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EDITORIAL COMMENT

Noninvasive Differentiation Between Active and Healed Myocarditis by Cardiac Magnetic Resonance

Are We There Yet?*

Heiko Mahrholdt, MD, Udo Sechtem, MD, FACC
Stuttgart, Germany

Myocarditis is a common cardiac disease. It appears to be a major cause of sudden death, and may progress to chronic dilated cardiomyopathy. From the clinical point of view, there are several challenges unique to the management of patients with myocarditis. The first challenge is to establish the diagnosis of myocarditis, which is usually based on clinical, pathological, or a combination of diagnostic criteria. The second challenge is to follow the disease activity to identify patients who may be at risk of chronic dilated cardiomyopathy development, which seems to be associated with ongoing myocardial inflammation (1) and viral persistence (2).

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Cardiac magnetic resonance (CMR) has recently emerged as a noninvasive tool to diagnose myocarditis (3–6), as well as to follow its course in living patients (3,7–9). Three features potentially associated with acute myocardial inflammation may be visualized by CMR: 1) tissue edema, which may result in an elevated T2 signal; 2) capillary leakage, which is speculated to be associated with an increased signal on T1-weighted spin-echo images after gadolinium administration (elevated global relative enhancement [gRE]); and 3) myocardial necrosis or scarring as indicated by the presence of late gadolinium enhancement (LGE).

Whereas no histological proof exists that the edema described pathologically in patients with myocarditis (10) correlates with the T2-signal elevation measurable in high-quality T2-weighted MR images, the association of T2 elevation and edema has been histologically proven in other conditions. Hence, the concept that T2-signal elevation indicates myocardial edema may make sense.

Hyperemia associated with capillary leakage or muscular inflammation was also never directly shown to be the cause of increased interstitial uptake of gadolinium in acute myocarditis. Theoretically, such studies could be performed in appropriate mouse models (11) using modern MR scanners (12). Unfortunately, there are no data yet from such animal studies, which would be crucial to prove the concepts of elevated T2 signal and gRE ratio to be good parameters to demonstrate myocardial inflammation.

In contrast to the 2 previous features, the presence of LGE has been repeatedly shown to be associated with histological proof of acute myocarditis (4,8). However, if scarring is the result of acute myocarditis it will—although often significantly smaller and sometimes beyond the resolution of CMR due to scar shrinking—remain when the acute inflammation has long subsided.

The concept of the Berlin group is that clinically acute inflammation is usually associated with T2-signal elevation, as well as an increase in gRE ratio. Consequently, they postulate that normalization of these 2 parameters will indicate the absence of acute inflammation. To prove their concept, in this issue of *iJACC*, Zagrosek et al. (13) serially assessed T2 signal, gRE ratio, and LGE at initial presentation, as well as after 18

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From the Department of Cardiology, Robert-Bosch-Medical Center, Stuttgart, Germany.

Table 1. Basic Meta-Analysis of Most Data Available on CMR in Human Myocarditis

T2 Sensitivity	Ratio* Specificity	gRE Sensitivity	Ratio* Specificity	Late Sensitivity	GE Specificity	Combined Sensitivity	Approach* Specificity
74%	74%	87%	84%	76%	91%	76%	83%
n = 80	n = 23	n = 117	n = 48	n = 372	n = 106	n = 25	n = 57

*No systematic comparison to histopathology available for myocarditis; combined approach contains T2, gRE, and late GE. Studies included in this meta-analysis are Friedrich et al. (3), n = 19; Roditi et al. (15), n = 12; Rieker et al. (16), n = 9; Laissy et al. (17), n = 20; Mahrholdt et al. (4), n = 32; Abdel-Aty et al. (5), n = 25; Hunold et al. (18), n = 6; Laissy et al. (19), n = 24; Ingkanisorn et al. (20), n = 21; De Cobelli et al. (6), n = 23; Mahrholdt et al. (8), n = 87; Gutberlet et al. (21), n = 49; Yilmaz et al. (22), n = 71; and Baccouche et al. (unpublished data, November 2008), n = 82.
CMR = cardiac magnetic resonance; GE = gadolinium enhancement; gRE = global relative enhancement.

