JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 15, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.02.036

EDITORIAL COMMENT

# How Should We Diagnose Myocarditis, and Is its Recognition Really Clinically Relevant?*

G. William Dec, MD

Although the clinical spectrum of acute myocarditis varies from cardiogenic shock to asymptomatic electrocardiographic abnormalities during community viral outbreaks, its 3 most common clinical presentations are chest pain mimicking acute myocardial infarction, ventricular arrhythmias, and heart failure due to new-onset dilated cardiomyopathy (DCM) (1,2). Cardiac magnetic resonance (CMR) imaging has proven extremely valuable for assessment of clinically suspected myocarditis, by virtue of its ability to detect myocardial inflammation, myocardial edema, necrosis, and fibrosis (3). Several imaging sequences can accurately identify tissue characteristics associated with both acute and chronic myocarditis. Myocardial T1 (the spin-lattice longitudinal relaxation time) is shortened by increased interstitial space (e.g., scar, diffuse fibrosis, or infiltration) after administration of gadolinium-based contrast. T2-weighted (the spin-spin transversal relaxation time) mapping is used to detect myocardial edema, whereas early enhancement is felt to display capillary leakage and myocardial hyperemia. Contrast imaging with gadolinium enables detection of early capillary leakage based on T1-weighted early enhancement and accurate diagnosis of myocardial fibrosis based on late enhancement (LGE). LGE is frequently observed in patients with acute myocarditis in a pattern that is distinctive from ischemic myocardial injury (3). Recently, novel quantitative T1 and T2 mapping techniques, including quantification of extracellular volume, have been applied to the evaluation of patients with suspected myocarditis. Although the endomyocardial biopsy (either right, left, or biventricular) has long been the gold standard for diagnosing myocarditis, a recent European Society of Cardiology position statement recommends the use of CMR in clinically stable patients suspected of myocarditis before endomyocardial biopsy using a combined methodology of T1-weighted early gadolinium enhancement, LGE, and T2-weighted edema imaging. This combined method has been termed the "Lake Louise criteria" (4). The presence of 2 of the 3 CMR characteristics described in the Lake Louise criteria results in a sensitivity of 67%, specificity of 91%, and negative predictive value of 69% for the diagnosis of biopsy-proven myocarditis (3). Given the relatively low sensitivity, additional improvements in CMR techniques are needed.

Two recent studies have addressed the diagnostic utility of myocardial T1 mapping. Hinojar et al. (5) reported the use of T1 mapping for differentiating acute from convalescent myocarditis. These authors studied 165 patients early and 6 months after clinical onset of myocarditis. Compared with 40 control subjects, T1 values >5 SD above controls were associated with acute myocarditis; values between 2 and 5 SD were found 6 months later. Native T1 mapping outperformed LGE in detecting acute myocarditis (sensitivity 98% vs. 72%), whereas LGE was more sensitive (86% vs. 76%) in more longstanding disease. Unfortunately, myocarditis was diagnosed solely by clinical criteria; thus, the true sensitivity for detecting actual myocarditis in the acute or convalescent setting is speculative. Bohnen et al. (6) studied 31 consecutive patients with recent-onset heart failure who underwent endomyocardial biopsy and CMR imaging. Active myocarditis was defined by

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts. Dr. Dec has reported that he has no relationships relevant to the contents of this paper to disclose.

ongoing inflammation on biopsy and was detected in 52% of patients. Clinical characteristics, standard Lake Louise CMR criteria, global myocardial T1 mapping, or extracellular volume fraction did not differentiate between patients with or without active myocarditis. However, mean global myocardial T2 was significantly higher in patients with active myocarditis. Using a global cutoff of T2 >60 ms provided sensitivity, specificity, and negative and positive predictive values of 94%, 60%, 90%, and 71%, respectively, for active myocarditis. Importantly, duration of symptoms did not differ between groups and averaged 31 days (range 6 to 64). Finally, findings by Lurz et al. (7) have confirmed the low diagnostic accuracy of Lake Louise criteria among patients presenting with symptoms >2 weeks in duration, which is the rule rather than the exception for the majority of patients with recent-onset heart failure.

