Editorial

Seeing Beyond the Obvious

Subclinical Cardiac Sarcoidosis Revealed by Cardiovascular Magnetic Resonance Mapping

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Sarcoidosis: A Systemic Inflammatory Disease

Sarcoidosis is a systemic inflammatory disease characterized by the deposition of noncaseating granulomas in multiple organs, including the lungs, skin, central nervous system, and heart. The diagnosis of cardiac sarcoidosis is important because it confers a poorer prognosis, with an increased risk of ventricular arrhythmias, heart failure, and sudden cardiac death. The early detection of cardiac involvement in sarcoidosis may provide an opportunity for early intervention using immunosuppressive therapies, and identification of high-risk patients may warrant device therapy using implantable cardioverter defibrillator to prevent sudden cardiac death.

See Article by Greulich et al

Cardiovascular Magnetic Resonance for the Detection of Cardiac Sarcoidosis

The detection of cardiac sarcoidosis can be challenging using conventional modalities such as echocardiography because of the fact that areas of granulomatous deposition, inflammation, and fibrosis may not always be obvious when assessing for regional or global systolic function. Fluorodeoxyglucose positron emission tomography can noninvasively detect the associated myocardial inflammation, albeit with lower spatial resolution than cardiovascular magnetic resonance (CMR) imaging. CMR offers high spatial resolution for cardiac function and superior tissue characterization. In cardiac sarcoidosis, late gadolinium enhancement (LGE) correlates to areas of dense fibrosis and granulomatous inflammation within patchy fibrosis and carries a poor prognosis for all-cause mortality and future arrhythmogenic events. Myocardial inflammation may be evident on early-gadolinium enhancement and T2-weighted imaging. Fusion imaging of fluorodeoxyglucose positron emission tomography and magnetic resonance imaging may have a role in the characterization of cardiac sarcoidosis.

The underlying magnetic resonance physics principles for novel CMR mapping techniques are discussed elsewhere. The basic principle for clinical applications is that each tissue type has a normal range of T1, T2, and extracellular volume (ECV) values, deviation from which may indicate disease or a change in physiology. Parametric maps are quantitative, and within a chosen method, can be directly compared within and between individuals. In general, when there is increased free water content in tissue (such as in myocardial edema and inflammation), T1 and T2 will prolong significantly, in line with the expansion of ECV.

Mapping in Myocardial Inflammation: Current Evidence

Mapping techniques have demonstrated clinical utility in the detection of myocarditis and subclinical myocardial involvement as part of systemic inflammatory diseases, such as in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and pheochromocytoma. Crouser et al evaluated patients with histologically proven sarcoidosis using CMR LGE and T2 mapping and found that T2 values were significantly elevated in patients, including those with negative LGE findings; furthermore, T2 in combination with LGE better predicts ECG abnormalities and arrhythmias compared with either technique alone. In a follow-up study, they found that the patients with baseline T2 elevation showed significant reduction in T2 4 months after immunosuppressive therapy (70.0±5.5 versus 59.2±6.1 ms), with 83% of the immune suppression–treated subjects showing objective improvement in cardiac arrhythmias. These findings support that elevation in T2 relaxation times represents the manifestation of granulomatous inflammation that is potentially reversible with immune suppression therapy. A case report showed similar findings for native T1 mapping in cardiac sarcoidosis and a degree of reversibility with anti-inflammatory treatment.

Comprehensive CMR Assessment of Cardiac Sarcoidosis

In this issue of Circulation: Cardiovascular Imaging, Greulich et al reported the first systematic study incorporating all novel CMR parametric mapping techniques in addition to cine and LGE imaging at 1.5 T, to assess for myocardial involvement in 61 patients with sarcoidosis, compared with 26 healthy volunteers. Native T1 mapping, T2 mapping, and ECV quantification were performed on a midventricular short-axis slice, providing a global T1, T2, and ECV value for
each subject. There was no histopathologic confirmation for cardiac sarcoidosis, as endomyocardial biopsy was not clinically indicated.

The investigators found that, in patients with sarcoidosis, LV systolic function was normal, with 25% of patients demonstrating predominantly nonischemic LGE. Compared with controls, patients showed significantly higher median native T1 (994 versus 960 ms), T2 (52 versus 49 ms), and ECV (28 versus 25%), even in LGE-negative patients. Native T1 mapping was the best discriminator between patients and healthy controls. In patients with ECG abnormalities, both LGE and elevated T2 were more frequent than those without ECG abnormalities, although the median native T1 was equally elevated in both groups.

