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Cardiac Magnetic Resonance Monitors Reversible and Irreversible Myocardial Injury in Myocarditis

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OBJECTIVES We sought to assess the value of cardiac magnetic resonance (CMR) to monitor the spectrum of myocarditis-related injuries over the course of the disease.

BACKGROUND Myocarditis is associated with a wide range of myocardial tissue injuries, both reversible and irreversible. Differentiating these types of injuries is a clinical demand.

METHODS We studied 36 patients (31 males, age 33 ± 14 years) hospitalized with myocarditis during the acute phase and 18 ± 10 months thereafter. CMR was performed on 2 1.5T scanners and included the following techniques: steady-state free precession (to assess left ventricular function and volumes), T2-weighted (myocardial edema), early (global relative enhancement [gRE], reflecting increased capillary leakage) and late T1-weighted after gadolinium-DTPA injection (late gadolinium enhancement [LGE], reflecting irreversible injury).

RESULTS In the acute phase, T2 ratio was elevated in 86%, gRE in 80%, and LGE was present in 63%. At follow-up, ejection fraction increased from 56 ± 8% to 62 ± 7% ($p < 0.0001$) while both T2 ratio (2.4 ± 0.5 to 1.9 ± 0.2; $p < 0.0001$) and gRE (7.6 ± 8 to 4.4 ± 4; $p = 0.018$) significantly decreased. LGE persisted in all but 1 patient in whom LGE completely resolved. No patient had simultaneous elevation of T2 and gRE during the convalescent phase, resulting in a negative predictive value of 100% to differentiate the 2 phases of the disease. The acute phase T2 ratio correlated significantly with the change of end-diastolic volume over time (beta = 0.47; $p = 0.008$). This relation remained significant in a stepwise regression analysis model including T2 ratio, gRE, LGE extent, baseline ejection fraction, age, and creatine kinase, in which only T2 emerged as an independent predictor of the change in end-diastolic volume.

CONCLUSIONS A comprehensive CMR approach is a useful tool to monitor the reversible and irreversible myocardial tissue injuries over the course of myocarditis and to differentiate acute from healed myocarditis in patients with still-preserved ejection fraction. (J Am Coll Cardiol Img 2009;2: 131–8) © 2009 by the American College of Cardiology Foundation

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The acute inflammatory reaction of the myocardium is characterized by a wide spectrum of tissue injuries (1). Although some of these injuries are mild or reversible, others are severe and may persist during the chronic phase of myocarditis. Noninvasive differentiation of these injuries is clinically important and may emerge as a novel means for patient prognostication (2). Because of its versatility and unique tissue characterization capability, cardiac magnetic resonance (CMR) has managed to provide new insights into myocarditis-related tissue injuries (3). Some of these injuries, such as edema or capillary leakage, are even difficult to assess histopathologically whereas others, such as tissue necrosis, can be demonstrated with high spatial resolution allowing differentiation of myocarditis from coronary syndromes (4,5).

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ABBREVIATIONS AND ACRONYMS

CK = creatine kinase

CMR = cardiac magnetic resonance

EDV = end-diastolic volume

EF = ejection fraction

gRE = global relative enhancement

LGE = late gadolinium enhancement

LV = left ventricular

So far, however, investigators have mostly focused on assessing either acute (6) or chronic (7) myocarditis or have attempted to monitor only 1 of these injuries, for example, tissue necrosis (8). As such, the exact temporal evolution of the wide range of myocarditis-related injuries over the course of myocarditis in the same group of patients has not been reported. In fact, studying different groups of patients has led to some apparently conflicting results. For example, some investigators have found that tissue edema as assessed by T2-weighted imaging is not a feature of chronic myocarditis (7) and, accordingly, is a reversible acute-phase injury, whereas others have recently noticed T2 abnormalities in a substantial fraction of these patients (9).

The same controversy (6,9,10) exists for capillary leakage as imaged by global relative enhancement (gRE). Clinically, establishing the pattern and reversibility of injuries in myocarditis noninvasively is crucial because based on the most recent guidelines (11), myocarditis patients who usually present with preserved ejection fraction (EF) may not be indicated to receive endomyocardial biopsy. Finally, differentiating acute from healed myocarditis is a diagnostic challenge because of the frequently vague clinical presentation and limited time window of laboratory markers of acute myocardial injury. We have previously shown the ability of CMR to detect different tissue injuries in acute myocarditis (12). In the current report, we provide both the follow-up data of this cohort as well as additional de novo data in a prospective setting.

METHODS

Patients with clinically defined acute myocarditis presenting to the emergency room were studied twice: within the first week and 18 ± 10 months later. Twenty-five of these patients have already been described in a previous publication (12) and were included retrospectively. Eleven consecutive patients were included prospectively. For inclusion, patients had to fulfill each of the following clinical criteria: new onset of chest pain or shortness of breath; arrhythmias and/or pathological electrocardiographic findings (ST-segment changes, T-wave inversion, and atrioventricular block); elevation of cardiac serum markers (creatine kinase [CK] or troponin T or I); and exclusion of coronary artery disease by conventional coronary angiography, except for patients <25 years of age with low pre-test probability for coronary artery disease.

