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Cardiovascular Magnetic Resonance of Myocardial Fibrosis, Edema, and Infiltrates in Heart Failure

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Disclosure

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Key words

Cardiac MRI, Tissue Characterisation, Mapping, Gadolinium Enhancement, Myocardial Edema, Myocardial Fibrosis

KEY POINTS

- Cardiac Magnetic Resonance (CMR) is a unique imaging modality for non-invasive tissue characterisation.
- Distribution patterns of myocardial edema and fibrosis guide the differential diagnosis and aid the identification of the underlying condition.
- Novel CMR techniques of parametric mapping are increasingly recognised and utilised as part of the diagnostic capability for tissue characterisation.

SYNOPSIS

Cardiac Magnetic Resonance (CMR) imaging is a unique imaging modality, which provides accurate non-invasive tissue characterisation. Various CMR sequences can be utilised to identify and quantify patterns of myocardial edema, fibrosis and infiltrates, which are important determinants for the diagnosis and prognostication of heart failure. We describe the available methods of tissue characterisation imaging applied in CMR, including advantages and disadvantages of each technique. We relate the presence and patterns of abnormal tissue characterisation to common aetiologies of heart failure and the techniques employed to demonstrate this. CMR provides the opportunity to identify the aetiology of heart failure (both ischemic and non-ischemic) based on the recognition of different patterns of myocardial abnormalities such as fibrosis, edema and infiltration.

INTRODUCTION

Cardiac Magnetic Resonance (CMR) is a novel and unique imaging tool providing non-invasive tissue characterisation. In particular, it can assess the presence and extent of myocardial fibrosis, edema and infiltrates of various aetiologies. The ability to assess aetiology based on various imaging sequences demonstrates the non-invasive diagnostic capability of cardiac MRI, which is particularly relevant in heart failure patients.

Different types of sequences are employed to image these different aspects of myocardial composition. Typically, the CMR test begins with anatomical and functional cine imaging using a steady state free precession (SSFP) sequence, providing information on the size of the cardiac chambers, as well as the regional and global function of the left and right ventricles and valve assessment. T2-weighted imaging is added to assess the presence and extent of myocardial edema or inflammation typically using a short tau inversion recovery sequence (T2-STIR). Tissue characterisation for myocardial fibrosis is achieved with a T1-weighted sequence following the administration of a gadolinium-chelate contrast agent (GBCA). This technique can image infarct fibrosis, replacement fibrosis and infiltration.

The newer CMR relaxometry techniques such as T1-, T2-mapping and extracellular volume (ECV) add a semi-quantitative dimension to the assessment of myocardial fibrosis and edema. Uniquely, ECV allows the determination of interstitial myocardial fibrosis. These sequences are available for both 1.5 Tesla (T) and 3.0 T scanners.

We describe these sequences and focus on the imaging patterns relevant for clinical practice. We briefly appraise the advantages and disadvantages of each technique and relate each to common aetiologies of heart failure with their associated patterns of myocardial edema, fibrosis and infiltrates.

IMAGING MYOCARDIAL EDEMA

Edema can be imaged using T2-weighted imaging sequences. *T2-weighted short tau inversion recovery* (T2-STIR) is the most commonly used sequence to image myocardial edema and inflammation. It is a breath-held black-blood segmented turbo spin-echo technique using triple inversion-recovery preparation module to suppress signal from flowing blood and fat¹. On CMR, it is used to identify myocyte swelling and interstitial

edema. The T2 sequences need to be acquired before the administration of gadolinium-based contrast agent which will not just shorten the T1 properties of the myocardium, but it will also alter its T2 properties.

It is therefore important to adequately protocol each clinical request to include T2 imaging (when indicated) prior contrast administration, if relevant to the clinical question.

It is an important technique to help differentiate between acute and chronic infarction, to identify the area at risk (AAR)^{2,3} but also to determine the acute phase of non-ischemic processes, such as acute vs chronic myocarditis and acute vs chronic sarcoidosis¹.

There are alternative sequences to image myocardial edema and inflammation. *Acquisition for cardiac unified T2 edema* (ACUT2E) imaging is a hybrid turbo spin-echo SSFP pulse sequence that does not require a black-blood preparation or a T2 preparation⁴. This combination of sequences into one imaging sequence leads to better differentiation of edema whilst delineating blood-pool and myocardium in acute infarctions.