months in 36 patients diagnosed with acute myocarditis by clinical criteria. The authors found an elevated T2-signal ratio during the clinically acute phase in 86% of patients, an abnormal gRE ratio was detected in 80%, and LGE was found in 63% of patients, respectively. During follow-up, the T2-signal ratio decreased from 2.4 to 1.9, the gRE-signal ratio decreased from 7.6 to 4.4, and the amount of LGE decreased from 38% to 22% of left ventricular mass. These findings are in line with pervious publications describing the individual time courses of each of those CMR parameters (4,7,14) in myocarditis patients. Based on these results Zagrosek et al. (13) conclude that the combined approach is capable of differentiating reversible and irreversible myocardial damage noninvasively. They also state that if none, or just 1 of T2-signal and gRE ratios is elevated, this has a negative predictive value of 100% to differentiate active from healed myocarditis in living patients.

How should one put these results into perspective with the existing body of literature? The largest study examining patients with clinically suspected chronic myocarditis by CMR and histopathology (9) found absence of T2 elevation in 33%, and no elevated gRE ratio in 37% of those shown to have inflammation by histology. Hence, one-third of patients with persisting inflammation would have elevation of 1 of these 2 CMR parameters.

Unfortunately, the study of Gutberlet et al. (9) does not tell us how often both parameters were below the pre-defined cutoff values even though histology indicated the persistence of inflammation. De Cobelli et al. (6) found absence of T2-ratio elevation in 78% of patients with chronic inflammation by histopathological criteria. However, these investigators did not perform gRE imaging, perhaps because the image quality is frequently suboptimal for this pulse sequence. Taken together, these 2 studies cast serious doubt on whether the finding by Zagrosek et al. (13) that ongoing inflammation is 100% excluded in patients in whom 1 or both of the 2 parameters, T2 signal and gRE ratio, are normal can be applied to larger patient groups in whom biopsy is available.

A basic meta-analysis of most data available on CMR in human myocarditis (Table 1) (3–6,8,15–22) does not show an advantage of the combined approach compared with each individual technique, contradicting the report of Abdel Aty et al. (5), who first described a substantial benefit of adding T2 signal and gRE ratio to LGE imaging for myocarditis workup. This discrepancy most likely can also be explained by the fact that CMR findings for T2 signal and gRE ratio have never been systematically confirmed by histopathology. Following Bayes' principle of boolean information processing, combining tests with suboptimal sensitivities and specificities does not necessarily improve the performance of the combined approach. Thus, multicenter data using histopathological evaluation as the gold standard are needed.

When managing patients with inflammatory heart disease today, it should be kept in mind that despite the merits of CMR, which is capable of giving clues on the presence and distribution of inflammatory damage in the myocardium, as well as helping to guide endomyocardial biopsy to minimize sampling error (4), endomyocardial biopsy is the only technique that can directly assess the presence and intensity of myocardial inflammation in vivo. Therefore, it is the technique of choice if clinically indicated to differentiate between active and healed myocarditis. Biopsy samples can be safely obtained from the right as well as from the left ventricle, yielding a rate of severe complications that is not significantly different from the complication rate of standard coronary angiography (≈0.1% in experienced centers) (23–25). Endomyocardial biopsy also provides information on the underlying cause of inflammation, such as viral or bacterial infec-

tion of the myocardium, or myocardial autoimmune processes, such as giant cells, or Churg-Strauss syndrome. This information, however, which CMR imaging will not be able to obtain in the near future, is essential for patient management decisions. The importance of endomyocardial biopsy is reflected in the current guidelines recommending it for basically all patients with developing nonischemic heart failure, as well as for several other nonischemic conditions (26).

Nevertheless, Zagrosek et al. (13) are to be congratulated on systematically collecting 18 months of follow-up data on patients with myocarditis who all underwent a combined CMR triple protocol including T2, gRE, and LGE. Their results underscore that the time is now ready for evaluating this combined CMR approach in a larger multicenter study (ideally with endomyocardial biopsy of many patients as the standard of reference). More data are needed before we can be reasonably sure that the combined CMR approach holds promise to reshape myocarditis patient management in the future.

