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EDITORIAL COMMENT

CMR in Myocarditis

Valuable Tool, Room for Improvement*

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Myocarditis can be difficult to diagnose due to varied clinical presentations, with onset ranging from insidious to acute. Endomyocardial biopsy has been the diagnostic "gold standard" but is now seldom used due to the invasive nature, high rate of sampling error, and variability in diagnostic criteria and interpretation.

Over the last decade, a body of literature has emerged that indicates a role for cardiac magnetic resonance (CMR) in diagnosing acute myocarditis. Sensitivity and specificity for myocarditis have been demonstrated for 3 quantifiable magnetic resonance imaging (MRI) "tissue parameters": 1) localized or global/diffuse elevation of myocardial T_2 signal intensity (from tissue edema in inflammation); 2) excessive percent enhancement of myocardial T_1 signal intensity early after injection of gadolinium contrast (thought to reflect hyperemia with increased vascular permeability and extracellular fluid space in inflammation); and 3) abnormal late ("delayed") myocardial enhancement (LE) post-gadolinium (reflecting injury, necrosis, and fibrosis). To account for variations in absolute signal intensity due to technical factors, the first 2 parameters are normalized by dividing with the T2 signal intensity or the percent post-gadolinium enhancement measured within skeletal muscle in the same slice, yielding an edema ratio (ER) or global relative enhancement (gRE) ratio, respectively.

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The *Journal of the American College of Cardiology* publications supporting the use of CMR for diagnosis of myocarditis include the 2006 Appropriateness Criteria, the 2010 Multi-Society Expert Consensus Document, and the 2009 White Paper (1). The latter (1) reviewed all the data available to date and concluded that the CMR diagnostic performance is best when all 3 of the afore-mentioned sequences are acquired, and they are considered consistent with myocarditis if at least 2 parameters are abnormal. However, the data were believed to be limited by relatively small studies with diverse patient selection, imaging protocol, and diagnostic criteria, and often absence of biopsy validation.

In this issue of *iJACC*, Lurz et al. (2) have undertaken a large and rigorous study to address these shortcomings. A total of 132 consecutive patients with strong clinical suspicion of myocarditis prospectively underwent a comprehensive CMR examination for myocarditis, selective coronary angiography, and multiple left ventricular endomyocardial biopsies. Biopsy analysis included histology, immunohistochemistry, and polymerase chain reaction for viral genomic analysis.

Patients were divided on the basis of symptom duration into 2 clinical groups: acute myocarditis (symptom duration $\leq$14 days; n = 70) or chronic myocarditis (symptom duration >14 days; n = 62) (2). Within the acute group, a subgroup with infarct-like myocarditis was identified (chest pain, ST-segment elevation, and elevated troponin levels; n = 37). The positive endomyocardial biopsy results were also divided into 2 histological groups: acute (n = 7) or chronic (n = 75) myocarditis determined on the basis of the presence of myocyte

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injury/necrosis versus fibrosis, respectively, accompanying the inflammatory infiltrate.

Left ventricular biopsy results demonstrated inflammation consistent with myocarditis in 83 of 132 patients (2). With this standard, the sensitivity, specificity, and accuracy of CMR for diagnosing myocarditis in the overall patient cohort was 76%, 54%, and 68%, respectively, when using the "2 of 3 criteria" approach. These figures improved to 81%, 71%, and 79%, respectively, in the patient group with acute symptoms and improved further to 86%, 75%, and 84% in the subgroup with infarct-like myocarditis. The authors' explanation for this favorable trend is plausible: more acute and intense symptoms may be expected to demonstrate increasing myocardial edema, hyperemia, and injury/necrosis, resulting in more definitive CMR abnormalities. For all 3 patient groups, sensitivity, positive and negative predictive values, and overall diagnostic accuracy are better using the 2 of 3 approach compared with any of the 3 parameters individually.

This study (2) relies on endomyocardial biopsy to make the correct diagnosis of myocarditis. However, the threshold of 14 leukocytes/mm^2 involves a sensitivity versus specificity trade-off of its own, and the issue of biopsy sampling error is well known. In an oft-quoted postmortem study of hearts from patients who died with lymphocytic myocarditis, this diagnosis could be demonstrated by using histology from a single biopsy specimen only 17% to 20% of the time (3). When the number of biopsy specimens was increased to 10, the diagnosis could still be made only 55% to 63% of the time. This issue correlates with key information demonstrated by delayed enhancement imaging: The lesions identified in myocarditis are almost invariably located in the subepicardial to mid-myocardial layers of the ventricular wall, and are therefore not readily accessible by endomyocardial biopsy. CMR offers a global view of the myocardium, but when tested against biopsy findings, a lower calculated accuracy becomes inevitable. A patient with myocarditis whose MRI scan is positive and yet has a falsely negative biopsy result will be erroneously counted as a false positive, which will lower the apparent specificity of CMR.

