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Imaging (Q Truong, Section Editor)

Cardiac MRI Evaluation of Myocarditis

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Abstract

Purpose of review Cardiac MRI (CMR) is the non-invasive test of choice for the assessment of myocarditis. In 2009, the Lake Louise Criteria for the diagnosis of myocarditis using CMR were first released. The decade since that time has vastly improved our understanding of CMR's strengths and limitations. Traditional CMR methods including T2-weighted imaging and late gadolinium enhancement have proven their diagnostic value, but diagnostic performance is dependent on patient presentation.

Recent findings Newer parametric mapping techniques have begun to be more comprehensively studied and may improve diagnostic accuracy of CMR in an expanded set of clinical scenarios. Additionally, the prognostic value of CMR has begun to solidify. These advances culminated in an update to the Lake Louise Criteria at the end of 2018.

Summary In this review, we discuss the evolution of the diagnostic criteria for CMR in the assessment of myocarditis. We also discuss the pathophysiologic premises behind the use of specific MRI sequences and an up-to-date summary of their individual utility.

Introduction

Myocarditis is the most common cause of troponin-positive chest pain with unobstructed coronary arteries [1], yet it remains underdiagnosed as a cause of heart failure [2•] due to the challenges of diagnosis. Clinical presentation consists of non-specific features such as chest pain, arrhythmia, and heart failure. The gold standard for diagnosis of acute myocarditis is endomyocardial biopsy (EMB), but biopsy is infrequently performed. A 2007 statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology (ESC) gave class I recommendations for EMB in the relatively

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limited settings of unexplained acute heart failure with hemodynamic instability, ventricular arrhythmia, or heart block [3, 4]. While the ESC issued an updated position statement in 2013 that advocated for expanded indications [5], biopsy is still seldom pursued due to a variety of reasons such as procedural risks, sampling error, or lack of local expertise. Among non-invasive methods, EKG and echocardiography are useful for excluding other causes of cardiomyopathy, but findings are not specific to myocarditis. In comparison, cardiac MRI (CMR) enables more specific tissue characterization and has thus become the preferred modality for non-invasive diagnosis of myocarditis. In this paper, we discuss non-invasive imaging of myocarditis using CMR.

Background

Etiology

The most common etiology of myocarditis is viruses [6], but numerous other entities have been identified including autoimmune disease, bacterial/parasitic pathogens, and medications/toxins. CMR appears to be sensitive to the pathophysiologic changes of myocarditis regardless of etiology, and contemporary case reports have documented positive CMR findings with giant cell myocarditis [7], necrotizing eosinophilic myocarditis [8], immune modulators such as anti-PD-1 agents [9, 10] and high-dose IL-2 [11], mesalazine [12], antipsychotics such as clozapine [13], scorpion envenomation [14], Lyme disease [15], Ebola virus [16], and antisynthetase syndrome, a type of autoimmune inflammatory myopathy [17].

Pathophysiology and natural history

Cardiac MRI is useful for diagnosis of myocarditis because it is able to identify correlates of myocarditis pathophysiology. Therefore, it is useful to provide a brief overview.

Three stages of disease have been described in the case of viral etiologies, which are the best understood based on animal models [18–20, 21•]. In the first stage, occurring in approximately during the first four days of infection, the innate immune system is activated through direct activation by pathogens and exposure of cardiac proteins from cellular damage. Cytokine release leads to inflammation with corresponding hyperemia and expansion of the extracellular space. The second stage consists of viral replication and the adaptive immune response, lasting until approximately two weeks from initial presentation. This phase is characterized by further inflammation, and endomyocardial biopsy will typically contain large numbers of macrophages, neutrophils, and lesser numbers of T cells, B cells, dendritic cells, and mast cells. Continued cellular damage and inflammation results in both intracellular and extracellular edema with expansion of the extracellular space. In the final stage, inflammation may completely resolve or smolder chronically with resulting necrosis/fibrosis in the setting of persistent viral replication or autoimmune mechanisms. The course of disease is hence quite variable with some cases completely resolving, others resulting in rapid heart failure leading to transplant or death, and still others leading to progressive or chronic disease, often manifesting as dilated cardiomyopathy [22].