Criteria of exclusion were previous myocardial infarction and known contraindications to CMR. Of 64 patients presenting to our hospital with suspicion of acute myocarditis, 36 patients were eligible to participate in the study based on these inclusion and exclusion criteria. All participants gave informed written consent including retrospective analysis of data, and the study was approved by the local ethics committee.

At follow-up, patients were asked to fill out questionnaires regarding heart failure symptoms, cardiac arrhythmias, and compliance to medical treatment.

CMR. The CMR studies were performed on 2 1.5-T systems (Signa CV/*i*, GE Medical Systems, Milwaukee, Wisconsin, and Sonata, Siemens Medical Solutions, Erlangen, Germany). The same protocol was followed during the acute and the follow-up examinations. After localization, steady-state free precession images of true anatomical axes of the heart were acquired. For the T2-weighted and T1-weighted spin-echo sequences, which were used for a quantitative evaluation, the body coil was used. We applied a breath-hold, black-blood, T2-weighted triple inversion-recovery sequence (repetition time (TR) 2 × R to R interval (RR), echo time (TE) 65 ms, inversion time (TI) 140 ms) in 3 (basal, mid-ventricular, and apical) short-axis slices (slice thickness 15 mm, gap 5 mm, field of view 34 to 38 cm, matrix 256 × 256). Breath-hold cine

steady-state free precession images (TR 3.8 ms, TE 1.6 ms) were acquired in 2- and 4-chamber views to assess global ventricular function. We then applied a free breathing T1-weighted spin-echo sequence (6) in 3 identical axial slices both before and after (without any change in parameters in between) intravenous injection of 0.1 mmol Gadolinium-DTPA (Magnevist, Bayer Schering Pharma, Berlin, Germany) using an automated injector (Medrad, Inc., Indianola, Pennsylvania). The post-contrast part of the sequence was started immediately after injection and lasted 3 to 4 min; thus, the images reflect gadolinium enhancement at a mean of 2 min. After the acquisition of spin-echo images, an additional dose (0.1 mmol) of gadolinium-DTPA was injected, and a breath-hold, contrast-enhanced, inversion-recovery gradient-echo sequence (TR 5.5 ms, TE 1.4 ms, TI 225 to 320 ms as individually optimized to null normal myocardial signal, matrix 256 × 192, slice thickness/gap 15/5 mm) was applied after a delay of 10 min (late gadolinium enhancement [LGE]) in 3 short- and 3 long-axis (2-, 3-, and 4-chamber views, respectively) slices.

Coronary angiography. Coronary angiography was performed on a standard angiography suite (Hicor, Siemens Medical Solutions) in 24 patients to exclude the presence of significant coronary artery disease (>70% stenosis).

Clinical analysis. Clinical analysis was done by observers blinded to CMR data who assessed the clinical course of the patients during their hospital stay and follow-up visit. We defined acute and convalescent clinically, based on the duration between the clinical disease onset and the CMR examination.

Laboratory measurements. CK–myocardial band, C-reactive protein, and troponin were measured on admission. To standardize expressing the results, we related the troponin value from each patient to that of the cutoff of either troponin T or I, which we defined as "troponin fold."

Image analysis. Acute and follow-up images were analyzed by 1 observer blinded to all nonimaging data.

CINE IMAGES. The endocardial and epicardial contours were manually traced, and the end-diastolic and end-systolic volumes (absolute as well as indexed to height in cm), EF, and myocardial mass were calculated. The change (delta) in these parameters was then calculated as: value at follow-up minus value during the acute phase.

SPIN-ECHO IMAGES. Regions of interest covering the left ventricular (LV) myocardium as well as within a skeletal muscle (erector spinae or latissimus dorsi) in the same slice were manually drawn in the pre-contrast images and were copied to the post-contrast images. The gRE was calculated as previously described (6).

T-2 weighted images. QUANTITATIVE ANALYSIS. Regions of interest were drawn covering the LV myocardium and within a skeletal muscle in the same slice. The myocardial signal intensity was related to that of the skeletal muscle to calculate the T2 ratio (12). The cutoffs of T2 ratio and gRE were defined on each of the 2 scanners separately by examining a group of healthy volunteers. This yielded T2 and gRE cutoffs of 1.9 and 4.0, respectively for the GE scanner, while the corresponding values on the Siemens scanner were 1.8 and 5.0 (n = 95, unpublished data, H. Abdel-Aty, February 2007).

LGE. Images were visually assessed for the presence, number, and transmurality of LGE areas. The spatial extent of these lesions was quantified (areas with signal intensity more than that of the normal myocardium + 2 SD) and was expressed as a percentage of the total myocardial volume.

Statistics. All statistical tests were performed using a commercially available statistical program (SPSS version 13 for Macintosh, SPSS Inc., Chicago, Illinois). Data are presented as mean ± SD. Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test, and noncontinuous data using the chi-square test. Differences between the acute and convalescent phases were compared using the paired *t* test. Data were correlated using Pearson or Spearman correlation coefficients as well as linear regression. A p value < 0.05 was considered significant.

