] Captur G, Manisty C, Moon JC. Cardiac MRI evaluation of myocardial disease. *Heart*. 2016;102:1429–1435.
- [11] Hamilton-Craig C, Kermeen F, Dunning JJ, *et al*. Cardiovascular magnetic resonance prior to surgical treatment of chronic thrombo-embolic pulmonary hypertension. *Eur Heart J*. 2010;31:1040.
- [12] Ambale-Venkatesh B, Lima JA. Cardiac MRI: a central prognostic tool in myocardial fibrosis. *Nat Rev Cardiol*. 2015;12:18–29.
- [13] Hundley WG, Bluemke D, Bogaert JG, *et al*. Society for Cardiovascular Magnetic Resonance guidelines for reporting cardiovascular magnetic resonance examinations. *J Cardiovasc Magn Reson*. 2009;11:5.s
- [14] Schulz-Menger J, Bluemke DA, Bremerich J, *et al*. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update : Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson*. 2020;22:19.
- [15] Haaf P, Garg P, Messroghli DR, *et al*. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson*. 2016;18:89.
- [16] Kawel N, Nacif M, Zavodni A, *et al*. T1 mapping of the myocardium: intra-individual assessment of the effect of field strength, cardiac cycle and variation by myocardial region. *J Cardiovasc Magn Reson*. 2012;14:27.
- [17] Ntusi NA, Piechnik SK, Francis JM, *et al*. Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis—a clinical study using myocardial T1-mapping and extracellular volume quantification. *J Cardiovasc Magn Reson*. 2014;16:21.
- [18] Busse A, Rajagopal R, Yücel S, *et al*. Cardiac MRI-Update 2020. *Kardiale MRT – Update 2020. Radiologe*. 2020;60:33-40.
- [19] Chen Y, Ren D, Guan X, *et al*. Quantification of myocardial hemorrhage using T2* cardiovascular magnetic resonance at 1.5T with ex-vivo validation. *J Cardiovasc Magn Reson*. 2021;23:104.
- [20] Ferreira VM, Schulz-Menger J, Holmvang G, *et al*. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol*. 2018;72:3158–3176.
- [21] Amzulescu MS, De Craene M, Langet H, *et al*. Myocardial strain imaging: review of general principles, validation, and sources of discrepancies. *Eur Heart J Cardiovasc Imaging*. 2019;20:605–619.
- [22] Kraigher-Krainer E, Shah AM, Gupta DK, *et al*. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63:447–456.
- [23] Mavrogeni SI, Bratis K, Karabela G, *et al*. Cardiovascular Magnetic Resonance Imaging clarifies cardiac pathophysiology in early, asymptomatic diffuse systemic sclerosis. *Inflamm Allergy Drug Targets*. 2015;14:29–36.
- [24] De Luca G, Palmisano A, Campochiaro C, *et al*. Cardiac magnetic resonance in systemic sclerosis myocarditis: the value of T2 mapping to detect myocardial inflammation. *Rheumatology (Oxford)*. 2022;61:4409–4419.
- [25] Pointron V, Chatelus E, Canuet M, *et al*. T1 mapping cardiac magnetic resonance imaging frequently detects subclinical diffuse myocardial fibrosis in systemic sclerosis patients. *Semin Arthritis Rheum*. 2020;50:128–134.
- [26] Thuny F, Lovric D, Schnell F, *et al*. Quantification of myocardial extracellular volume fraction with cardiac MR imaging for early detection of left ventricle involvement in systemic sclerosis. *Radiology*. 2014;271:373–380.
- [27] Bordonaro V, Bivort D, Dresselaers T, *et al*. Myocardial T1 mapping and extracellular volume quantification as novel biomarkers in risk stratification of patients with systemic sclerosis. *Clin Radiol*. 2021;76:162.
- [28] Markousis-Mavrogenis G, Bournia VK, Panopoulos S, *et al*. Cardiovascular Magnetic Resonance Identifies High-Risk Systemic Sclerosis Patients with Normal Echocardiograms and Provides Incremental Prognostic Value. *Diagnostics (Basel)*. 2019;9:220.
- [29] Tzelepis GE, Kelekis NL, Plastiras SC, *et al*. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced magnetic resonance imaging study. *Arthritis Rheum*. 2007;56:3827–3836.
- [30] Mavrogeni S, Gargani L, Pepe A, *et al*. Cardiac magnetic res-

- onance predicts ventricular arrhythmias in scleroderma: the Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS). *Rheumatology (Oxford)*. 2020;59:1938-1948.
- [31] Gotschy A, Jordan S, Stoeck CT, *et al.* Diffuse myocardial fibrosis precedes subclinical functional myocardial impairment and provides prognostic information in systemic sclerosis. *Eur Heart J Cardiovasc Imaging*. 2023;24:373–382.
- [32] Rodríguez-Reyna TS, Morelos-Guzman M, Hernández-Reyes P, *et al.* Assessment of myocardial fibrosis and microvascular damage in systemic sclerosis by magnetic resonance imaging and coronary angiotomography. *Rheumatology (Oxford)*. 2015;54:647–654.
