Assessment of acute myocarditis by cardiac magnetic resonance imaging: Comparison of qualitative and quantitative analysis methods

Massimo Imbriaco, MD,[a] Carmela Nappi, MD,[a] Marta Puglia, MD,[a] Marco De Giorgi, MD,[b] Serena Dell'Aversana, MD,[a] Renato Cuocolo, MD,[a] Andrea Ponsiglione, MD,[a] Igino De Giorgi, MD,[c] Maria Vincenza Polito, MD,[b] Michele Klain, MD,[a] Federico Piscione, MD,[b] Leonardo Pace, MD,[b] and Alberto Cuocolo, MD[a]

[a] Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy
[b] Department of Medicine and Surgery, University of Salerno, Salerno, Italy
[c] Department of Diagnostic Imaging and Radiotherapy, A.O. San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

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Background. **To compare cardiac magnetic resonance (CMR) qualitative and quantitative analysis methods for the noninvasive assessment of myocardial inflammation in patients with suspected acute myocarditis (AM).**

Methods. **A total of 61 patients with suspected AM underwent coronary angiography and CMR. Qualitative analysis was performed applying Lake-Louise Criteria (LLC), followed by quantitative analysis based on the evaluation of edema ratio (ER) and global relative enhancement (RE). Diagnostic performance was assessed for each method by measuring the area under the curves (AUC) of the receiver operating characteristic analyses. The final diagnosis of AM was based on symptoms and signs suggestive of cardiac disease, evidence of myocardial injury as defined by electrocardiogram changes, elevated troponin I, exclusion of coronary artery disease by coronary angiography, and clinical and echocardiographic follow-up at 3 months after admission to the chest pain unit.**

Results. **In all patients, coronary angiography did not show significant coronary artery stenosis. Troponin I levels and creatine kinase were higher in patients with AM compared to those without (both $P < .001$). There were no significant differences among LLC, T2-weighted short inversion time inversion recovery (STIR) sequences, early (EGE), and late (LGE) gadolinium-enhancement sequences for diagnosis of AM. The AUC for qualitative (T2-weighted STIR 0.92, EGE 0.87 and LGE 0.88) and quantitative (ER 0.89 and global RE 0.80) analyses were also similar.**

Conclusions. **Qualitative and quantitative CMR analysis methods show similar diagnostic accuracy for the diagnosis of AM. These findings suggest that a simplified approach using a shortened CMR protocol including only T2-weighted STIR sequences might be useful to rule out AM in patients with acute coronary syndrome and normal coronary angiography. (J Nucl Cardiol 2019;26:857–65.)**

Key Words: Myocarditis • cardiac imaging • magnetic resonance imaging

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Reprint requests: Massimo Imbriaco, MD, Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy; *mimbriaco@hotmail.com*

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Abbreviations

AM	Acute myocarditis
CMR	Cardiac magnetic resonance
LLC	Lake-Louise Criteria
EGE	Early gadolinium-enhancement
LGE	Late gadolinium-enhancement
STIR	Short time inversion recovery
ER	Edema ratio
RE	Relative enhancement
ROI	Region of interest
AUC	Area under the curve
ROC	Receiver operating characteristic

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INTRODUCTION

Acute myocarditis (AM) generally is under diagnosed due to the low sensitivity of cardiac biomarkers, ECG, and viral serology.[1,2] New imaging techniques, such as cardiac magnetic resonance (CMR), have been introduced for the evaluation of patients with suspected AM. CMR is an innovative noninvasive diagnostic tool capable of characterizing the typical patterns of myocardial inflammation.[3,4] The recommended CMR diagnostic criteria for AM are based on T2-weighted imaging and two different contrast-enhanced techniques, the early gadolinium-enhancement (EGE), and late gadolinium-enhancement (LGE).[5] According to the Lake-Louise Criteria (LLC), CMR can diagnose AM in the presence of at least two of the following three findings on the respective sequences: 1) myocardial edema detected by T2-weighted imaging; 2) myocardial hyperemia detected by EGE technique; and 3) myocardial damage with non-ischemic pattern detected by LGE technique. EGE imaging has generally been considered the least robust of the three components of the LLC; furthermore, LGE imaging visualizes irreversible injury only and thus exhibits poorer sensitivity, likely due to less severe disease without ''macroscopic'' necrosis.[6] Therefore, a marked variation in sensitivity and negative predictive value has been reported in the literature, reflecting the intrinsic drawbacks of current diagnostic criteria, which are mainly based on the use of conventional CMR sequences. The aim of this study was to compare CMR qualitative and quantitative analysis methods for the evaluation of patients with suspected AM.