Other potential causes for false-positive CMR studies in the acute setting include stress-induced (takotsubo) cardiomyopathy and acute coronary syndromes. Two of 3 MRI parameters evaluated in myocarditis (the ER and gRE ratios) can reportedly also be abnormal in stress cardiomyopathy; however, late enhancement is generally not present (4). Six of 84 patients with late enhancement in this study showed a predominantly subendocardial pattern. Subendocardial involvement has previously been relied on to differentiate ischemic lesions from myocarditis, and subendocardial infarction may occasionally be seen in the absence of angiographically significant epicardial coronary disease. Detailed angiographic data are not provided, nor do we know the specific biopsy findings in these 6 patients.

Dividing the patients into "acute" and "chronic" clinical subgroups provides valuable information by defining when current CMR techniques for detecting myocarditis are less likely to be helpful. Importantly, with symptoms lasting >14 days, the sensitivity, specificity, and diagnostic accuracy of CMR were surprisingly poor (63%, 40%, and 52%, respectively) (2). This unexpected finding questions the utility of adding the full complement of myocarditis sequences to look for evidence of inflammation when CMR is done to evaluate unexplained heart failure, increasing ventricular ectopy, or dilated cardiomyopathy of recent (but >14 days') onset. The basis for this lower performance with increasing chronicity is likely 2-fold: as the authors suggest, chronicity is likely associated with a lower intensity of myocardial inflammation, making the MRI abnormalities more subtle, thereby lowering sensitivity. Furthermore, the patient group with more insidious symptom onset will have a broad interface with a spectrum of other cardiac conditions with similar clinical presentation and potential for some overlap in MRI findings. For example, a wide range of nonischemic conditions have been identified where myocardial delayed enhancement is present. Mid-wall fibrosis associated with idiopathic dilated cardiomyopathy or physiological hypertrophy (e.g., in aortic stenosis), or even residual fibrosis from a remote episode of myocarditis, could occasionally mimic myocarditis. Hypertrophic cardiomyopathy or active cardiac sarcoidosis may demonstrate delayed enhancement lesions that colocalize with focal myocardial T_2 hyperintensity. Infiltrative cardiomyopathies such as amyloid, or conceivably diffuse interstitial fibrosis found in chronic heart failure of multiple etiologies, may cause elevation of the gRE ratio. These situations increase the odds of false-positive CMR studies for myocarditis, which would lower specificity, and vigilance by the CMR reader regarding the possible presence of other entities is always required.

This study (2) provides strong support for using CMR for confirmation when a diagnosis of myo-

carditis is entertained in patients who present with acute (up to 14 days) onset of symptoms. It also indicates a need for improvement before CMR can be relied on to differentiate myocarditis from multiple other forms of heart disease when the presentation is more chronic. This realistic assessment of CMR for the diagnosis of myocarditis is enhanced by the "real-world" design of this study, meaning the unselected inclusion of "all comers" in whom myocarditis is suspected, not acceptance of technically suboptimal studies. Quantitative accuracy of the calculated parameters deteriorates if image quality becomes impaired, which undermines the diagnostic reliability of the examination. Incremental gains in diagnostic performance of CMR may thus be realized if gains in image quality are achieved, for example, in new CMR-capable centers as they gain broader experience. Development of more robust pulse sequences is anticipated and should improve image quality. Additional work is needed to determine whether and how much the diagnostic thresholds need to be adjusted for variations in technique, such as use of alternative gadolinium agents or dose, or performing the studies at different magnetic field strengths (3.0-T instead of 1.5-T). Possible confounding of the normalized ER and gRE ratios if there is associated skeletal muscle myositis could ideally be addressed more rigorously. New approaches, such as T_2- and possibly T_1-mapping techniques or use of macrophage-avid or other targeted contrast agents, may provide additional opportunities for CMR in the future to answer the crucial question of whether myocardial inflammation is present or not among patients who present with heart failure/cardiomyopathy of more intermediate (longer than 14 days) duration.

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REFERENCES

1. 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.
2. 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.
3. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. Mayo Clin Proc 1989;64:1235–45.
4. Eitel I, Lucke C, Grothoff M, et al. Inflammation in takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging. Eur Radiol 2010;20:422–31.

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