Presentation

The clinical presentation of myocarditis is variable, but four primary profiles were identified in the 2013 ESC position statement [5]. Recognition of these categories in the context of CMR is particularly important since diagnostic performance of CMR has been found to depend heavily on clinical context. Briefly, these include the following: (1) acute coronary syndrome-like myocarditis (also known as infarct-like myocarditis), consisting of chest pain, ST/T wave changes, and possible ventricular dysfunction or troponin leak; (2) new onset or worsening heart failure in the absence of CAD over 2 weeks to 3 months with impaired ventricular function; (3) chronic heart failure (>3 months) in the absence of CAD and a known cause; (4) life-threatening condition with cardiogenic shock, arrhythmia, and severely impaired left ventricular function.

Indications for CMR

CMR has become an integral part of the work-up of suspected myocarditis and is indicated in cases of suspected myocarditis with elevated troponin and/or ventricular dysfunction without identification of an alternative cause. The 2013 position statement from the ESC [5] includes CMR in two of four diagnostic criteria: (1) functional and structural abnormalities on cardiac imaging using echo, angiography, or MRI and (2) tissue characterization by CMR. Diagnosis of "clinically suspected myocarditis" can be made on the basis of a typical clinical presentation and one of four diagnostic criteria or alternatively two diagnostic criteria without a typical clinical presentation [5]. Therefore, diagnosis can theoretically be made solely on the basis of CMR findings. A subsequent 2016 guideline from the ESC on the work-up of patients with known or suspected heart failure gave a class I recommendation for cardiac MR in cases of suspected myocarditis [23].

Diagnosis of myocarditis by cardiac MRI: evolving criteria

While cardiac MRI enables improved specificity in non-invasive evaluation for myocarditis, the field is rapidly evolving and both diagnostic criteria and methods have changed over the past decade. In this section, we give an overview of these changes.

Classic cardiac MR techniques: 2009 Lake Louise Criteria

In 2009, the Lake Louise Criteria (LLC) for diagnosis of myocarditis on cardiac MR were formulated based on expert consensus [24]. Imaging sequences focused on traditional imaging CMR techniques including T2-weighted imaging, early gadolinium enhancement, and late gadolinium enhancement (LGE), corresponding to markers of edema, capillary leak, and necrosis/scarring, respectively. These are discussed in more detail below. As no single component is specific to the diagnosis of myocarditis, criteria for myocarditis based on CMR was defined as signal abnormality on two out of the three sequences. Existing data demonstrated a pooled accuracy of 78% and positive predictive value of 91% using these criteria. In addition, pericardial effusion [25] or left ventricular wall motion abnormalities were

recognized as being supportive of myocardial inflammation, though neither is necessary or sufficient for diagnosis.

Lake Louise Criteria after 10 years

The decade since the 2009 LLC raised questions about the value of LLC when compared with abbreviated protocols or even its individual components. An oft-cited study from Chu and colleagues found that using T2-weighted imaging and/or LGE as criteria for diagnosis yielded a similar diagnostic accuracy as Lake Louise Criteria but improved sensitivity, though full LLC had greater positive predictive value [26].

Recently, two meta-analyses were published which evaluated the performance of LLC and its individual components. The initial studies used to establish LLC included both biopsy-proven cases but also clinically diagnosed myocarditis. A 2017 meta-analysis by Wei and colleagues included nine studies using only-biopsy proven cases of acute and chronic myocarditis and found that CMR based on LLC does not substantially improve accuracy when compared with the individual components [27•]. All three individual components achieved an area under the curve (AUC) in the range of 0.67–0.72, and LLC obtained an AUC of 0.70. Seven of the studies reported diagnostic accuracy of LLC. A 2018 meta-analysis from Kotanidis and colleagues [28••] evaluated a total of 22 acute myocarditis studies. Similar results were obtained, with the eight studies using the full LLC criteria yielding an AUC of 0.83 and individual components resulting in an AUC of 0.78–0.87. However, caution must be taken in interpreting these results as a majority of the included studies were at high risk for bias. As discussed in the latter work, this bias often stems from study design such as case-control studies in which control patients are healthy volunteers. One reflection of this is that the sensitivity and specificity for T2-weighted images from the examined studies ranged from 0.45–1.0 and 0.43–1.0, respectively [28••].

The performance of LLC has also been found to depend heavily on clinical presentation. Good sensitivity is obtained in cases of acute myocarditis presenting with chest pain, ST elevation changes on ECG, and troponin leak as opposed to presentations primarily characterized by arrhythmia or cardiomyopathy [29]. Diagnostic accuracy appears particularly poor in the subacute or chronic setting [30].