- [33] Hromádka M, Seidlerová J, Suchý D, *et al.* Myocardial fibrosis detected by magnetic resonance in systemic sclerosis patients - Relationship with biochemical and echocardiography parameters. *Int J Cardiol*. 2017;249:448–453.
- [34] Hachulla AL, Launay D, Gaxotte V, *et al.* Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. *Ann Rheum Dis*. 2009;68:1878–1884.
- [35] Antonopoulos AS, Vrettos A, Androulakis E, *et al.* Cardiac magnetic resonance imaging of pericardial diseases: a comprehensive guide. *Eur Heart J Cardiovasc Imaging*. 2023;24:983–998.
- [36] Alexander EL, Firestein GS, Weiss JL, *et al.* Reversible cold-induced abnormalities in myocardial perfusion and function in systemic sclerosis. *Ann Intern Med*. 1986;105:661–668.
- [37] Follansbee WP, Curtiss EI, Medsger TA Jr, *et al.* Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. *N Engl J Med*. 1984;310:142–148.
- [38] Kellman P, Hansen MS, Nielles-Vallespin S, *et al.* Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. *J Cardiovasc Magn Reson*. 2017;19:43.
- [39] Dumitru RB, Bissell LA, Erhayiem B, *et al.* Subclinical Systemic Sclerosis Primary Heart Involvement by Cardiovascular Magnetic Resonance Shows No Significant Interval Change. *ACR Open Rheumatol*. 2023;5:71–80.
- [40] Lee DC, Hinchcliff ME, Sarnari R, *et al.* Diffuse cardiac fibrosis quantification in early systemic sclerosis by magnetic resonance imaging and correlation with skin fibrosis. *J Scleroderma Relat Disord*. 2018;3:159–169.
- [41] Mavrogeni S, Karabela G, Koutsogeorgopoulou L, *et al.* Pseudo-infarction pattern in diffuse systemic sclerosis. Evaluation using cardiovascular magnetic resonance. *Int J Cardiol*. 2016;214:465–468.
- [42] Mavrogeni S, Koutsogeorgopoulou L, Dimitroulas T, *et al.* Imaging patterns of stress perfusion-fibrosis in systemic sclerosis using cardiovascular magnetic resonance. *J Scleroderma Relat Disord*. 2016;1:31.
- [43] Allanore Y, Meune C. Primary myocardial involvement in systemic sclerosis: evidence for a microvascular origin. *Clin Exp Rheumatol*. 2010;28:S48-S53.
- [44] Mavrogeni SI, Sfikakis PP, Dimitroulas T, *et al.* Can cardiovascular magnetic resonance prompt early cardiovascular/rheumatic treatment in autoimmune rheumatic diseases? Current practice and future perspectives. *Rheumatol Int*. 2018;38:949–958.
- [45] Ninagawa K, Kato M, Tsuneta S, *et al.* Beneficial effects of nintedanib on cardiomyopathy in patients with systemic sclerosis: a pilot study. *Rheumatology (Oxford)*. 2023;62:2550–2555.
- [46] Mavrogeni S, Pepe A, Gargani L, *et al.* Cardiac inflammation and fibrosis patterns in systemic sclerosis, evaluated by magnetic resonance imaging: An update. *Semin Arthritis Rheum*. 2023;58:152126.
- [47] Montecucco F, Pende A, Mach F. The renin-angiotensin system modulates inflammatory processes in atherosclerosis: evidence from basic research and clinical studies. *Mediators Inflamm*. 2009;2009:752406.
- [48] Keenan NG, Captur G, McCann GP, *et al.* Regional variation in cardiovascular magnetic resonance service delivery across the UK. *Heart*. 2021;107:1974–1979.
- [49] Menacho K, Ramirez S, Segura P, *et al.* INCA (Peru) Study: Impact of Non-Invasive Cardiac Magnetic Resonance Assessment in the Developing World. *J Am Heart Assoc*. 2018;7:e008981.
- [50] Fotaki A, Puyol-Antón E, Chiribiri A, *et al.* Artificial Intelligence in Cardiac MRI: Is Clinical Adoption Forthcoming? *Front Cardiovasc Med*. 2022;8:818765.
- [51] Ruijsink B, Puyol-Antón E, Oksuz I, *et al.* Fully Automated, Quality-Controlled Cardiac Analysis From CMR: Validation and Large-Scale Application to Characterize Cardiac Function. *JACC Cardiovasc Imaging*. 2020;13:684–695.
- [52] Nensa F, Kloth J, Tezgah E, *et al.* Feasibility of FDG-PET in myocarditis: Comparison to CMR using integrated PET/MRI. *J Nucl Cardiol*. 2018;25:785–794.
- [53] Chowdhary A, Garg P, Das A, *et al.* Cardiovascular magnetic resonance imaging: emerging techniques and applications. *Heart*. 2021;107:697–704.