METHODS

Patients

From December 2014 to March 2017, a total of 85 subjects were admitted to our chest pain unit with suspected AM. Following current guidelines,[7] all patients underwent 12-lead ECG, determination of cardiac biomarkers (troponin I and creatine kinase) and echocardiography within the first 20 min after admission to the chest pain unit. Cardiac troponin I concentration was measured using a commercially available immunoassay method (Boehringer, Mannheim, Germany) and the results were determined according to manufacturer's instructions. All patients also underwent coronary angiography within 12 h of admission and CMR within 6.8 ± 4 days. Twenty patients were excluded from the study due to history of prior myocardial infarction and/or coronary revascularization procedures, and chronic troponin I elevation. Four patients with contraindications to CMR (e.g. claustrophobia or pacemaker), renal insufficiency (estimated glomerular filtration rate $\leq$30 mL/min/1.73 m^2), and evidence of LGE ischemic pattern by CMR were also excluded. Therefore, 61 patients (44 men, mean age 45 ± 6 years, age range 24-72 years) were enrolled in the study. The final diagnosis of AM was based on symptoms and signs suggestive of cardiac disease (acute chest pain, dyspnoea, palpitations), evidence of myocardial injury as defined by electrocardiogram changes (ST-segment changes, conductions defects), elevated troponin I, exclusion of coronary artery disease by coronary angiography, and clinical and echocardiographic follow-up at 3 months after admission to the chest pain unit. Informed consent, a requirement of the protocol approved by the Institutional Clinical Research Subpanel on Human Studies at our Institute, was obtained from all patients.

CMR Imaging Protocol

CMR was performed using a superconducting system 1.5T MR (Philips Medical System, Best, The Netherlands) with a maximum gradient capability of 30 mT/m and maximum slew rate of 150 mT/ms. MR acquisition was triggered by ECG and included a T1-weighted sequence and cine-MR fast field echo images in the short-axis, vertical long-axis, and horizontal long-axis planes for evaluation of cardiac contraction. Short time inversion recovery (STIR) T2-weighted sequence was obtained to suppress fatty tissue signal, in the short-axis, and horizontal long-axis planes. Thereafter, a short-axis T1-weighted gradient echo IR sequence was obtained (slice thickness, 8 mm) both before and after (without any change of parameters in between) an i.v. bolus of 0.1 mmol/kg gadolinium-diethylenetriamine pentaacetate (Gd-DTPA, Magnevist, Bayer Schering Pharma, Berlin, Germany) using an automated injector (Medrad, Indianola, USA). The post-contrast measurements started immediately after the injection of contrast material and lasted for 3-4 min, thus, the images reflected gadolinium-enhancement at a mean of 2 min (EGE). Finally, a breath-hold IR sequence (slice thickness, 8 mm) was applied after a delay of 15 min (LGE) in short and long-axis covering the LV. TI were adjusted to null normal myocardium using the Look-Locker sequence.[6,8] Images were reviewed in consensus by three radiologists (M.I., I.D.G and M.P.), with, respectively, 18 years, 12 years, and 6 years of experience in CMR imaging. Analysis of CMR images, including left ventricular (LV) function, and mass, was performed using certified CMR analysis software (Viewforum, Philips Medical

System). Epicardial and endocardial borders were traced manually by one physician and LV function was determined using standard methods. LV mass was determined at end-systole.[6,8]

Qualitative Imaging Analysis

CMR criteria suggestive for AM were based on LLC.[5] Qualitative analysis of LGE images was conducted to identify regional increases in myocardial signal intensity. Positive LGE was further classified as sub-epicardial, mid-wall, sub-endocardial, or transmural and localized based on the American Heart Association 17 segment model.[9] Similarly, a regional increase of myocardial signal intensity on T2-weighted STIR images was considered to be indicative of areas of edema secondary to myocardial inflammation. The possibility of artifacts was carefully evaluated excluding areas of increased signal intensity that did not respect anatomical structures. CMR findings were classified in advance by giving a score from 1 to 3, where 1 was considered low probability of AM (clinically significant AM was highly unlikely to be present), based on the presence of normal findings on T2-weighted STIR, EGE, and LGE images; 2 as intermediate probability (presence of clinically AM was equivocal) based on the presence of mild or inconsistent increase of myocardial signal intensity on T2-weighted STIR and mild or inconsistent enhancement on EGE and LGE images; and 3 as high probability (clinically significant AM was likely to be present) based on the presence of significant increase of myocardial signal intensity on T2-weighted STIR and consistent enhancement on EGE and LGE images. Scores 2 and 3 were grouped based on post hoc review of receiver operating characteristic (ROC) data and were considered positive for AM.