Emerging imaging techniques: parametric mapping and the 2018 update to Lake Louise Criteria

Newly developed parametric mapping techniques have emerged in recent years as an important complement to LLC components based on early results that demonstrate excellent accuracy equaling or exceeding traditional methods [28••, 31, 32•]. Rather than creating images based on relative differences in MR signal characteristics, these techniques derive image maps of biophysical parameters such as T1 time, extracellular volume (ECV), and T2 time, which are elevated in the setting of inflammation, necrosis, or fibrosis. The Society for Cardiac Magnetic Resonance (SCMR) issued a 2017 statement stating that parametric mapping has proven clinical utility for the diagnosis of myocarditis and more generally should be considered in the diagnostic evaluation of all patients with heart failure and unexplained troponin elevation [33••].

At the end of 2018, an update to LLC was released [34••] which incorporated experiences with LLC and parametric mapping. The 2018 LLC update recommends use of at least one edema-sensitive technique (T2-weighted sequence or T2 mapping) and at least one T1-based sequence (T1 map, ECV, or T1-weighted late gadolinium enhancement). The presence of a signal abnormality on both a T2- and T1-based imaging constitutes a diagnosis, which can be thought of as a "two out of two" approach rather than a "two out of three" in the original LLC. While the "two out of two" approach is optimal for specificity, some flexibility is given in the guidelines, and abnormalities using a single technique are still supportive of myocarditis in the appropriate clinical scenario. As was true when the 2009 LLC were initially issued, there is still relatively little experience with the recommended diagnostic approach and additional studies are needed for validation.

Specific cardiac MRI techniques

In the following section, we provide a more detailed discussion of the individual cardiac MRI sequences and techniques that are used in the evaluation of myocarditis.

T2-weighted imaging

Myocardial edema as visualized on T2-weighted images is thought to be the result of acute inflammation in the early stages of myocarditis. Edema is typically seen in the septum or lateral wall in a non-vascular distribution (Fig. 1a), though any wall may be involved [35, 36]. Whereas edema in acute infarct involves the subendocardial layer, edema in myocarditis spares this region and predominantly involves the subepicardial and mid-myocardial layers of the heart. A ratio of T2 hyperintensity of the myocardium to the skeletal muscle greater than or equal to 2.0 indicates inflammation (though there is some variation in the cutoff used ranging from 1.8–2.2) [24, 31]. However, this method can fail in the setting of systemic inflammation, in which there is elevated signal intensity of both the skeletal and cardiac muscles or in cases where the inflammation is localized to a small portion of the myocardium.

T2-weighted or black blood images are typically acquired as a triple inversion recovery fast spin echo sequence (TIR-FSE), consisting of two initial inversion pulses for suppression of blood signal and a third inversion pulse for suppression of fat. Alternatively, fat saturation may be performed via a spectrally selective pulse [35]. Black blood images typically use fast spin echo techniques in combination with parallel imaging.

As above, the true sensitivity and specificity of T2-weighted images alone for acute myocarditis is somewhat unclear given the range of reported values in the literature [28••] but does improve diagnostic performance when combined with late gadolinium enhancement alone [26]. If present on initial presentation, T2-weighted imaging can be useful for monitoring disease activity (Fig. 1c) [37, 38]. The presence of abnormal T2 signal was correlated with major adverse cardiac events in one study but was not as strong a predictor as late gadolinium enhancement [39••].