The newer *T2-mapping* is increasingly recognised and utilised in clinical practice and guidelines^{5,6}. It is a balanced SSFP breath-held technique allowing direct quantification of myocardial inflammation and edema, overcoming the limitations of T2-STIR and other sequences, such as blood pooling and loss of signal due to cardiac movement during acquisition. Images are formed in a pixel-related colour map with a colour scale indicating the different T2 values.

Early Gadolinium Enhancement (EGE) is a breath-held gradient-echo sequence usually acquired 1-3 minutes after administration of GBCA⁷. EGE demonstrates hyperaemia, which

is a marker of acute inflammation. . However, EGE images are also useful to identify states of markedly reduced or absent perfusion such as microvascular obstruction (MVO) in the context of acute myocardial infarction, or the presence of intracavity thrombus, both entities appearing as hypo-enhanced areas.⁸

A comparative study of four available methods to imaging myocardial edema has concluded that T2 mapping is the most reproducible method.⁹

Validation of CMR in Myocardial Edema Imaging

The ability of CMR to detect myocardial edema has been validated against histology. Kim et al. demonstrated that in vivo measurement of infarct size by ²³Na magnetic resonance imaging correlated with triphenyltetrazolium chloride staining, with increases in Na⁺ levels being secondary to myocardial ischemia and to edema-related extracellular space expansion¹⁰. More recently, T2-weighted sequences and contrast-enhanced cine-SSFP sequences for the measurement of the AAR and final infarct size showed comparable results to histologic analysis with Evan blue dye and triphenyltetrazolium chloride staining, respectively¹¹. It has also been shown that the AAR measured by fluorescent microspheres at the time of coronary occlusion in an animal model correlated with the size of increased signal intensity on T2-weighted imaging¹². Finally, in a human study on acute myocardial infarction, myocardium at risk as measured on T2-weighted images correlated with that measured on single photon emission computed tomography performed early after reperfusion¹³.

IMAGING MYOCARDIAL FIBROSIS & INFILTRATES

Myocardial fibrosis and infiltrates are most commonly defined with T1-weighted imaging post-GBCA administration. Imaging of fibrosis is important as it often conveys relevant information in disease prognostication¹⁴.

Late Gadolinium Enhancement (LGE) imaging is performed 5-15 minutes after administration of GBCAs. It is a major part of tissue characterisation on CMR. Gadolinium-chelate contrast is an extracellular agent which accumulates in abnormal myocardium where extracellular space has increased due to pathology. The accumulation of GBCAs shortens T1-values leading to higher signal on T1-weighted images. Since washout of the contrast agent from abnormal myocardium is delayed, these areas will be enhanced and appear bright. The patterns of LGE, alongside edema imaging, can differentiate between ischemic and non-ischemic pathology. Ischemic aetiologies typically show subendocardial to transmural enhancement reflecting the wavefront of the ischemic damage. Mid-myocardial or subepicardial patterns are hallmarks of non-ischemic pathologies of different aetiologies¹⁵.

Fibrosis imaging in both ischemic and non-ischemic pathology is further advanced by the inclusion of CMR relaxometry techniques, namely *T1-mapping*^{16,17} and *Extracellular Volume (ECV)*. There are various sequences available to perform T1 mapping and ECV, with the majority utilising single shot balanced SSFP imaging. The most common method for T1-mapping is the Modified Look-Locker inversion recovery (MOLLI) sequence¹⁸. Other available sequences include saturation recovery (SASHA)¹⁹, and a shortened sequence (ShMOLLI)²⁰, which allows quicker acquisition of data without a detrimental impact on image quality. ECV is calculated as the ratio of native (pre-contrast) T1-mapping and post-contrast T1 mapping, which is a validated surrogate marker for interstitial fibrosis²¹. Blood

haematocrit needs to be included in the ECV formula in order to correct for the red blood cell density in the blood pool, but recent research suggested novel methods of “synthetic haematocrit” allowing ECV calculations without the need for serum blood haematocrit^{22,23}.

Diffuse infiltrative processes will also prolong T1 values and therefore the specificity of T1 mapping in these scenarios is reduced⁶.