Quantitative Imaging Analysis

Quantitative analysis was performed based on the evaluation of the edema ratio (ER) and global relative enhancement (RE). Each parameter was calculated globally on an entire short-axis section, drawn in the LV myocardial slice most representative for pathology. ER was calculated on the T2-weighted STIR by drawing a first region of interest (ROI) including the entire section of the LV myocardial wall and a second ROI including the skeletal muscle (i.e. pectoralis muscle). The mean myocardial and skeletal muscle signal intensity (SImyo and SIskm) were obtained and ER was expressed as SImyo/Siskm. A similar approach was used to calculate the global RE on the pre and post-contrast T1-weighted images. Global RE was expressed as REmyo/REskm. REmyo represents the relative enhancement value for the myocardium, defined as (postSImyo—preSImyo)/preSImyo. Where postSImyo indicates the myocardial signal intensity on the T1-weighted post-contrast sequence and preSImyo the myocardial signal intensity on the T1-weighted pre-contrast sequence. REskm represents the skeletal muscle relative enhancement value, defined as (postSIskm—preSIskm)/preSIskm. Where postSIskm indicates the muscle signal intensity on the T1-weighted post-contrast sequence and preSIskm the muscle signal intensity on the T1-weighted pre-contrast sequence. To estimate the presence of active inflammation, we used a cut off value ≥ 2 for ER and ≥ 4 for global RE.[10,11]

Statistical Analysis

Data was expressed as mean ± standard deviation or as percentages. The diagnostic performance of qualitative and quantitative CMR analyses was assessed measuring the area under the curve (AUC) of the ROC analysis.[12] AUC differences among parameters were analyzed using a two-tailed Student's t test for paired data, corrected for multiple comparison analysis. Diagnostic accuracy, sensitivity, and specificity, with corresponding 95% confidence intervals, were determined for each CMR sequence using the best cutoff on each ROC. The relationship between qualitative and quantitative CMR parameters was assessed by Spearman's rank correlation coefficient (ρ). A P value $< .05$ was considered statistically significant. MedCalc Statistical Software version 13.1.2 was used for statistical analysis.

RESULTS

Acute chest pain was the most common clinical presentation in all patients studied, often resembling ischemia-like chest pain. No significant risk factors were identified in our patient population; they had a low cardiac risk with no other underlying cardiac dysfunction. Demographic data and clinical characteristics stratified according to the presence or absence of myocarditis at CMR imaging are described in Table 1. ECG abnormalities were detectable in 16 (26%) of the patients. An evident viral syndrome was present in 15 (25%) patients. In all patients, coronary angiography did not show significant coronary artery stenosis. Minimal atherosclerotic abnormalities were detectable in 18 (29%) patients. A final diagnosis of AM was made in 49 (80%) patients. Of these, 44 (72%) patients were men. Troponin I levels were higher ($P < .001$) in patients with AM (242 ± 13 ng/mL) compared to those without (0.99 ± 0.8 ng/mL). Similarly, creatine kinase was higher ($P < .001$) in patients with AM (169 ± 20 ng/mL) compared to those without (13 ± 8 ng/mL). Conversely, LV ejection fraction was not different between patients with (47 ± 15%) and without (54 ± 14%) AM.

Qualitative Analysis

No significant differences were found among LLC, T2-weighted STIR, EGE, and LGE sequences for diagnosis of AM (Table 2). As illustrated in Figure 1, the AUC obtained from the ROC analysis were 0.92 for T2-weighted STIR, 0.87 for EGE, and 0.88 for LGE (P = NS).

Quantitative Analysis

ER (2.8 ± 0.6 vs. 1.3 ± 0.3, $P < .001$) and global RE (6.3 ± 0.7 vs. 2.3 ± 0.6, $P < .001$) were significantly higher in patients with AM compared to those without. Figure 2 shows the comparison between the AUC obtained from the ROC analysis for ER and global RE (0.89 vs. 0.80, $P =$ NS).

Comparison Between Qualitative and Quantitative Analyses

No significant differences were observed among qualitative and quantitative methods in the identification of patients with AM (Table 2). The relationship between qualitative and quantitative parameters is reported in Table 3. Figure 3 illustrates a representative example of concordance between T2-weighted STIR, EGE, and LGE.

DISCUSSION

The major finding of this study is that qualitative and quantitative CMR methods commonly used for the diagnosis of AM have similar diagnostic accuracy suggesting that a simplified and shortened CMR protocol including only T2-weighted STIR sequences might be considered in the diagnostic work up of patients with suspected AM. To the best of our knowledge, our study is the first comparing qualitative and quantitative methods for the evaluation of patients with suspicion of AM. Our results suggest that T2-weighted STIR sequences alone, without the need of contrast material administration, in the context of a shortened CMR protocol might be proposed as screening tool not only for the evaluation of myocardial edema but also for the diagnosis of AM.

