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Review

Assessment of myocardial fibrosis with T1 mapping MRI

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Myocardial fibrosis can arise from a range of pathological processes and its presence correlates with adverse clinical outcomes. Cardiac magnetic resonance (CMR) can provide a non-invasive assessment of cardiac structure, function, and tissue characteristics, which includes late gadolinium enhancement (LGE) techniques to identify focal irreversible replacement fibrosis with a high degree of accuracy and reproducibility. Importantly the presence of LGE is consistently associated with adverse outcomes in a range of common cardiac conditions; however, LGE techniques are qualitative and unable to detect diffuse myocardial fibrosis, which is an earlier form of fibrosis preceding replacement fibrosis that may be reversible. Novel T1 mapping techniques allow quantitative CMR assessment of diffuse myocardial fibrosis with the two most common measures being native T1 and extracellular volume (ECV) fraction. Native T1 differentiates normal from infarcted myocardium, is abnormal in hypertrophic cardiomyopathy, and may be particularly useful in the diagnosis of Anderson–Fabry disease and amyloidosis. ECV is a surrogate measure of the extracellular space and is equivalent to the myocardial volume of distribution of the gadolinium-based contrast medium. It is reproducible and correlates well with fibrosis on histology. ECV is abnormal in patients with cardiac failure and aortic stenosis, and is associated with functional impairment in these groups. T1 mapping techniques promise to allow earlier detection of disease, monitor disease progression, and inform prognosis; however, limitations remain. In particular, reference ranges are lacking for T1 mapping values as these are influenced by specific CMR techniques and magnetic field strength. In addition, there is significant overlap between T1 mapping values in healthy controls and most disease states, particularly using native T1, limiting the clinical application of these techniques at present.

Introduction

Myocardial fibrosis is integral to the pathology of a number local and systemic disease processes affecting the heart and its presence adversely predicts prognosis.[1–3] Myocardial fibrosis has traditionally been defined by histology of endomyocardial biopsies: the reference standard

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investigation for tissue characterisation of cardiomyopathies; however, this invasive technique brings with it a risk of serious complications (0.6–0.8%)[4] and is prone to sampling error. As such a non-invasive whole-heart method of assessing myocardial fibrosis is required.

Cardiac magnetic resonance imaging (CMR) is non-invasive and allows accurate assessment of cardiac structure and function. Most importantly, it provides detailed tissue characterisation, which is the key strength of CMR and is integral to its ability to aid diagnosis, prognosis, and treatment decisions. Over the last two decades, late gadolinium enhancement (LGE) imaging techniques have been developed that identify areas of focal replacement fibrosis in the myocardium. Their widespread clinical use is supported by expanding data showing that the presence of LGE is strongly associated with an adverse prognosis in several pathologies including myocardial infarction (MI),[5–8] dilated cardiomyopathy (DCM),[9] hypertrophic cardiomyopathy (HCM),[10,11] and aortic stenosis (AS).[1,12,13]

Although LGE is a useful imaging biomarker, it detects end-stage, irreversible tissue damage with replacement fibrosis. There is, therefore, considerable interest in developing novel techniques that allow earlier detection of potentially reversible diffuse fibrosis, frequently missed using LGE. Such early tissue characterisation can be achieved using MRI techniques that quantify myocardial T1 values and are starting to enter clinical practice. In this review, we will examine the novel imaging techniques used in the assessment of myocardial fibrosis, primarily focussing on the development of T1 mapping techniques, and discuss their clinical application.

LGE

This technique was first described in 1999[14] using the administration of gadolinium pentetate digmeglumine (Gd-DTPA). Following intravenous bolus administration, Gd-DTPA enters healthy myocardium down a concentration gradient (wash-in) within 1–3 minutes. As gadolinium is cleared from the blood pool by the kidneys, the contrast medium slowly exits the myocardium along the reverse concentration gradient (wash-out) over 10–30 minutes.

The large molecular size of gadolinium chelate prevents it from crossing cell membranes leading to accumulation in the extracellular space. Gadolinium potently shortens T1 related to its concentration in the tissue being imaged. Expansion of extracellular space will retain a higher concentration of gadolinium and therefore appear bright on inversion-recovery T1-weighted (T1W) sequence.[15] The inversion time (TI) can be manually adjusted to "null" the normal myocardium so that it appears black, providing the optimum visual contrasts for LGE detection. Newer phase-sensitive inversion recovery (PSIR) techniques use a background phase map, which is acquired at the same time as the image that can be used to produce intensity normalised images. This is less sensitive to TI selection, and so can avoid artefact. Although PSIR images have a lower spatial resolution, they also reduce background noise and improve the contrast-to-noise ratio[16] making them particularly useful in smaller volume centres.

Extracellular matrix (ECM) expansion and replacement fibrosis is seen in chronic MI leading to accumulation of gadolinium in these areas. In the acute setting of myocardial necrosis, there is a loss of cell membrane integrity leading to intracellular accumulation of gadolinium in the area of infarction. LGE sequences have shown excellent reproducibility and validation with histology in MI.[14] LGE imaging in the days following acute MI relates to acute cellular necrosis and myocardial oedema rather than scar and fibrosis, which usually occupies a smaller volume when it ultimately forms.[17] LGE is the reference-standard imaging technique to diagnose prior MI and offers important information on infarct size, myocardial salvage, and microvascular obstruction, all predictors of adverse outcome.[5–8,18] Importantly, these measures provide incremental prognostic information above clinical risk scores and left ventricular (LV) ejection fraction (LVEF).[8] In addition, LGE is present in a significant proportion of patients with DCM, HCM and advanced AS. Its presence in these conditions is also strongly linked with poor prognosis.[9]

LGE is essentially a difference test providing a binary assessment as to the presence or absence of LGE and requiring regions of normal myocardium to provide the necessary contrast; therefore, it has several major limitations. First, interpretation of LGE images requires a comparison between affected and unaffected myocardium and is therefore less able to detect diffuse pathological processes affecting the entire myocardium homogeneously. Second, the requirement to select manually an appropriate inversion time in order to "null" normal myocardium requires radiographer expertise and experience and introduces a potential source of error. Third, although quantification of fibrosis volume (FV) is possible, there is no universally accepted technique, and it has not been sufficiently validated for routine clinical use.[19] Finally, there is a small risk of nephrogenic systemic fibrosis with gadolinium administration, precluding its use in those with severe renal impairment,[20] although this is less of a concern with the newer cyclic agents.

T1 mapping technique

The most studied technique for assessment of diffuse myocardial fibrosis is assessment of T1 relaxation times, termed T1 mapping. A T1 map is a two-dimensional slice image where each voxel of the image displays the T1 relaxation time as signal intensity using a colour scheme for easier visual assessment. High T1 relaxation times are observed in diffuse fibrosis, protein deposition, and water in oedema. Low T1 values are seen in iron or lipid deposition.[21]

The multipoint approach to T1 sampling first described by Look and Locker (LL) in the 1970s involved continuous sampling of the T1 relaxation curve at multiple time points after an initial preparation pulse[22]; however, cardiac motion prevented the acquisition of a voxel-by-voxel T1 map and limited spatial resolution. Subsequently, the development