T2* imaging is a multi-echo gradient echo sequence used at 1.5 T and best performed with dark-blood sequences^{24,25}. It is most commonly used for assessment of iron loading and is performed with a single breath-hold^{26,27}. Simultaneous evaluation of the liver and myocardium can be done allowing assessment of both hepatic and myocardial iron loading. This should be performed only on 1.5T scanning with a three tier grading system²⁸. Reference to prior scans should be made in order to assess serial measurements.

Validation of CMR in Imaging Myocardial Fibrosis

CMR fibrosis imaging techniques have been widely validated with recognition of its importance in disease prognostication²⁹. Histological correlation of ischemic scar and LGE on CMR has been demonstrated in both animal and human studies and compares favourably against SPECT^{13,30,31,32}. CMR has demonstrated both histological correlation and clinical validity in both ischemic and non-ischemic pathologies^{33,34} with the use of CMR fibrosis imaging being explored in valvular heart disease³⁵. The advent of T1-mapping techniques provides additional diagnostic quantification of myocardial fibrosis in non-ischemic pathologies with increasing recognition of its relevance and validity in clinical practice^{36,37,38}.

CLINICAL PATTERNS OF DISEASE

The unique capability of tissue characterisation by CMR can aid differential diagnosis of aetiologies of heart failure. These can be separated into ischemic and non-ischemic with specific patterns recognised in each. The combination of both T2- and T1-weighted imaging helps identifying diagnosis, as well as the chronicity of disease.

Edema is a hallmark of an acute myocardial insult, with fibrosis more reflective of a chronic process. Edema usually resolves within 3 months, both in ischemic and non-ischemic aetiologies³⁹. The presence of fibrosis in different heart failure aetiologies is often correlated with poorer prognosis.

Features of both edema and fibrosis imaging are summarised in **Figure 1**. Cardiovascular diseases and patterns of recognition of myocardial edema and fibrosis are briefly summarised below but addressed specifically in the other contributions of this Edition.

ISCHEMIC CONDITIONS

Myocardial Infarction

As further discussed in the 'Cardiovascular Magnetic Resonance in Ischemic Cardiomyopathy' section of this Edition, it should be reminded that ischemic patterns of late gadolinium enhancement (LGE) follow the ischemic wavefront, with subendocardial or transmural enhancement, in cases of full thickness myocardial infarction¹⁵. The subendocardial predominance is unique to ischemic damage and not generally seen in non-ischemic aetiologies of heart failure, with the exception of amyloidosis and endomyocardial fibrosis.

NON-ISCHEMIC CONDITIONS

Myocarditis

Imaging in acute myocarditis demonstrates edema with increased myocardial signal on T2-weighted imaging, which is the most used method. Generally, edema changes in acute myocarditis follow a non-coronary distribution with a subepicardial/mid-wall predominance. It is often seen in the lateral wall⁴⁰ but may be seen, in up to 70% of patients, as a diffuse pattern, particularly on T2-mapping. New diagnostic criteria for acute myocarditis require one T1- and one T2-weighted criterion to be met, either by standard weighted sequences or by the newer mapping techniques⁶. Chronic myocarditis is typically characterised by the absence of edema on T2-weighted imaging.

Takotsubo's Cardiomyopathy

CMR has a pivotal role in differentiating takotsubo cardiomyopathy (TCM) from acute myocarditis and acute coronary syndrome (ACS), in particular in cases of myocardial infarction with non-obstructed coronary arteries (MINOCA)⁴¹. The presence of significant myocardial edema and absence of myocardial scarring on LGE sequences in TCM is a main differentiating marker from ACS. In the acute phase, edema commonly presents a circumferential pattern with mid to apical predominance and associated regional wall motion abnormalities. Subtle late enhancement, although not often seen, may be present with a patchy appearance; this represents expanded interstitial space due to edema⁴².

Since TCM is generally recognised as a reversible cardiomyopathy, the chronic phase of this pathology should demonstrate a resolution in edema with no evidence of myocardial scarring. However, persistent edema extending beyond 3 months has been reported and associated with a more unfavourable outcome, particularly in the context of arrhythmic presentation^{43,44}.

Sarcoidosis

CMR has been recognised to aid prognostication and risk stratification in patients with sarcoidosis, with LGE being a predictor of mortality⁴⁵. LGE is usually seen in the mid-myocardium or subepicardium with a patchy appearance^{46,47}. This pattern is most commonly observed in the basal septum or lateral wall. It can, however, mimic an ischemic pattern, not following a coronary distribution, with transmural infiltrations and wall thinning.