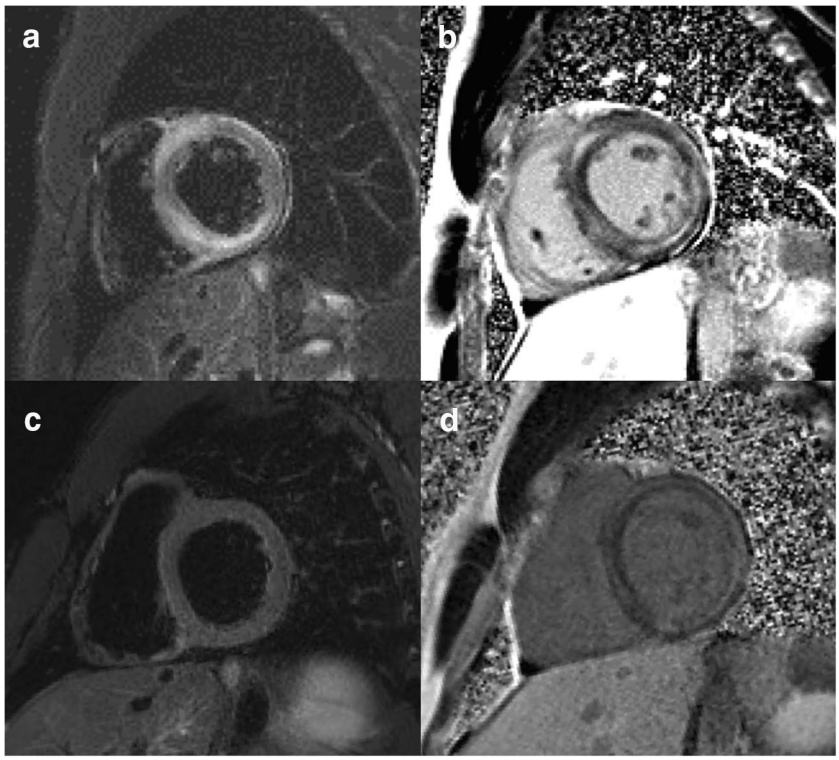

Fig. 1. A 29-year-old male presenting with chest pain and elevated troponins; catheter-based coronary angiography was negative. **a** Short-axis T2-weighted image through the base of the left ventricle demonstrates elevated mid-myocardial signal intensity of the septum and inferior wall, indicating the presence of edema. **b** Corresponding late gadolinium enhancement is seen nearly throughout the left ventricular base, greatest within the anteroseptal and inferolateral segments. **c** Follow-up scan after 6 months demonstrates resolution of myocardial edema. **d** Circumferential mid-myocardial delayed enhancement has improved but persists, indicating the presence of scar.

Early gadolinium enhancement

Early global gadolinium enhancement is thought to represent hyperemia in the setting of acute inflammation. Early global gadolinium enhancement was defined in the 2009 LLC the global enhancement ratio of the myocardium to the skeletal muscle greater than or equal to 4.0 [31]. A T1-weighted fast spin echo sequence through the myocardium is obtained before the administration of contrast and repeated in the same plane 3 min after administration of contrast to obtain this ratio. As discussed above, this ratio can be elevated in systemic myositis with skeletal muscle involvement. In addition, on short axis imaging, it can be difficult to locate a "robust" piece of the skeletal muscle in the chest wall that can be used for accurate measurements, especially in chronically ill and/or older patients. Therefore, an absolute increase in signal intensity by 45% following contrast administration can be substituted [24].

While early gadolinium enhancement was included in the 2009 LLC, omission of EGE does not appear to significantly change diagnostic accuracy [26]. Because of this, EGE was omitted from the 2018 LLC although the guideline authors note that institutions with EGE experience may prefer to use the 2009 LLC [40].

Late gadolinium enhancement

Late gadolinium sequences are generally obtained as gradient echo (GRE) sequences 10 min following contrast injection, though the exact time may vary from 8 to 20 min. With this sequence, the normal myocardium appears black by nulling its signal. This is done using an inversion pulse and then initiating the sequence when longitudinal magnetization reaches zero. Alternative methods/optimizations may be possible; for instance, in one study, contrast-enhanced steady-state free precession (SSFP) images 5 min after administration of contrast were found to have equivalent information to delayed enhancement images but improved contrast to noise ratio [41].

Because gadolinium-containing contrast localizes to the extracellular space, late gadolinium enhancement (LGE) corresponds with necrosis or extracellular edema in the acute setting [7, 21•, 22, 34••] and scar in the chronic setting (Fig. 1b, d). Although late gadolinium enhancement is described as being more common in the inferolateral and anteroseptal segments [22, 24], it can occur in any wall. Enhancement is most often subepicardial or mid-myocardial and rarely transmural. Isolated subendocardial enhancement is not seen, and enhancement rarely corresponds to a vascular distribution [42]. Additionally, delayed enhancement of the right ventricular myocardium is not uncommon.

