JACC: CARDIOVASCULAR IMAGING VOL. 13, NO. 1, 2020

PUBLISHED BY ELSEVIER

EDITORIALS AND VIEWPOINTS

CMR in Nonischemic Myocardial Inflammation

Solving the Problem of Diagnosing Myocarditis or Still Diagnostic Ambiguity?

Eike Nagel, MD, PhD,[a] Raymond Y. Kwong, MD, MPH,[b] Y.S. Chandrashekhar, MD, DM[c]

The recent publication of the expert consensus on cardiac magnetic resonance (CMR) imaging in nonischemic myocardial inflammation (1) is a highly welcome update of the methods and value of CMR in the diagnostic work-up of these patients. The update has been required due to the advent of novel methods such as T1 and T2 mapping which allow the assessment of quantitative data and diffuse disease rather than previous methods which relied on either regional differences within the myocardium or between the myocardium and reference tissues (2–5). These novel techniques have been compared with those described in the Lake Louise Criteria (6) and have consistently shown similar or superior diagnostic accuracy (7).

The recent updated recommendations by Ferreira et al. (1) added new diagnostic pathways to the assessment of acute myocardial inflammation (**Figure 1**). The original Lake Louise Criteria (6) were the first pathway based on edema, hyperemia, and necrosis, using T2-weighted, early gadolinium enhancement, and late gadolinium enhancement (LGE) imaging. Using prespecified cutoff values, 2 of these 3 criteria must be fulfilled for a positive diagnosis of myocardial inflammation. The second pathway is based on a combination of a T2-based marker for myocardial edema, such as T2-weighted imaging or T2-mapping, with a T1-based marker for associated myocardial injury (including edema), such as native T1-mapping, LGE, or extracellular volume. Findings including pericardial effusion and left ventricular wall motion abnormality serve as supportive criteria in either pathway.

The updated consensus takes the recent published reports of mapping techniques into account, which consistently demonstrate a similar or higher diagnostic accuracy of mapping than the original Lake Louise Criteria and provide a strong pathophysiological rationale for the diagnostic algorithm. The original Lake Louise Criteria were supported by reports from "centers with good experience," but significant heterogeneity existed in the overall publications. Compared to the original Lake Louise Criteria, novel T2-based and T1-based mapping methods are more quantitative and potentially add diagnostic objectivity and "offer at least a theoretical advantage over the original Lake Louise Criteria." The expert consensus panel statement provides updated recommendations including a second pathway, which may increase the diagnostic accuracy for acute myocardial edema, based on a positive T2-map and a positive T1-based map. In patients with a "significant" pre-test probability with an "appropriate clinical scenario" positivity of 1 of the 2 markers (T1 or T2) may still support a diagnosis of acute myocardial inflammation. Abnormalities may be regional or global. Due to possible differences among different technical approaches, no specific recommendation for contrast agents, post-processing methods, or cutoff values for positivity could be provided.