Amyloidosis

CMR is the imaging modality of choice clearly identifying structural and physiological features of cardiac amyloidosis⁴⁸. Tissue characterisation from CMR can mitigate the need for high-risk invasive tissue biopsy and has an important role in diagnosis and prognosis in patients with cardiac amyloidosis.

The inability to sufficiently null the myocardium reflects abnormal myocardial and blood-pool gadolinium kinetics due to the accumulation of amyloid in the heart. There is usually a global endocardial LGE although transmural enhancement can be seen. The latter is more commonly seen in hereditary trans-thyretin (ATTR) amyloid compared to primary amyloidosis (AL) and infers a poorer prognosis with higher mortality rates⁴⁹.

Haemochromatosis

CMR is the gold standard for non-invasive measurement of myocardial iron deposition, which preferentially occurs in the subepicardium. Current accepted practice requires a single mid left ventricular T2*-weighted short axis slice with a region of interest over the septum to reduce susceptibility artefact⁵⁰. Long-term surveillance and serial assessments

are important as detection of changes on T2* imaging will determine adjustments to ongoing treatment^{51,52}.

Storage Diseases

Use of CMR is an important tool in storage diseases to identify presence of fibrosis. LGE in *Anderson-Fabry (AFD)* disease is commonly seen in the mid-myocardial inferolateral wall and corresponding low native T1 values on native T1-mapping in areas of fat deposits without LGE^{53,54}.

Transplant disease

Twenty-four percent of cardiac transplant patients will have acute rejection within the first year of surgery⁵⁵. Whilst endomyocardial biopsy (EMB) remains the gold-standard for diagnosing acute rejection in a transplanted heart, it requires an invasive procedure and can be complicated by life-threatening events such as cardiac tamponade and arrhythmias.

A global subendocardial pattern is observed with LGE imaging post- cardiac transplant but a diffuse patchy LGE pattern is seen in both acute and chronic rejection. Current literature suggests that combination of T1- and T2-weighted imaging techniques, including parametric mapping, can accurately assess and diagnose the presence of acute rejection⁵⁶. Elevated signal on T2-mapping in acute rejection is in keeping with myocardial edema⁵⁷, whilst expansion of the extracellular space resulting in fibrosis, is reflected by increased T1 and ECV values. The tissue characterisation achieved by CMR is invaluable in assessing long-term function in cardiac transplant patients and limiting the need for repeated EMB.

LIMITATIONS OF IMAGING MYOCARDIAL EDEMA, FIBROSIS AND INFILTRATES

Whilst CMR is often considered the imaging modality of choice for many of the conditions discussed, it does, however, have some limitations. Patients with heart failure may present acutely or as part of their chronic management. Depending on the severity of their disease, image acquisition may be limited by their ability to lie supine and relatively still for accurate image quality. CMR techniques require breath-holding and this may be difficult for those who are symptomatic with dyspnoea or have significant fluid overload which may preclude this.

Whilst techniques can be applied to minimise scanning time, these inadvertently will reduce image quality. Heart rate is an important factor that could affect image quality, a particularly atrial fibrillation. Free-breathing and real-time are technique that can facilitate imaging acquisition in patients with limited breath-holding abilities but image quality and precision of the measurements (particularly volumes and ejection fraction) is reduced.

Magnetic-resonance (MR) conditional cardiac devices, particularly pacemakers and implantable cardioverter defibrillators (ICD) have expanded the indication of CMR in these patients. Of note, recent evidence suggests that even patients with legacy (the non MR-conditional) devices are no longer a contraindications for MRI, and that these patients can be scanned safely.⁵⁸ .

SUMMARY

CMR is an invaluable tool for the diagnosis of heart failure given its non-invasive tissue characterisation ability to identify the underlying aetiologies of heart failure. It provides specific and sensitive information to allow differentiation between ischemic and non-ischemic cardiomyopathies. Novel imaging techniques are improving the ability to image

patients with heart failure and improve diagnostic accuracy. . Finally, the CMR imaging findings do not only facilitate the identification of the underlying diagnosis but allow robust prognostication of patients with heart failure.

Figure Legends

Figure 1. Clinical Scenarios of Heart Failure and CMR Patterns.

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