In the setting of viral myocarditis, CMR studies with LGE have been used for several years, first looking at the diagnostic performance of the technique, followed by prognostic data.[13] It is well known that a positive CMR with evidence of LGE is associated with an adverse outcome and patients with LGE are at increased risk of suffering adverse cardiac events. In particular, Grün et al.[14] demonstrated in more than 220 patients with biopsy-proven viral myocarditis that the presence of LGE is the best independent predictor of all-cause mortality and of cardiac mortality. In addition, patients with no evidence of LGE show an excellent prognosis. Schumm et al.[15] confirmed these findings in a larger study with more than 400 patients with suspected AM. Patients with a normal CMR scan had a good prognosis, independent of their clinical symptoms and other findings. Nevertheless, it should be considered that although not all patients with LGE will suffer an event, they are at an increased risk.

Abnormal signal intensity on T2-weighted STIR imaging points out increased myocardial water content (*myocardial edema*) linked to the inflammatory response in AM. In particular, the T2-weighted STIR technique includes a third 180° inversion pulse integrated into the classical double-inversion recovery black blood turbo spin echo pulse sequence. The first and second inversion pulses create a black blood effect; the third inversion pulse leads to the suppression of the signal from fatty tissue and from other stationary tissue with a T1 relaxation time of approximately 200-250 ms. Another important effect of the third pulse enabling the detection

Table 1. Baseline demographic data and clinical characteristics according to the presence or absence of myocarditis at cardiac magnetic resonance imaging

	With myocarditis ($n = 49$)	Without myocarditis ($n = 12$)	*P* value
Age (years)	44 ± 16	47 ± 16	0.48
Male gender	37 (75%)	7 (58%)	<.001
LV ejection fraction (%)	47 ± 15	54 ± 14	0.08
End-diastolic volume (mL)	132 ± 45	167 ± 82	0.11
End-systolic volume (mL)	68 ± 42	86 ± 84	0.48
Stroke volume (mL)	62 ± 21	81 ± 19	<.001
LV mass (g)	98 ± 30	92 ± 27	0.68
Troponin I (ng/mL)[a]	242 ± 13	0.99 ± 0.8	<.001
Abnormal troponin I	21 (43%)	3 (25%)	0.34
Creatine kinase (ng/mL)[b]	169 ± 20	13 ± 8	<.001

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects
LV, left ventricular
[a]Normal value <.1 ng/mL
[b]Normal value 0–4 ng/mL

Table 2. Performance of qualitative and quantitative cardiac magnetic resonance methods for diagnosis of acute myocarditis

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
Lake-Louise Criteria	73% (59–85)	100% (74–100)	78% (67–89)	100% (74–100)	48% (28–68)
T2-weighted STIR	81% (67–91)	100% (74–100)	85% (76–94)	100% (74–100)	57% (35–79)
Early gadolinium-enhancement	75% (60–86)	100% (74–100)	80% (70–90)	100% (74–100)	50% (30–70)
Late gadolinium-enhancement	77% (62–88)	100% (74–100)	81% (71–91)	100% (74–100)	52% (31–73)
Edema ratio	71% (56–83)	100% (74–100)	77% (66–88)	100% (74–100)	46% (26–66)
Global relative enhancement	66% (49–78)	92% (62–99)	71% (59–83)	97% (70–100)	42% (23–61)

CI, confidence intervals; *PPV*, positive predictive value; *NPV*, negative predictive value; *LLC, STIR,* short time inversion recovery

of edema is the effect of the inversion of the long T1 on final signal intensity, so the T1 lengthening related to edema contributes to the increased signal of edematous tissue, together with T2 lengthening.[16] These sequences provide additional information to LGE imaging and can help to differentiate acute and chronic forms of myocarditis through the evaluation of myocardial edema.[3,5,17] The signal abnormality observed on the T2-weighted STIR sequences may be focal in approximately 30% of patients and diffuse in the remaining 70%. Focal areas of high T2-weighted signal intensity generally occur in a transmural or sub-epicardial myocardial distribution; less often it is possible to appreciate sub-endocardial signal abnormalities. A focal increase of T2-weighted signal intensity is not always associated with LGE, but there is usually a strong association between the two patterns. This association is probably linked to a special ''time window'' of the pathology.[18,19] Generally, myocardial edema should increase both T2 myocardial signal intensity as well as the distribution of gadolinium-DTPA with a following increment of myocardial enhancement. It has been previously suggested that myocardial edema results in a degree of capillary compression and then it hinders the smooth circulation of the contrast agent.[20]

In this study, we have shown that no differences are present among commonly used qualitative and quantitative methods for the evaluation of patients with suspected AM. Furthermore, T2-weighted STIR sequence alone shows an excellent specificity and positive predictive value in patients with acute chest pain and clinical suspicion of AM. These data suggest a possible use of CMR in a clinical scenario of patients with suspicious AM, using a ''*fast*'' CMR protocol without the need of contrast material administration, considering the no statistically significant difference observed among T2-weighted STIR, EGE, and LGE sequences.

