CMR Mapping For Myocarditis: Coming Soon to a Center Near You

Vanessa M. Ferreira, SB MD DPhil[1]

[1]Oxford Centre for Clinical Magnetic Resonance Research, Radcliffe Department of Medicine, University of Oxford

Brief title: CMR Mapping For Myocarditis

Address: Level 0 – OCMR, John Radcliffe Hospital,
Headley Way, Oxford,
United Kingdom,
OX39DU

Telephone: +44 1865 221172

Fax: +44 1865 740449

Email: vanessa.ferreira@cardiov.ox.ac.uk

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Myocarditis is a form of acute myocardial injury with a range of possible causes, including infectious, auto-immune and toxic etiologies. It is challenging to diagnose with certainty, due to its varied presentation and need for multiple tests. Frequently, patients are subjected to invasive procedures, including coronary catherization and endomyocardial biopsy (EMB), in the best attempt to provide an accurate diagnosis. In this regard, cardiovascular magnetic resonance (CMR) has, over the past 20 years, matured as the most promising non-invasive imaging tool with the most to offer patients with acute myocarditis. Even though CMR does not replace EMB in the ability to directly confirm myocardial inflammation and etiology on a histopathologic level, its clinical utility in this group of patients is well-established. CMR has a class I indication for assessment of myocarditis and storage diseases in the current European Society of Cardiology (ESC) guidelines on acute and chronic heart failure (1). CMR also provides incremental value to the standard ESC Position Statement Criteria in the workup of patients presented with suspected myocarditis (2).

Imaging myocarditis using CMR – The Lake Louise Criteria 2009

Myocardial inflammation leads to pathophysiologic changes detectable using conventional CMR techniques. These include edema (T2-weighted imaging), hyperemia and capillary leak (early gadolinium enhancement, EGE), and myocyte necrosis and fibrosis (late gadolinium enhancement, LGE). The Lake Louise Criteria 2009 for evaluating patients with suspected myocarditis (3) recommends “any two out of three” positivity, achieving a higher CMR diagnostic accuracy of acute myocarditis compared to single CMR techniques alone.

The advantages of CMR to help diagnose myocarditis include its non-invasiveness, ability to visualize areas of myocardial involvement not accessible to EMB, and to rule out acute coronary syndrome in most cases as a cause of the patient’s presentation. The drawbacks

include its relatively limited availability, recognized technical challenges (especially EGE and T2-weighted CMR) in acutely ill patients, and that the MR signal changes alone cannot confirm the etiology of the myocarditis. Nevertheless, CMR is the best non-invasive imaging modality available for evaluating acute myocarditis.

Novel CMR Mapping Techniques For Myocardial Tissue Characterization

T1 and T2 relaxation times are MR properties of tissues that are dependent on intrinsic tissue characteristics, the surrounding biological environment, and extrinsic factors, including the software and hardware used to measure them (4). In contrast to traditional weighted CMR techniques, mapping techniques generate pixel-wise, quantitative maps of the myocardium. Each pixel of the map provides a numerical T1 or T2 value of the imaged tissue with high spatial resolution, and does not rely on relative image signal intensities to diagnose disease. Each tissue type, including the myocardium, has a characteristic range of normal T1 or T2 values, deviation from which may indicate disease or a change in physiology. T1 and T2 relaxation times are highly sensitive to detecting increased free water content in tissues, whether intra- or extra-cellular. This makes T1- and T2-mapping ideal for detecting acute myocardial inflammation.

CMR Mapping For Evaluating Acute Myocarditis

The diagnostic targets in acute myocarditis, including edema, hyperemia, capillary leak and acute myocyte necrosis, all lead to increased T1 and T2 relaxation times and expansion of the extracellular volume (ECV). Mapping techniques saw a recent surge in clinical evidence demonstrating their excellent ability to detect acute myocarditis, chronic myocarditis, and even asymptomatic subclinical myocarditis as part of systemic diseases (5-9). Many of these initial studies demonstrate superiority over conventional CMR techniques, and even

equivalent diagnostic performance to the powerful LGE, raising the possibility of gadolinium-free protocols in the future.