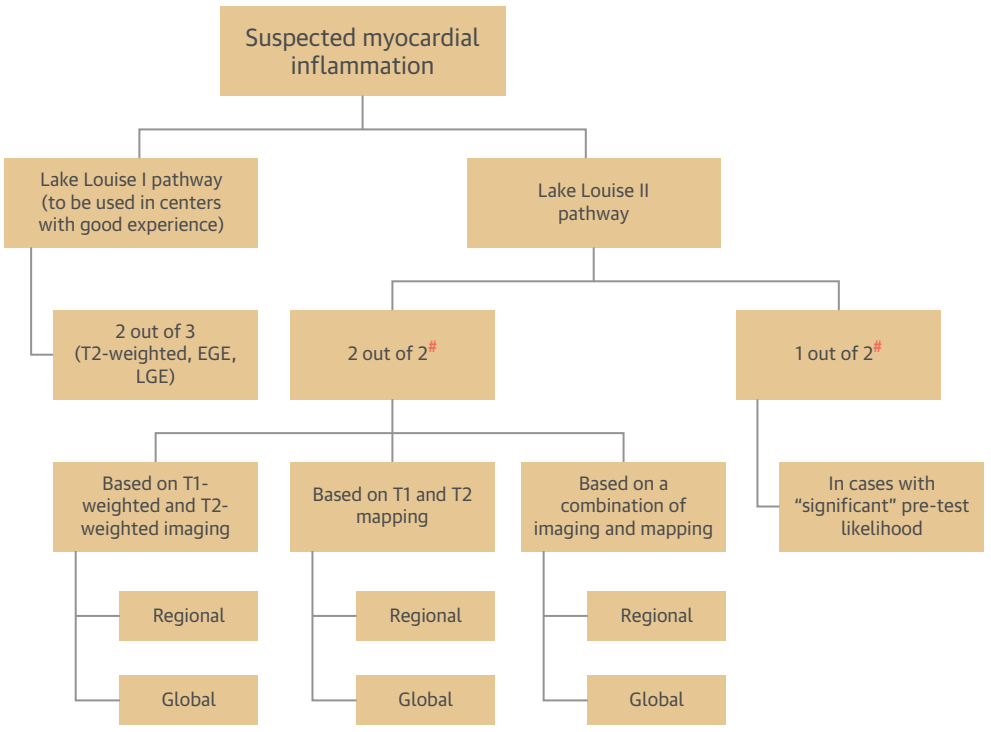
INTEGRATING MAPPING INTO THE DIAGNOSTIC ALGORITHM HAS 3 MAJOR ADVANTAGES

First, mapping detects regional and diffuse disease (8). This is important, because in the course of myocarditis, the very early damage may be regional, whereas

From the [a]DZHK Centre for Cardiovascular Imaging, Institute for Experimental and Translational Cardiovascular Imaging, German Centre for Cardiovascular Research, Centre for Cardiovascular Imaging, Rhine-Main, Goethe University Frankfurt, Frankfurt am Main, Germany; [b]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; and the [c]Department of Cardiology, University of Minnesota, Minneapolis, Minnesota. Dr. Nagel has received research grants and speaker honoraria from Bayer AG; and has received speaker honoraria from Siemens Healthineers. Dr. Kwong has received research grants from Alynlam, MyoKardia, and Society for Cardiovascular Magnetic Resonance. Dr. Chandrashekhar has reported that he has no relationships relevant to the contents of this paper to disclose. Michael Salerno, MD, PhD, served as Guest Editor for this paper.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2019.10.023

FIGURE 1 Diagnostic Algorithms



The symbol # indicates T2-based criteria (T2W imaging or T2 mapping) or T1-based criteria (T1 mapping, ECV, or LGE imaging).
ECV = extracellular volume; EGE = early gadolinium enhancement; LGE = late gadolinium enhancement.

the rapidly resulting autoimmune process is usually diffuse. Nonmapping CMR techniques, such as T2-weighted imaging, early gadolinium enhanced imaging, and LGE, rely on regional differences of signal to generate tissue contrast. Because LGE is based on nulling the signal of presumed normal myocardium, it will detect regional acute necrosis or scar, whereas homogenously diffuse abnormalities are suppressed and may be left undetected. Similarly, T2-weighted imaging can be best interpreted if there are areas of high signal intensity neighboring areas of low signal intensity. The original Lake Louise Criteria recommended comparing the signal in the myocardium with skeletal muscle to account for diffuse disease. Due to these limitations, LGE and T2 imaging perform best in diseases with regional predominance such as acute or chronic myocardial infarction with strong differences between affected and normal myocardium but struggle in diffuse disease processes.