One of the major limitations of this study is the lack of validation of the CMR findings with endo-myocardial biopsy. In fact, the final diagnosis was based on the synopsis of clinical, laboratory, and imaging findings and on clinical/instrumental follow-up obtained at 3 months after admission to the chest pain unit. However, the value of biopsy as gold standard is questionable unless a targeted approach is used, for example, using LGE-CMR imaging to guide biopsy.[21] Furthermore, while biopsy is often accepted as a standard of reference, it has limited sensitivity due to sampling errors. Using the recommended minimal number of 5 right ventricular samples, a postmortem study has demonstrated endo-myocardial biopsy to yield only 45% sensitivity for the diagnosis of myocarditis.[22] Another ex vivo study has found endo-myocardial biopsy to require more than 17 samples per patient, to yield a sensitivity of about 80%.[23] Therefore, even in the clinically unlikely scenario of taking as much as 18 samples, one would still miss myocarditis in 1 of 5 patients using biopsy.[22] Our definition of AM, based on combined clinical criteria has been widely used and indicates a very high likelihood of disease.[7] In addition, the correctness of the CMR-based diagnosis can at least partly be explained by an imaging bias, as the cardiological diagnosis was influenced by the results of CMR in this clinical setting. Despite this bias, the fact that one test enabled a correct diagnosis in the majority of patients, clearly demonstrates the value of CMR in the acute setting.

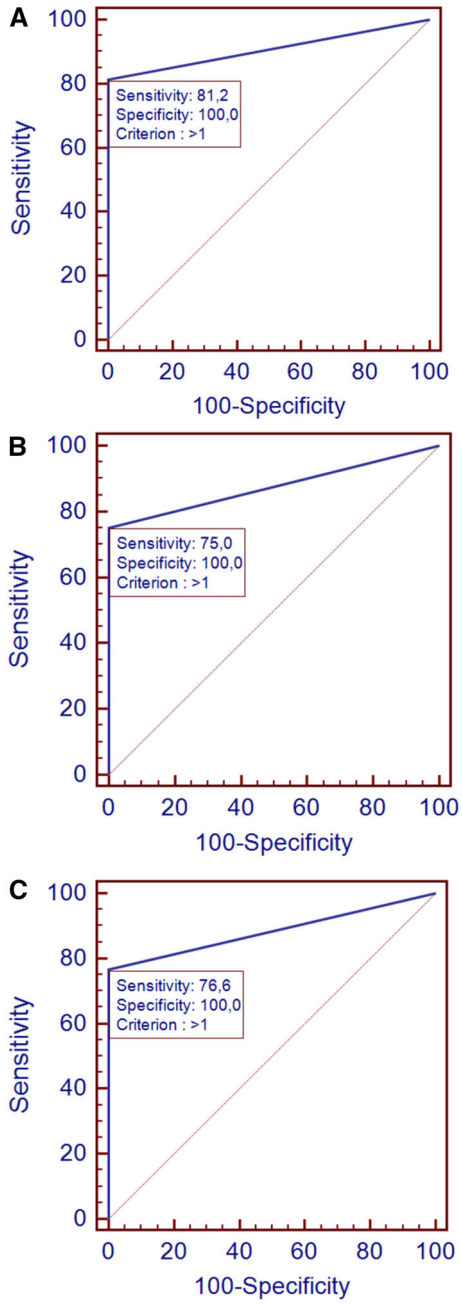

Figure 1. ROC analysis for T2-weighted short inversion time inversion recovery (STIR) sequences (**A**), early gadolinium-enhancement (EGE) (**B**), and late gadolinium-enhancement LGE (**C**). AUC were 0.92 for T2-weighted STIR, 0.87 for EGE, and 0.88 for LGE (P = NS).