In this issue of the *Journal of American College of Cardiology Cardiovascular Imaging* [**********reference**********], Kotanidis et al. conducted a systematic review of studies to-date that evaluate the diagnostic accuracy of CMR in detecting acute myocarditis. The investigators used the Quality Assessment of Diagnostic Accuracy Studies-2 tool to screen the quality of the studies, including bias. The use of hierarchical receiver operator curves and areas-under-the-curve (AUC) allowed comparison of the diagnostic performance of these techniques reported by relatively heterogenous studies in the literature. The results from such a rigorous statistical approach demonstrated high diagnostic accuracies of CMR mapping, with clear stratification of these techniques, showing non-overlapping confidence intervals: T1-mapping (AUC 0.95, CI 0.93-0.97), T2-mapping (AUC 0.88, CI 0.85-0.91) and ECV (AUC 0.81, CI 0.78-0.85). These are in comparison to T2-weighted imaging (AUC 0.80, CI 0.76-0.83), EGE (AUC 0.78, CI 0.74-0.81), LGE (AUC 0.89, CI 0.86-0.92) and the Lake Louise Criteria 2009 (AUC 0.81, CI 0.77-0.84). Native T1-mapping, but not ECV, appeared to be superior compared to all techniques, while T2-mapping was superior to T2-weighted and EGE imaging. Native T1-mapping also appeared to have surpassed the diagnostic accuracy of LGE, while LGE had better diagnostic accuracy than T2-weighted and EGE, with similar accuracy to T2-mapping and ECV.

The strengths of study include the meticulous and systematic effort to summarise and present the current evidence, using careful methodology to partially account for the greatly heterogenous studies currently in the literature. Many of these studies suffer from bias, as the authors have pointed out, and this is especially true for newer techniques: frequently,

investigators may choose the most severe cases to demonstrate their ability to detect changes in disease, as a first proof-of-principle. In this sense, the novel mapping techniques may have an unfair advantage in a review conducted at this time when compared to the older CMR techniques for assessing myocarditis. Additionally, mapping techniques often differ, with unique metrological properties and sensitivities to disease; when added to different scanning (whole heart coverage versus three short-axis slices) and image analysis protocols, all these factors make direct, fair comparison extremely challenging at best.

Despite these difficulties, the overall findings and conclusions seem reasonable and intuitive, but deserve a few comments. Although T1-mapping is highly sensitive to an increase in tissue free water content, native T1 detects signal from both intra- and extracellular compartments, as well as in chronic changes (e.g. in areas of focal and diffuse fibrosis), and thus is non-specific; there is some recent evidence that T2-mapping, also sensitive to acute increase in free water content, may be more specific for acute inflammatory changes, and less confounded by chronic changes (10). Thus, the use of T1-mapping for detecting acute myocardial inflammation may require approaches that allow differentiation between acute and chronic changes. ECV did not appear superior to other index CMR tests; indeed, a case may need to be made for when ECV is actually required to assess myocardial inflammation, beyond native mapping techniques and LGE. If a patient presents with predominantly acute global myocardial edema but no LGE, T2-mapping should be able to detect this; an expanded ECV would help confirm this finding. Perhaps if the image quality of T2-mapping is non-diagnostic, and other techniques have failed to detect other changes associated with acute myocarditis, ECV may have a role, to justify lengthening scan time. Future studies are required to directly evaluate these points, and to also assess the prognostic value of these novel imaging biomarkers.

Future Directions of CMR Imaging of Myocarditis

Implementing CMR mapping for clinical applications is not without its challenges. There are a variety of mapping techniques with different normal ranges, dependent on MR systems, platforms and sequence design. Ensuring stability of a chosen method would be paramount for clinical decision-making. Acquisition protocols should be optimized for evaluating the disease in question, such as whole heart coverage where possible for a condition like acute myocarditis, in which areas of myocardial involvement are often unpredictable; a single mid-ventricular slice with a limited region of interest restricted to the septum may not be adequate to maximise the utility of these powerful, pixel-wise maps that could potentially offer much more than LGE tissue characterization. CMR mapping has potential to provide a safe diagnostic test that is non-invasive, radiation-free and contrast-agent free.

Currently, it is still early to definitively determine whether mapping can replace some or all of the conventional Lake Louise Criteria for evaluating myocarditis, although results thus far point to their potential superiority. To truly evaluate their relative diagnostic performance, head-to-head comparison studies would be ideal, preferably multicentre with standardized protocols and interpretation. MR signals are not specific; making a diagnosis for individual patients would require interpretation within the clinical context, often in combination with other diagnostic tests.

For integration into clinical workflows, mapping techniques must be easy to use; visual diagnostics would be a major goal for full translation. The CMR community, with support from bodies such as the Society for Cardiac Magnetic Resonance (SCMR) and European Association for Cardiovascular Imaging (EACVI), is actively working towards many of these

goals, having published two consensus papers already on the topic of mapping techniques (4,11). Further investigation is now needed to evaluate the true clinical utility of CMR mapping as medical tools that not only aid in the diagnosis of heart disease, but also guide clinical decision-making. Ultimately, mapping techniques have shown great initial promise for evaluating not only myocardial inflammation, but also myocardial tissue characterization across a wide range of cardiac diseases; they are expected to form an integral part of a comprehensive CMR imaging protocol designed to help answer challenging questions faced by clinicians looking after cardiac patients in the near future.

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