Second, mapping allows the use of quantitative cutoff values for a more objective diagnostic process. Like other biomarkers used in clinical practice (e.g., high-sensitivity troponin assays), quantitative CMR parameters, including T1 and T2, require a standardized setup for imaging and post-processing, development of normal values, and assessment of effect size. In addition, scanning equipment and postprocessing differ across CMR imaging equipment vendors in their approaches and solutions. Standardized approaches have been successfully transferred between centers and vendors (9,10). Advantages of quantification are the ability to obtain nonbiased information for the severity and acuity of disease (4), to monitor disease activity using follow-up data, and to assess the effect of therapy. Unfortunately, the expert consensus panel could not presently provide any guidance on pre-specified cutoff values relevant to various mapping techniques due to known variability of the mapping results. Like T1- or T2-weighted imaging, there is no general agreement on which imaging parameters to use.

Third, mapping with native imaging potentially allows diagnosis and follow-up without the use of contrast agents. Although the assessment of LGE improves diagnostic accuracy especially in subacute

or chronic myocarditis, the main changes over time can be determined with a rapid non–contrast-enhanced scan, saving time and costs and further minimizing any potential risks of gadolinium-containing contrast agents.

LIMITATIONS OF THE UPDATED CONSENSUS RECOMMENDATIONS

The main limitation of the novel consensus suggestions is the provision of multiple different pathways including 2 of 3, 2 of 2, and 2 of 2 in high-risk patients, in combination with various imaging techniques suggested for each of the criteria. Although this allows inclusivity of multiple directions, it does not provide strong clinical guidance for the field. There is also a risk of slowing down future development by offering various "reference" standards based on different pathophysiologies.

Clinically, several important questions relevant to the care of patients with myocarditis remain: How important is edema, which can be detected by CMR but not by biopsy? How important is virus persistence and immune histochemical parameters, which can be assessed by biopsy but not CMR? Is the surrogate measurement of edema or necrosis by CMR rather than inflammatory cells by biopsy sufficient for clinical purposes, thus obviating the need to perform a biopsy to demonstrate inflammatory infiltrate? How should management decisions be adjusted when disagreements in imaging findings exist between the original Lake Louise Criteria and Lake Louise II Criteria, given the lack of validation against tissue biopsy or clinical outcomes? Although the field tries to reconcile the results of imaging and endomyocardial biopsy, it may be that the different imaging techniques do not fully harmonize with the pathophysiologies across the spectrum of the disease. In such situations of discordance, the next questions are which of the parameters are most prognostically important, which ones can be targeted by therapy, and whether and when can myocarditis be diagnosed solely by CMR and obviate the need of a myocardial biopsy?

WILL THE NEW CRITERIA CHANGE CLINICAL PRACTICE?

By including mapping techniques, the new criteria are major steps forward. This will allow generation of quantitative data, hopefully providing information for the severity of disease to predict outcome, assess the need for myocardial biopsy, and support the development of a therapeutic intervention. Unfortunately, presently these data remain limited and controversial. Presently, many of the following major issues concerning the diagnosis, prognosis, and therapy of myocarditis remain unsolved:

1. The definition of inflammation and myocarditis according to the European Society of Cardiology guidelines is based on the proof of inflammation or necrosis in endomyocardial biopsy (EMB) (11). This is a Class I recommendation, but the level of evidence is Level of Evidence: C (expert consensus). Due to this definition, any new test results will be measured against EMB, and any differences between the 2 will be counted against the new test. The new Lake Louise Criteria provide little advice as to how the proposed diagnostic pathways can integrate with the roles of EMB. Given the procedural risk, the inherent limitations, and the limited therapeutic implications inferred from EMB in most patients with suspected myocarditis, clinical reliance on EMB in this setting has been reduced. These authors believe CMR can obviate the need for EMB in a significant proportion of patients suspected of having acute myocarditis, but key research studies are needed for defining CMR as a gatekeeper for EMB.
2. The pathogenesis of myocarditis varies by pathogen (12). Little is currently known about CMR findings and inciting pathogen types or viral subtypes (13), which carry important information toward disease natural history and patient prognosis. It remains unclear how the diagnostic pathway can inform regarding the different causes of myocarditis. However, EMB too provides very limited information about evidence-based specific therapies. Thus, the need for proving a specific cause remains unclear.
3. The lack of a proven immunosuppressing treatment remains for myocarditis. This lack is partially propagated by a fear of potential patient harm (e.g., by using immunosuppression in acute stages); prior negative clinical trial (performed in patients with chronic myocarditis and reduced ejection fraction) (14); the need for biopsy in research studies, as described above; and the perceived recovery ad integrum in most patients. Although the above factors are important considerations, they are supported by limited data and may prohibit advances in clinical science.
4. More sensitive tests lead to a higher prevalence of disease, which in turn generates more awareness and testing with a further increase in prevalence. This perceived increase in prevalence should not be interpreted as an epidemic but rather as a better