Reprint requests and correspondence: Dr. Heiko Mahrholdt, Robert-Bosch-Medical Center, Auerbachstrasse 110, Stuttgart 70376, Germany. *E-mail: heiko.mahrholdt@rbk.de.*

REFERENCES

1. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. Circulation 2008;118:639–48.
2. Kühl U, Pauschinger M, Seeberg B, et al. Viral persistence in the myocardium is associated with progressive cardiac dysfunction. Circulation 2005; 112:1965–70.
3. Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation 1998;97: 1802–9.
4. Mahrholdt H, Goedecke C, Wagner A, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 2004;109:1250–8.
5. Abdel-Aty H, Boye P, Zagrosek A, et al. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. J Am Coll Cardiol 2005;45:1815–22.
6. De Cobelli CF, Pieroni M, Esposito A, et al. Delayed gadolinium-enhanced cardiac magnetic resonance in patients with chronic myocarditis presenting with heart failure or recurrent arrhythmias. J Am Coll Cardiol 2006;47:1649–54.
7. Wagner A, Schulz-Menger J, Dietz R, Friedrich MG. Long-term follow-up of patients paragraph sign with acute myocarditis by magnetic paragraph sign resonance imaging. Magma 2003;16:17–20.
8. Mahrholdt H, Wagner A, Deluigi CC, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. Circulation 2006;114:1581–90.
9. Gutberlet M, Spors B, Thoma T, et al. Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 2008;246:401–9.
10. Weber MA, Ashworth MT, Risdon RA, Malone M, Burch M, Sebire NJ. Clinicopathological features of paediatric deaths due to myocarditis: an autopsy series. Arch Dis Child 2008; 93:594–8.
11. Taylor JA, Havari E, McInerney MF, Bronson R, Wucherpfennig KW, Lipes MA. A spontaneous model for autoimmune myocarditis using the human MHC molecule HLA-DQ8. J Immunol 2004;172:2651–8.
12. Gilson WD, Epstein FH, Yang Z, et al. Borderzone contractile dysfunction is transiently attenuated and left ventricular structural remodeling is markedly reduced following reperfused myocardial infarction in inducible nitric oxide synthase knockout mice. J Am Coll Cardiol 2007;50:1799–807.
13. Zagrosek A, Abdel-Aty H, Boyé P, et al. Cardiac magnetic resonance monitors reversible and irreversible myocardial injury in myocarditis. J Am Coll Cardiol Img 2009;2: 131–8.
14. Zagrosek A, Wassmuth R, Abdel-Aty H, Rudolph A, Dietz R, Schulz-Menger J. Relation between myocardial edema and myocardial mass during the acute and convalescent phase of myocarditis—a CMR study. J Cardiovasc Magn Reson 2008;10:19.
15. Roditi GH, Hartnell GG, Cohen MC. MRI changes in myocarditis—evaluation with spin echo, cine MR angiography and contrast enhanced spin echo imaging. Clin Radiol 2000; 55:752–8.
16. Rieker O, Mohrs O, Oberholzer K, Kreitner KF, Thelen M. [Cardiac MRI in suspected myocarditis]. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2002;174:1530–6.
17. Laissy JP, Messin B, Varenne O, et al. MRI of acute myocarditis: a comprehensive approach based on various imaging sequences. Chest 2002;122: 1638–48.
18. Hunold P, Schlosser T, Vogt FM, et al. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. AJR Am J Roentgenol 2005;184:1420–6.
19. Laissy JP, Hyafil F, Feldman LJ, et al. Differentiating acute myocardial infarction from myocarditis: diagnostic value of early- and delayed-perfusion cardiac MR imaging. Radiology 2005; 237:75–82.
20. Ingkanisorn WP, Paterson I, Calvo KR, et al. Cardiac magnetic resonance appearance of myocarditis caused by high dose IL-2: similarities to community-acquired myocarditis. J Cardiovasc Magn Res 2006;8: 353–60.
21. Gutberlet M, Spors B, Thoma T, et al. Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 2008;246:401–9.
22. Yilmaz A, Mahrholdt H, Athanasiadis A, et al. Coronary vasospasm as the underlying cause for chest pain in patients with PVB19 myocarditis. Heart 2008;94:1456–63.
23. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. J Am Coll Cardiol 1992;19:43–7.

24. Pophal S, Sigfusson G, Booth K, et al. Complications of endomyocardial biopsy in children. J Am Coll Cardiol1999;34:2105–10.
25. Holzmann M, Nicko A, Kühl U, et al. Complication rate of right ventricular endomyocardial biopsy via the femoral approach. A retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period. Circulation 2008;118: 1722–8.
26. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914–31.

Key Words: myocarditis ■ endomyocardial biopsy ■ cardiac MR.