JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 3, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.01.005

EDITORIAL COMMENT

Diagnostic Accuracy of CMR in Biopsy-Proven Acute Myocarditis*

Jeanette Schulz-Menger, MD
Berlin, Germany

Antagonisms are the driving forces and the fundament of all existence.
—Hegel (1)

Heart failure is a leading problem in clinical cardiology. The causes are diverse, and treatment must be tailored according to underlying mechanisms. Inflammatory causes are a particular challenge. With their study, reported in this issue of *iJACC*, Francone et al. (2) intend to narrow the gap in our current knowledge regarding the diagnostic workup of inflammatory heart disease, particularly as related to viral cardiac infections. Whereas endomyocardial biopsy (EMB) remains the gold standard to identify viral pathogens specifically, the current guidelines suggest the need for EMB in only in few settings (3). EMB is not dangerous in experienced hands (4), and the decision for or against EMB is predicated on specific therapeutic relevance and the chances for recovery (5). A noninvasive workup is preferable to guide decisions regarding EMB. Cardiovascular magnetic resonance (CMR) has gained utility in the diagnostic armamentarium (5). This is because CMR is able to distinguish between ischemic and nonischemic processes and to separate acute from chronic disease, and it predicts reversibility. Interestingly, myocardial injuries are already detectable in preserved left ventricular function applying CMR.

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Francone et al. (2) studied patients with biopsy-proven acute myocarditis and assessed the sensitivity of CMR in this setting. They evaluated 57 consecutive patients who had clinical histories of disease <3 months in duration. They combined a CMR protocol aimed at detecting edema, hyperemia, and/or fibrosis or necrosis. The diagnosis of myocarditis on the basis of CMR findings was established when ≥2 CMR criteria were present. Clinically, Francone et al. (2) defined 3 distinct myocarditis groups: infarctlike, cardiomyopathic, and arrhythmic. The incidence of CMR findings was different within the groups. The investigators conclude that in acute myocarditis, CMR's sensitivity is high for the infarctlike pattern, low for the cardiomyopathic pattern, and very low for the arrhythmic constellation. These results led the investigators to conclude that EMB may be required in CMR-negative subjects with electrical instability (arrhythmias) and/or cardiac deterioration (worsening heart failure) for a final diagnosis.

A notable strength in the presentation is the direct comparison between CMR and EMB. Nevertheless, as the investigators themselves point out, the applied CMR sequences they used are different from the sequences that are currently recommended. As a matter of fact, every researcher has the right and the duty to develop his or her own tools and parameters. In this case, though, the investigators used published semiquantitative measures and cutoffs, but they did not use the dedicated underlying technique (6,7). That means that their CMR diagnosis of inflammation to semiquantify edema and hyperemia was based on cutoff values that may not reflect the characteristics of the applied sequence. Thus, the use of the published cutoff values in their study is difficult. As a result, the definition of CMR diagnosis of myocarditis, if 2 or more of the investigators' criteria are positive, could vary for technical reasons. This is not a failure of CMR. Other biomarkers, such as troponin, have internationally accepted cutoff values,

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

From the Cardiac Magnetic Resonance Group, Experimental and Clinical Research Center, Max-Delbrück Center for Molecular Medicine and Charité Medical Faculty, and the Department of Cardiology, HELIOS Klinikum-Berlin, Clinic for Cardiology and Nephrology, Berlin, Germany. Dr. Schulz-Menger has reported that she has no relationships relevant to the contents of this paper to disclose.

although these are subject to variation depending on the kit manufacturer (8).

There is no absolute "right or wrong," as Georg Hegel implied (1). Nonetheless, this publication strengthens the call for standardization. Often, when a new method enters the arena, several approaches are applied, and apparently conflicting results are published. This state of affairs was also the case with CMR-driven assessment of inflammation. The apparent contradictions were based on different scan protocols and/or the assessment of variable study populations. The definition of the acuity is also unclear and varies among studies. The present trial defined acuity as disease duration of <3 months. Other investigators have defined acuity as <4 weeks. The underlying pathology, as well as its impact, may be different within these time frames. Furthermore, the timing of the scan also influences the accuracy of CMR.

The incidence of edema, hyperemia, and necrosis or fibrosis, as late gadolinium enhancement (LGE) images indicate, is influenced by age and sex (9). This observation means that the relationship between the clinical patterns, as defined by Francone et al. (2), and as based on CMR findings, may be also influenced by these variables. It was demonstrated recently that a positive LGE image indicates that the patient's prognosis is worse (10). However, it is well known that LGE does not occur in all patients (6). The other CMR parameters are even more difficult to assess and are based on the semiquantitative analysis previously discussed. Whereas edema imaging is in the meantime accepted, evaluation of hyperemia using the early gadolinium enhancement method is still under debate, mainly for technical reasons. However, it has been shown that early gadolinium enhancement as well as T2 leads to a higher positive likelihood ratio (sensitivity/[1 – specificity]) (11). Interestingly, early gadolinium enhancement and LGE had the best correlation for the development of heart failure (12). Thus, it makes sense to invest human and computing resources to improve these techniques, which may offer insights into different pathophysiologies.

It is assumed that newer quantitative techniques should overcome some limitations. Parametric mapping is an emerging technique with potential usefulness in myocarditis. Fortunately, several volunteer and/or standardization trials are already published, and first experiences in myocarditis are promising (13–16). Quantitative T2 mapping also warrants consideration as a robust technique to identify myocardial injury in patients with acute myocarditis (17). Diagnostic tools could be improved significantly if they could be standardized in advance rather than retrospectively. First steps are already in progress regarding scan protocols (18), post-processing (19), and T1 mapping (20). There is no doubt that noninvasive diagnostic tools must be improved. The investigators' contribution is a useful step in this direction.

Reprint requests and correspondence: Dr. Jeanette Schulz-Menger, Schwanebecker Chaussee 50, 13125 Berlin, Germany. *E-mail: jeanette.schulz-menger@charite.de.*

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Key Words: acute myocarditis ■ apoptosis ■ cardiac magnetic resonance ■ late gadolinium enhancement ■ necrosis.