Further improvement of CMR in the evaluation of patients with suspected AM has been the introduction of T1 o T2 mapping sequences, without the need of contrast administration. T1-mapping can play out its strengths, as a significant prolongation of T1 relaxation

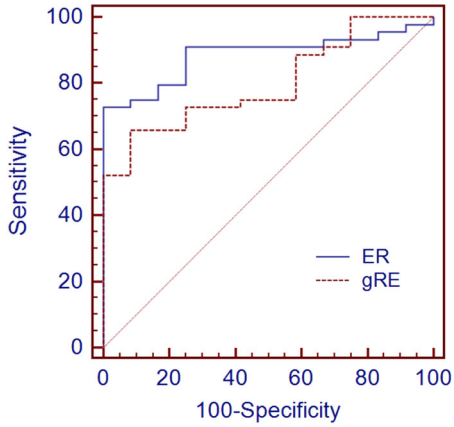

Figure 2. ROC analysis for edema ratio (ER) and global relative enhancement (RE). AUC were 0.89 for ER and 0.80 for global RE (P = NS).

times goes along with cellular edema, increased extracellular space, and myocyte necrosis, common findings in patients with AM.[24] T2-mapping has also been proposed as a quantitative approach to edema imaging, allowing the detection of either diffuse or even subtle changes in myocardial T2 relaxation times. One of the main limitation of myocardial T2-mapping is the high intra- and inter-observer variability of T2 times, leading to potential difficulties in discriminating between health and disease.[25] A recent study by Ferreira et al.[26] showed that native T1-mapping has a superior diagnostic role compared to conventional T2-weighted imaging, and an equivalent performance to LGE. Native T1-mapping can also display the typical non-ischemic patterns in AM, without the need for gadolinium contrast agents.[27] Radunski et al.[28] demonstrated the utility of extracellular volume quantification, as a measure of interstitial fibrosis in both acute and subacute severe myocarditis. They compared the diagnostic performance of T2, T1, and extracellular volume as novel quantitative tissue markers compared to the LLC. Extracellular volume quantification together with LGE imaging significantly improved the diagnostic accuracy of CMR compared with the LLC. More recent data support the value and robustness of T1 and T2-mapping techniques in the diagnosis of AM.[29,30] However, larger multicenter trials are needed to develop a standardized T1 and T2-mapping technique and to define widely accepted normal thresholds values among the different MR scanners.

NEW KNOWLEDGE GAINED

CMR is a primary noninvasive tool for the diagnosis of AM. Both qualitative and quantitative CMR methods may be used for the evaluation of patients with a

Table 3. Relationship between qualitative and quantitative cardiac magnetic resonance parameters

	Edema ratio		Global relative enhancement	
	ρ (95% CI)	*P* value	ρ (95% CI)	*P* value
T2-weighted STIR	0.53 (0.22–0.76)	<.001	0.36 (0.11–0.55)	<.01
Early gadolinium-enhancement	0.33 (0.08–0.54)	<.01	0.42 (0.14–0.61)	<.001
Late gadolinium-enhancement	0.30 (0.05–0.52)	<.05	0.31 (0.10–0.52)	<.05