Among cardiac MRI techniques, LGE has the best established prognostic value. The presence of LGE portends left ventricular dysfunction/dilation on follow-up [43] and poor outcome including death [39••, 44•, 45–47]. Moreover, recent studies have shown that the location of LGE is important, with mid-myocardial LGE or involvement of the anteroseptal segments as most predictive of adverse cardiac events [39••, 43, 44•]. Right ventricular involvement [48] and a patchy distribution may also be independent predictors of adverse cardiac events. When a 3-month follow-up MRI is obtained, stable or increased delayed gadolinium enhancement between the baseline study and follow-up is predictive of death, transplantation, or recurrence [49]. Some studies have found that the overall degree of LGE correlates with worse outcome [39••, 43], but data is conflicting and two large studies did not confirm this [44•, 50].

T1 mapping

Intrinsic T1 values of the myocardium elevate in the setting of myocardial edema, expansion of the extracellular space (for instance in the setting of an inflammatory infiltrate), and fibrosis and as such can indicate the presence of both myocardial inflammation and damage [51•]. Existing studies, though limited and often at risk for bias as discussed above, have thus far shown superior performance of T1 mapping when compared with LLC and other parametric mapping techniques in the diagnosis of acute myocarditis [32•, 52] with a pooled AUC of 0.95 [28••]. Most studies have focused on 1.5T magnets, but equivalent findings have been seen on 3T magnets [53]. A study by Hinojar and colleagues found that T1 mapping had nearly perfect accuracy in distinguishing between myocarditis and healthy patients and furthermore could reliably determine the difference between patients with acute myocarditis and those with "convalescent" myocarditis, in which symptoms and serologic markers had already normalized. They propose an algorithm of using a cutoff of native T1>5 standard deviations (SD) of normal for acute myocarditis and T1>2 SD for convalescent myocarditis which was validated prospectively [54].

T1 mapping requires acquisition at multiple inversion times for any particular cardiac plane. By then plotting intensity values over time and fitting a curve to the resulting plot, a T1 value can be calculated. The first practical T1 mapping sequence allowing single breath hold acquisition was MOLLI (MOdified Look-Locker Inversion recovery), which consists of a balanced steady-state free precession acquisition taken over the course of 17 heart beats. Since breath hold over 17 heart beats is not feasible in some patients, a modification to MOLLI known as ShMOLLI (Shortened MOdified Look-Locker Inversion recovery) is also commonly used, allowing acquisition over a total of 9 heart beats. Other popular methods include SASHA and SAPPHIRE; all methods have trade-offs in scan length, accuracy, and precision [55, 56].

A major barrier to widespread implementation of T1 mapping is the need for institution-specific derivation of normal values. There is considerable variability of normal myocardial T1 values both across different vendors, different magnet strengths, and different acquisition techniques. As such, the SCMR recommends establishing normal values with at least 15 healthy subjects or 20 patients referred for cardiac MR without abnormal findings [33••]. Even with such normal values established, it remains uncertain how to best apply published results to a diagnostic approach at one's own institution. In review of studies with parametric mapping, the diagnostic threshold for myocarditis had a considerable range from 852 to 1074 ms on 1.5T magnets [31]. Attempting to apply diagnostic criteria based on standard deviations from locally established T1 values of healthy volunteers is one possibility, but this approach has yet to be validated.

Extracellular volume

Measurement of extracellular volume (ECV) is a technique derived from a combination of T1 mapping and gadolinium-based contrast administration. T1 value is computed before and after administration of contrast. By using the blood pool and the patient's hematocrit as a reference standard, it becomes possible to calculate the ECV percentage on a per-voxel basis within an acquisition slice. In principle, this is desirable since it allows calculation of a physical parameter directly corresponding to abnormal filling of extracellular space such as a cellular infiltrate or fibrosis, rather than inferring such a process from changes in T1 values.

To date, ECV does not appear to have a clear advantage in diagnostic accuracy over T1 mapping or LLC for acute myocarditis [28••, 57••]. However, in a recent study, ECV was found to be an independent and stronger predictor of major adverse cardiac events compared with delayed enhancement [58•]. T1 mapping in this study was not predictive of adverse events. It is possible that ECV may have additional value in distinguishing between etiologies; in one study, ECV and post-contrast T1 time of the skeletal muscle provided the greatest accuracy in distinguishing between inflammation from acute viral myocarditis and myocarditis related to systemic myositis [59•]. AUC for these two methods was 0.95–0.96 and performance was superior to native T1 and T2 mapping.