SEE PAGE 1800

In this issue of the *Journal*, Lurz et al. (8) describe the diagnostic performance of a comprehensive CMR imaging protocol in assessing for acute or subacute myocarditis. T1 and T2 mapping, as well as calculation of extracellular volume, were compared with biventricular endomyocardial biopsy in 129 unselected consecutive patients with clinically suspected myocarditis. The effect of field strength was also assessed by comparing 1.5-T versus 3.0-T imaging.

Patients were divided into 2 groups based on symptom duration: acute (≤14 days) versus chronic (>14 days). In patients with acute symptoms, T1 mapping yielded the best diagnostic performance with an area under the curve (AUC) receiver-operating characteristic of 0.82, substantially better than the Lake Louise criteria AUC of 0.56. In patients with subacute presentations, T2 mapping was the only technique yielding an acceptable AUC (0.77). The authors correctly conclude that, in patients with acute symptoms, newer imaging methodologies are useful for diagnosing biopsy-proven myocarditis and are superior to previously recommended Lake Louise criteria.

This well-done study further extends our knowledge regarding the noninvasive diagnosis of clinically suspected myocarditis. Strengths include a moderately large sample size, state-of-the-art CMR imaging methodologies, use of biventricular endomyocardial biopsies for histological verification of disease, comparison to the currently accepted Lake Louise diagnostic criteria, and comparison of the diagnostic accuracy of 1.5-T versus 3.0-T imaging. Despite the study's considerable strengths, the authors recognize certain limitations of their findings. Endomyocardial biopsy remains the reference standard for diagnosing myocarditis, but potential sampling error due to the focal or multifocal nature of this disease may lead to underdiagnosis. The use of biventricular biopsy, which substantially improves the rate of histological detection of myocarditis (9), has decreased the possibility of sampling error but myocardial biopsy remains a less than ideal gold standard. The actual percentage of myocarditis cases that were actually detected by CMR imaging and missed by endomyocardial biopsy cannot be answered. Further, T2 imaging was only performed on the 1.5-T system so the true accuracy of imaging at 3-T field strength remains uncertain in nonacute presentations. Finally, imaging protocols continue to evolve and vary between centers. The methodologies validated in this study were the best available in 2012, but newer techniques may further increase sensitivity and specificity.

Several major issues must be considered in proper interpretation of the clinical relevance of these new findings. First, the authors have arbitrarily defined an acute group with symptoms ≤14 days (mean 6 days) versus a "chronic" group with symptoms >14 days (mean 30 days). The vast majority of prior studies have considered acute-onset cardiomyopathy to be present when symptoms exist for <6 to 8 weeks in duration (10). Thus, most prior studies would have considered all patients in the "acute" category. Patients in their acute cohort typically presented with chest pain syndromes rather than acute heart failure; mean ejection fraction in this group was 48%. Although establishing a pathological diagnosis is desirable, the vast majority of patients with acute myocarditis presenting with acute coronary syndrome-like symptoms and relative preservation of left ventricular ejection fraction (LVEF) have an excellent prognosis. Almost all of these patients spontaneously recover with supportive therapy. Thus, diagnosing acute myocarditis in this group, while intellectually interesting, seldom alters clinical management.

A second issue in evaluating any patient with new-onset DCM is the differentiation of active myocarditis from other forms of nonischemic cardiomyopathy (e.g., idiopathic, alcohol-related, metabolic, or genetic). The relatively high sensitivity and negative predictive value for T2 imaging accurately identifies patients with high likelihood of myocarditis from normal controls. A better comparison would have been patients with clinically suspected myocarditis to those with more common causes of nonischemic DCM.

Third, current CMR imaging cannot yet differentiate the 3 major types of myocarditis: lymphocytic, giant cell, and eosinophilic. Although lymphocytic myocarditis is, by far, the most prevalent form of

myocardial inflammation, its differentiation from giant cell disease and eosinophilic disease is highly relevant. Eosinophilic myocarditis is often easily reversible with cessation of the offending pharmacological agent and early use of corticosteroids. Conversely, giant cell myocarditis has a more aggressive histological pattern and a substantially poorer outcome despite aggressive immunosuppression (1). The ability to use clinical findings and imaging data to better identify patients before biopsy based on their likely histopathologic type would greatly expand the clinical importance of CMR in this disease.