CI, confidence intervals; *STIR,* short time inversion recovery

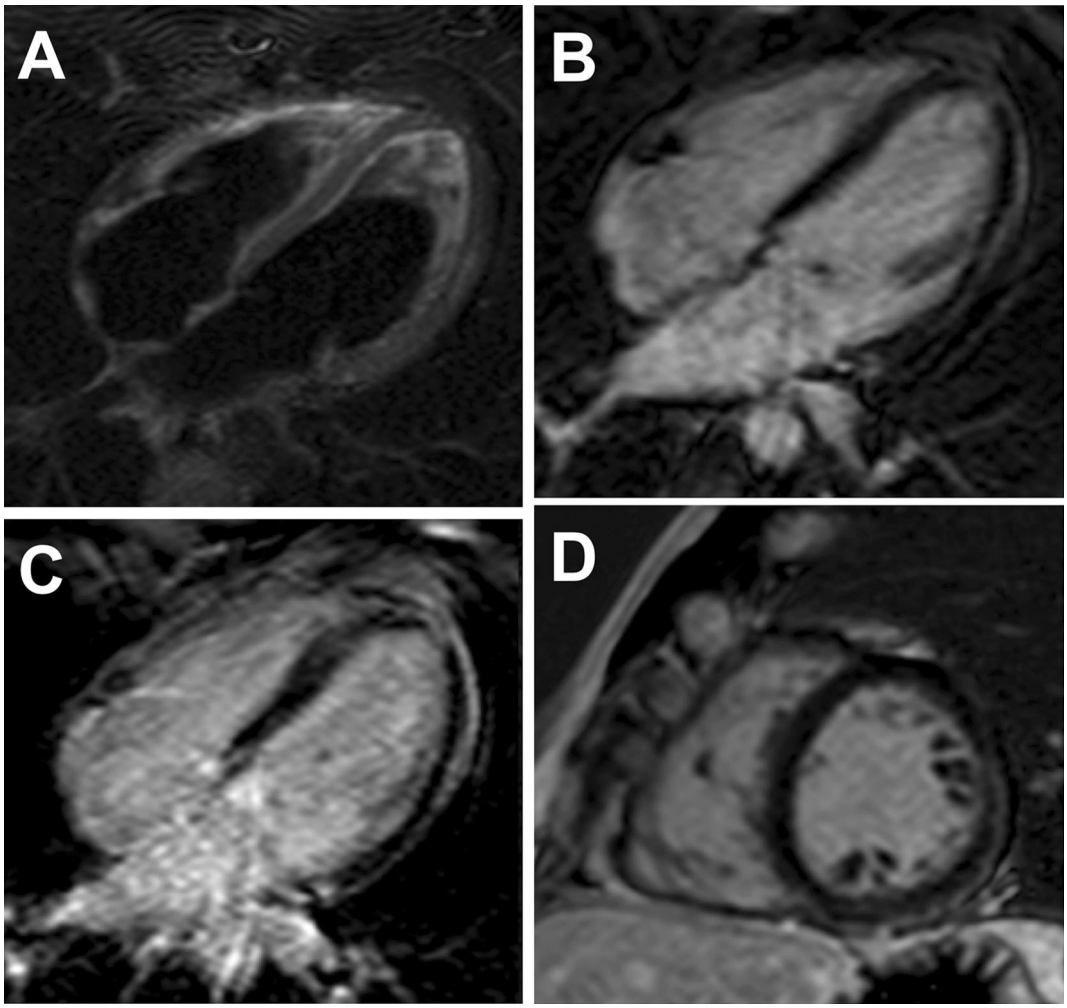

Figure 3. Acute myocarditis in a 42-year-old man presenting with fever, acute chest pain, and elevation of cardiac biomarkers. T2-weighted STIR images acquired in the four-chamber horizontal long-axis demonstrate myocardial edema in LV free wall (**A**). The typical pattern of sub-epicardial enhancement is shown on the corresponding four-chamber early gadolinium-enhancement sequences (**B**) as well as on the four-chamber and short-axis late gadolinium-enhancement sequences (**C** and **D**).

suspicion of AM. Our findings demonstrate that qualitative and quantitative CMR methods boast similar accuracy for the diagnosis of AM and suggest that a faster protocol including T2-weighted STIR sequences alone may be proposed as a screening tool without the need of contrast administration in patients with acute coronary syndrome and normal coronary angiography.

CONCLUSION

The results of this study demonstrate that qualitative and quantitative methods used for the evaluation of patients with suspected AM show similar diagnostic accuracy. Hence, T2-weighted STIR sequences alone with short CMR protocol without intravenous contrast administration may by proposed to rule out AM in patients with acute coronary syndrome and normal coronary angiography. Based on the results of this study, a revision of LLC would be desirable.

Disclosure

M. Imbriaco, C. Nappi, M. Puglia, M. De Giorgi, S. Dell'Aversana, R. Cuocolo, A. Ponsiglione, I. De Giorgi, M.V. Polito, M. Klain, F. Piscione, L. Pace, A. Cuocolo declare that they have no conflict of interest.