understanding of a previously existing problem. Physicians and patients need to learn how to deal with subclinical inflammation, which is highly prevalent not only after viral infection but also in patients with generalized inflammatory conditions, such as rheumatoid diseases, lupus, renal failure, or HIV. The higher sensitivity opens a better understanding of patients with atypical or diffuse chest pain or reduced fitness who, so far, were not regarded as cardiac patients and addresses preventive measures to potentially reduce the development of heart failure.

FUTURE DIRECTIONS

There is an urgent need for more research in myocarditis. Severity, acuity, and the resulting sequelae need better definitions. Given the lack of clarity on the best diagnostic test and its parameters, a large outcome study integrating standardized mapping parameters is paramount. Only with a long-term outcome study can a relevant reference standard for early diagnosis be established. The time is also ready for randomized controlled trials with immunomodulation or immunosuppression. At this stage, early safety studies based on CMR and/or biopsy would significantly add to our knowledge base. The results from the diagnostic outcome studies in combination with the safety studies should then form the basis for a large-scale randomized controlled outcome trial to reduce the burden of myocarditis.

Future updates of the diagnostic pathways in myocarditis will hopefully provide an exact algorithm for which test to use in which patient, which patients to image, when to proceed to biopsy, and provide guidance on the exact acquisition and postprocessing of the CMR biomarkers. This will allow clinicians to rapidly clarify the value of the pathway in larger clinical scenarios as well as compare other pathways with the consensus suggestion to move the field forward.

ADDRESS FOR CORRESPONDENCE: Dr. Eike Nagel, Goethe University Frankfurt, Institute for Experimental and Translational Cardiovascular Imaging, Frankfurt, Germany. E-mail: eike.nagel@cardiac-imaging.org.

REFERENCES

1. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158–76.

2. Ferreira VM, Piechnik SK, Dall'Armellina E, et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:42.

3. Ferreira VM, Piechnik SK, Dall'Armellina E, et al. T(1) mapping for the diagnosis of acute myocarditis using CMR: comparison to T2-weighted and late gadolinium enhanced imaging. J Am Coll Cardiol Img 2013;6:1048–58.

4. Hinojar R, Foote L, Arroyo Ucar E, et al. Native T1 in discrimination of acute and convalescent stages in patients with clinical diagnosis of myocarditis. J Am Coll Cardiol Img 2015;8:37–46.

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

6. 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.

7. Puntmann VO, Valbuena S, Hinojar R, et al. Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part I-analytical validation and clinical qualification. J Cardiovasc Magn Reson 2018;20:67.

8. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.

9. Puntmann VO, Carr-White G, Jabbour A, et al. T1-mapping and outcome in nonischemic cardiomyopathy. J Am Coll Cardiol Img 2016;9:40–50.

10. Puntmann VO, Carr-White G, Jabbour A, et al. Native T1 and ECV of Noninfarcted Myocardium and Outcome in Patients With Coronary Artery Disease. J Am Coll Cardiol 2018;71:766–78.

11. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, 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.

12. Heymans S, Eriksson U, Lehtonen J, Cooper LT. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol 2016;68:2348–64.

13. Mahrholdt H. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 2004;109:1250–8.

14. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269–75.

KEY WORDS cardiovascular magnetic resonance, diagnostic algorithm, editorial, myocarditis