Finally, the "elephant in the room" remains the controversy about whether diagnosing acute lymphocytic myocarditis has any real clinical relevance in 2016 because there is no consensus about effective treatment options. Although a variety of agents, including immunosuppressive drugs, immunoabsorption, and antiviral therapies such as interferon, have been evaluated, both in uncontrolled studies as well as in small-scale, randomized trials, their efficacy has been largely disappointing (1,2). A high rate of spontaneous improvement in LVEF is characteristic of acute myocarditis, and it has been difficult to demonstrate that treatment specifically directed at myocardial inflammation and/or edema can improve the odds of ventricular recovery. However, there may be a change in the treatment of biopsy-proven myocarditis on the horizon. A pivotal study by Frustaci et al. (11) examined prednisone and azathioprine immunosuppression in a cohort of 85 patients with biopsy-proven myocarditis and chronic (>6 months) heart failure symptoms unresponsive to conventional therapy. Unlike prior trials, these patients had failed to improve despite 6 months of pharmacological therapy and were then randomized to active treatment or placebo. In addition, viral genome was absent in all myocardial biopsy specimens. Overall, the immunosuppressed cohort showed a significant improvement in LVEF and decrease in left ventricular size compared with baseline. No change in ventricular size or function was noted in the placebo-treated control group (11). Current European Society of Cardiology guidelines now recommend consideration of immunosuppression for patients with active myocarditis and negative viral genome on biopsy (4). Clearly, the availability of a proven treatment for biopsy-confirmed myocarditis would have substantial clinical impact and make the early and accurate evaluation of myocardial inflammation/edema essential for optimal clinical management.

This study by Lutz et al. (8) extends earlier imaging studies and validates the sensitivity and specificity of T1 mapping in assessing very acute presentations of myocarditis as well as the modest predictive value of T2 mapping in a subacute form of disease. It is time to move beyond the Lake Louise criteria and utilize these findings in assessing patients who are being considered for endomyocardial biopsy. Whether CMR imaging alone will ever be sufficient to initiate active treatment or to guide immunosuppressive therapy remains uncertain. Nonetheless, the ability to detect myocarditis with a high degree of reliability will spare many patients from an invasive biopsy procedure and allow more precise targeting of specific therapies.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. G. William Dec, Cardiology Division, Massachusetts General Hospital, Yawkey 5B, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: gdec@partners.org.

## REFERENCES

**1.** Pollack A, Kontorovitch AR, Fuster VF, Dec GW. Diagnosis and treatment of viral myocarditis: current controversies and treatment options. Nature Rev Cardiol 2015;12:670–86.

**2.** Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol 2012;59:779–92.

**3.** Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475–87.

**4.** Caforio AL, Pankuweit S, Abrustini E, et al. Current status of knowledge of etiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48.

**5.** Hinojar R, Foote L, Arroyo Ucar E, et al. Native T1 in discrimination of acute and convalescent stage in patients with clinical diagnosis of myocarditis: a proposed diagnostic algorithm using CMR. J Am Coll Cardiol Img 2015;8:37–46.

**6.** Bohnen S, Radunski K, Lund GK, et al. Performance of T1 and T2 mapping cardiovascular magnetic resonance to detect active myocarditis in patients with recent-onset heart failure. Circ Cardiovasc Imaging 2015;8:1–7.

**7.** Lurz P, Eitel I, Adam J, et al. Diagnostic performance of CMR imaging compared with EMB in patients with suspected myocarditis. J Am Coll Cardiol Img 2012;5:513–24.

**8.** Lurz P, Luecke C, Eitel I, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-Trial. J Am Coll Cardiol 2016;67:1800–11.

**9.** Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with suspected cardiomyopathies: a retrospective study over a 28-year period. Circulation 2013;128:1531–41.

**10.** McNamara DM, Starling RC, Cooper LT, et al. Clinical and demographic predictors of outcomes in recent onset dilated cardiomyopathy. Results of the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 study. J Am Coll Cardiol 2011;58:1112–8.

**11.** Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J 2009;30:1995–2002.

**KEY WORDS** endomyocardial biopsy, extracellular volume, mapping, myocardial inflammation