References

1. Cooper LT. Myocarditis. N Engl J Med 2009;360:1526-38.
2. Jeserich M, Konstantinides S, Pavlik G, Bode C, Geibel A. Noninvasive imaging in the diagnosis of acute viral myocarditis. Clin Res Cardiol 2009;98:753-63.
3. Francone M, Di Cesare E, Cademartiri F, Pontone G, Lovato L, Matta G, et al; CMR Italian Registry Group, Ligabue G, Mancini A, Palmierir F, Restaino G, Puppini G, Centonze M, et al. Italian registry of cardiac magnetic resonance. Eur J Radiol 2014;83:e15-22.
4. Antony R, Daghem M, McCann GP, Daghem S, Moon J, Pennell DJ, et al. Cardiovascular magnetic resonance activity in the United Kingdom: A survey on behalf of the British Society of Cardiovascular Magnetic Resonance. J Cardiovasc Magn Reson 2011;13:57.
5. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol 2009;53:1475-87.
6. Chu GC, Flewitt JA, Mikami Y, Vermes E, Friedrich MG. Assessment of acute myocarditis by cardiovascular MR: Diagnostic performance of shortened protocols. Int J Cardiovasc Imaging 2013;29:1077-83.
7. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC committee for practice guidelines. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2011;32:2999-3054.
8. Kramer CM, Barkhausen J, Flamm SD, Kim RJ. Nagel E; Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, Society for Cardiovascular Magnetic Resonance: Board of Trustees Task Force on Standardized Protocols. J Cardiovasc Magn Reson 2008;10:35.
9. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Int J Cardiovasc Imaging 2002;18:539-42.
10. Gutberlet M, Spors B, Thoma T, Bertram H, Denecke T, Felix R, et al. Suspected chronic myocarditis at cardiac MR: Diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 2008;246:401-9.
11. Park CH, Choi EY, Greiser A, Paek MY, Hwang SH, Kim TH. Diagnosis of acute global myocarditis using cardiac MRI with quantitative T1 and T2 mapping: Case report and literature review. Korean J Radiol 2013;14:727-32.
12. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983;148:839-43.
13. Vermes E, Childs H, Faris P, Friedrich MG. Predictive value of CMR criteria for LV functional improvement in patients with acute myocarditis. Eur Heart J Cardiovasc Imaging 2014;15:1140-4.
14. Grün S, Schumm J, Greulich S, Wagner A, Schneider S, Bruder O, et al. Long-term follow-up of biopsy-proven viral myocarditis: Predictors of mortality and incomplete recovery. J Am Coll Cardiol 2012;59:1604-15.
15. Schumm J, Greulich S, Wagner A, Grun S, Ong P, Bentz K, et al. Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis. J Cardiovasc Magn Reson 2014;16:14.
16. Dwyer AJ, Frank JA, Sank VJ, Reinig JW, Hickey AM, Doppman JL. Short-T1 inversion-recovery pulse sequence: analysis and initial experience in cancer imaging. Radiology 1988;168:827-36.
17. Esposito A, Francone M, Faletti R, Centonze M, Cademartiri F, Carbone I, et al. Working Group of the Italian College of Cardiac Radiology by SIRM. Lights and shadows of cardiac magnetic resonance imaging in acute myocarditis Insights Imaging 2016;7:99-110.
18. Yelgec NS, Dymarkowski S, Ganame J, Bogaert J. Value of MRI in patients with clinical suspicion of acute myocarditis. Eur Radiol. 2007;17:2211-7.
19. Abdel-Aty H, Boyé P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, 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.
20. Manciet LH, Poole DC, McDonagh PF, Copeland JG, Mathieu-Costello O. Microvascular compression during myocardial ischemia: Mechanistic basis for no-reflow phenomenon. Am J Physiol 1994;266:H1541-50.
21. Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, et al. Cardiovascular magnetic resonance assessment of human myocarditis: A comparison to histology and molecular pathology. Circulation 2004;109:1250-8.
22. 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.
23. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. J Am Coll Cardiol. 1989;14:915-20.
24. Luetkens JA, Homsi R, Sprinkart AM, Sprinkart AM, Doerner J, Dabir D, et al. Incremental value of quantitative CMR including parametric mapping for the diagnosis of acute myocarditis. Eur Heart J Cardiovasc Imaging 2016;17:154-61.
25. Baeßler B, Schaarschmidt F, Dick A, Stehning C, Schnackenburg B, Michels G, et al. Mapping tissue inhomogeneity in acute myocarditis: A novel analytical approach to quantitative myocardial edema imaging by T2-mapping. J Cardiovasc Magn Reson 2015;23:115.
26. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Ntusi N, et al. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. J Cardiovasc Magn Reson 2014;23:36.
27. Greulich S, Ferreira VM, Dall'Armellina E, Mahrholdt H. Myocardial inflammation—are we there yet? Curr Cardiovasc Imaging Rep. 2015;8:6.
28. Radunski UK, Lund GK, Stehning C, Schnackenburg B, Boehnen S, Adam G, et al. CMR in patients with severe myocarditis: Diagnostic value of quantitative tissue markers including extracellular volume imaging. JACC: Cardiovasc Imaging 2014;7:667-75.
29. Bohnen S, Radunski UK, Lund GK, Ojeda F, Looft Y, Senel M, et al. Tissue characterization by T1 and T2 mapping cardiovascular magnetic resonance imaging to monitor myocardial inflammation in healing myocarditis. Eur Heart J Cardiovasc Imaging 2017 Mar 8. doi:10.1093/ehjci/jex007. [Epub ahead of print].
30. Spieker M, Haberkorn S, Gasti M, Behm P, Katsianos S, Horn P, et al. Abnormal T2 mapping cardiovascular magnetic resonance correlates with adverse clinical outcome in patients with suspected acute myocarditis. J Cardiovasc Magn Reson 2017;19:38.