T2 mapping

T2 mapping enables quantification of T2 time, which in turn is elevated by edema. In principle, T2 time should not be affected by the presence of fibrosis, which is a confounder for T1 mapping and LGE-based identification of acute

inflammation. T2 mapping appears to be more sensitive to myocardial changes compared with T2-weighted imaging and LGE, and in one study, an average of two additional myocardial segments were identified as abnormal using T2 mapping [60]. Overall diagnostic performance for acute myocarditis is similar or slightly lower than that of T1 mapping [28••, 32•] and possibly superior to LLC [28••, 57••]. However, its greatest value may lie in the ability to identify chronic myocarditis, as suggested by the MyoRacer trial [57••]. Patients with chronic myocarditis, defined in the study as a symptom duration of greater than 14 days, could be distinguished from healthy controls with an AUC of 0.77; T1 mapping, ECV, and LLC showed no significant difference between the two groups.

T2 mapping also shows potential for tracking disease activity over time, with one study demonstrating normalization of T2 values in a prospective cohort of acute myocarditis patients after 6 months in contradistinction to T1 values and LGE [61•]. Though medication has generally been ineffective for the treatment of myocarditis, T2 mapping may eventually prove useful for monitoring treatment response [38].

An intriguing avenue of recent research has been the investigation of T2 map texture rather than the global T2 values themselves for discriminating between disease states. In a study of a small cohort of suspected myocarditis patients with infarct-like presentation, T2 map texture could accurately distinguish between EMB-positive and EMB-negative patients with an AUC 0.88, which was a significant improvement over global T1/T2 values and LLC [62•]. Another avenue for future research is the prognostic implication of T2 mapping, with an initial study demonstrating a correlation between higher elevated global T2 time and adverse cardiac events [63•].

As with T1 mapping, T2 mapping also requires echo sampling at multiple inversion times. One method employs a black blood fast spin echo sequence but is prone to artifacts from blood flow. A second method uses a T2 preparation pulse followed by a bSSFP or gradient echo readout [64, 65] which is less vulnerable to artifacts. A final popular sequence called GraSE combines a spin echo excitation with gradient echo readout [66, 67] and appears to have advantages in reducing pixel inhomogeneity [68]. In contemporary studies, the latter two techniques are the most frequently employed.

Steady-state free precession

Steady-state free precession (SSFP) cine imaging is performed in nearly all cardiac MRI studies, providing the gold standard for ventricular size and function. Similar to echocardiography, findings of myocarditis identified on these sequences are non-specific, including global dysfunction, wall motion abnormalities, and ventricular enlargement. In addition, these sequences can be useful for identification of pericardial effusions. Diminished left ventricular ejection fraction has a strong association with adverse cardiac events [39••].

Additional MR methods

Several other methods in cardiac MRI have been studied but are still in early stages of investigation and have yet to be incorporated into standard MR protocols. The magnitude of left ventricular myocardial strain measured by MRI has been found to be lower in cases of myocarditis when compared with healthy controls [47, 69]. Moreover, lower magnitude of myocardial strain may

be associated with adverse cardiac events [47].

The use of ultra-small superparamagnetic particles of iron oxide (USPIO) such as ferumoxytol has been studied under the hypothesis that macrophages may proliferate and take up USPIO at sites of myocardial inflammation; however, an early study comparing 14 suspected cases of myocarditis with 10 healthy controls found no significant change in T2* imaging characteristics following administration of ferumoxytol in myocarditis patients versus healthy controls [70].

Conclusion

Cardiac MRI is the non-invasive method of choice for diagnosis of myocarditis. The last decade has seen the emergence of promising parametric mapping techniques which may significantly improve diagnostic accuracy of CMR. Further studies are needed to evaluate the 2018 update to the Lake Louise Criteria and comprehensively validate parametric techniques. A particularly exciting prospect is the potential for parametric mapping to accurately diagnosis myocarditis in the subacute to chronic setting, which has been a significant limitation of CMR to date. LGE and parametric mapping techniques also have prognostic value and in some cases can even provide hints to etiology. These developments are encouraging given that current treatment strategies of myocarditis are limited; one can hope that continued improvements in characterization of myocarditis by CMR may eventually provide insights on disease phenotype that can direct patients towards appropriate treatments.

Compliance with Ethical Standards

Conflict of Interest

Lewis Hahn reports personal fees from Arterys, Inc. Seth Kligerman declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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