Greulich et al15 make a worthwhile contribution, demonstrating that CMR mapping offers incremental value in detecting subclinical myocardial involvement in sarcoidosis, especially when LGE and LV systolic function were unrevealing. In chronic systemic inflammatory diseases, myocardial changes on CMR may encompass cumulative past injuries in the form of focal or diffuse fibrosis and active inflammation in the present, such that it may be difficult to date these changes at a single point in time. Although myocardial edema and inflammation lead to increases in T1, T2, and ECV, some evidence suggest that T2-weighted imaging, including T2 mapping, may be more specific to changes in active myocardial inflammation and edema.16 In addition to these, T1 mapping also detects a range of conditions associated with increased free water content, such as focal or diffuse fibrosis, and the increase in myocardial blood volume because of myocardial ischemia.6,17 Native T1 increases in acutely injured myocardium and decreases over time with resolution of disease but may also detect more chronic myocardial changes in healing myocarditis, such as focal and diffuse fibrosis.18 As such, changes in T1 and ECV are nonspecific and must be interpreted within the clinical context. It is, thus, not surprising that native T1 was the best discriminator of patients from controls and also detected significantly elevated T1 values both in patients with and without ECG abnormalities, likely because T1 is sensitive to a wider spectrum of pathologic signals from both intra- and extracellular spaces.

Mapping for Detecting Myocardial Inflammation and Changes: Normal Values and Thresholds

There is considerable interest in using mapping to directly quantify and track myocardial changes over time, which brings into discussion the concept of establishing normal values, disease thresholds, and comparability of techniques between centers. It is important to keep mapping methods stable within a study. In the report by Greulich et al,15 it is reassuring to note that, although the modified Look-Locker inversion recovery T1-mapping sequence is not a previously published variant, the normal values at 1.5 T (median T1=960 ms; interquartile range, 942–986 ms) concur with most established modified Look-Locker inversion recovery-based techniques at the same field strength.19,20 Furthermore, for disease thresholds, a study using shortened Look-Locker inversion recovery at 1.5 T established a cutoff at T1 >990 ms for detecting acute myocardial edema with a sensitivity and specificity of 92%,21 and the study by Greulich et al found comparable results in the patient cohort (median T1=994 ms; interquartile range, 975–1039 ms). The comparability of these results may warrant future application of consistent thresholds using topographical T1-map processing22 across similar techniques.

Greulich et al15 used the 95th percentile in normal controls to define cutoffs for abnormality. With the sample size being relatively small at 26 subjects, it means that the diagnostic thresholds are driven by only 1 to 2 outliers. This may have contributed to the findings that 17 patients were deemed abnormal by high native T1 values, whereas only 5 patients had high ECV values. Besides inherent differences between mapping techniques, it is possible that the 95th percentile thresholds do not scale proportionately, especially when derived using relatively small numbers of normal controls as recommended by current guidelines.23

Role of Advanced Image Analysis in Mapping for Detection of Disease

The diagnostic performance of mapping depends heavily on image quality and image analysis. Greulich et al15 astutely assigned importance to image quality assessment. Excluding artifacts is important in any imaging modality, and the availability of multiple raw images on mapping techniques makes it particularly easy to identify sources of artifacts. Furthermore, as the authors have also pointed out, advanced image analysis may provide additional information beyond a single average T1, T2, or ECV value because this approach can enhance the amount and type of information that can be extracted from the maps. Whole-heart mapping, together with threshold-based analysis, has been demonstrated to provide more diagnostic information, increasing the robustness in assessing the extent of myocardial involvement and revealing distinctive patterns in affected myocardium.22

Future Directions

Greulich et al15 have demonstrated that novel CMR mapping techniques can detect subclinical myocardial changes in sarcoidosis, adding value to the diagnosis of patients otherwise classified as having normal cardiac findings. Future studies correlating mapping findings to cardiac specimens or biopsy samples from patients with proven cardiac sarcoidosis would be helpful in elucidating the origins of these early signal changes. Additionally, it would be important to determine the prognostic power of mapping techniques in patients with cardiac sarcoidosis and their ability to follow disease course and monitor response to therapy. Sarcoidosis may affect the heart insidiously, and Greulich et al15 have demonstrated how novel CMR techniques may help identify this process early, paving the way for potential CMR-guided early treatment before irreversible damages occur in a vital organ, which may favorably alter prognosis for affected patients.

Disclosures

Dr Piechnik has patent authorship rights for US patent 9285446 B2, Systems and methods for shortened Look-Locker inversion recovery cardiac gated mapping of T1, granted March 15, 2016. All rights transferred to Siemens Medical Solutions. Drs Ferreira and Piechnik...
have received support from the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre at The Oxford University Hospitals NHS Foundation Trust and the University of Oxford.

References


Key Words: Editorials ◼ cardiomyopathy ◼ gadolinium ◼ granuloma ◼ magnetic resonance imaging ◼ myocarditis ◼ sarcoidosis
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Circ Cardiovasc Imaging. 2016;9:
doi: 10.1161/CIRCIMAGING.116.005592

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