RESULTS

Table 1 summarizes the characteristics of the study's population. In total, 36 patients were recruited, and 31 returned for follow-up assessment. Of the original 25 patients we previously reported, 21 returned for follow-up, 1 patient died during the acute phase, and 3 declined follow-up. Of the 11 newly recruited patients, 1 declined follow-up. Twelve patients (age 21 ± 3 years) did not undergo coronary angiography. All CMR examinations were of diagnostic quality. The acute CMR scan took place as soon as possible after the patient's admission to our institution. The average time between

Table 1. Characteristics of the Study Population

n	36
Age, yrs	33 ± 14
Sex (male/female)	31/5
Baseline ejection fraction, %	55 ± 9
Troponin T (n = 10), IU	3 ± 6
Troponin I (n = 14), IU	43 ± 55
Peak creatine kinase, IU	619 ± 607
C-reactive protein, mg%	43 ± 40
Duration between onset of cardiac symptoms and first CMR, days	5 ± 4
Hospital stay, days	9 ± 6
Follow-up time, months	18 ± 10

Normal cutoffs: troponin T <0.03 IU, troponin I <0.1 IU, creatine kinase <309 IU, C-reactive protein <5 mg.
CMR = cardiac magnetic resonance.

symptoms onset and the first CMR examination was 5 ± 4 days. The follow-up scan was performed at 18 ± 10 months after presentation.

Acute phase. The main cardiac symptom in the acute phase was acute chest pain (71%). Sixty-one percent of the patients reported recent history of infection before the onset of cardiac symptoms (respiratory tract infection in 12, gastroenteritis in 8, and skin/soft tissue infection in 2 patients). The T2 ratio was elevated in 86% (2.4 ± 0.5), and gRE was elevated in 80% (7.6 ± 8.0). LGE was present in 22 patients (61%) and was either intramural or subepicardial but never subendocardial. The posterolateral segments were mostly affected (59%), either as sole location or associated with septal (18%) or anterior (13%) lesions. Focal T2 lesions (Fig. 1) were observed in 44%, and there was a significant relationship between T2 and LGE foci (chi-square, $p < 0.0001$). There was a significant correlation between T2 ratio and troponin folds ($r = 0.49$; $p = 0.009$). The CK and troponin were not significantly different among patients with or without LGE. No significant correlation was found between CMR parameters of tissue injuries (T2 ratio, gRE, and LGE) and LV function or volumes.

Follow-up. At follow-up, all patients were free of symptoms, and the EF increased from 56 ± 8 to 62 ± 7 ($p < 0.0001$). In the group as a whole, the end-diastolic volume (EDV [acute, 164 ± 37 ml; follow-up, 159 ± 35 ml; p = NS]) as well as the EDV index (0.93 ml/cm vs. 0.90 ml/cm; p = ns) did not significantly change. Both T2 ratio (1.9 ± 0.2; $p < 0.0001$) and gRE (4.5 ± 4; $p = 0.018$) significantly decreased (Figs. 2 and 3). The LGE persisted in all but 1 patient, in whom LGE completely resolved. The extent of LGE decreased significantly ($p < 0.0001$) from the acute (38 ± 14%) to the healed phase (22 ± 14%). If T2 and gRE were considered together, this would have a 100% negative predictive value to differentiate acute from convalescent myocarditis, namely, no patient had simultaneous elevation of T2 and gRE at follow-up.

CMR and change in LV EDV. There was no relation between the degree of change in CMR parameters of tissue injuries (delta-T2 and -gRE, presence of LGE) and the change in functional parameters over the course of myocarditis. The extent of LGE in the

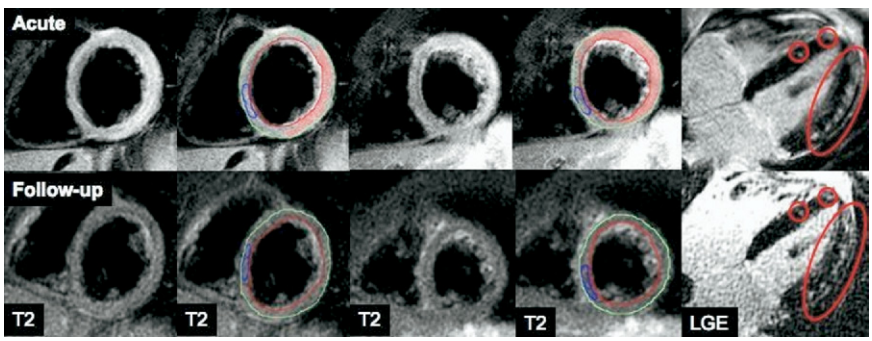

Figure 1. CMR Demonstrates Reversible and Irreversible Myocardial Injuries Over the Course of Myocarditis

Cardiac magnetic resonance (CMR) representative T2-weighted and late gadolinium enhancement (LGE) during the acute phase as well as at follow-up from Patient #23. The 22-year-old male patient presented with acute chest pain and elevated creatine kinase (1,896 IU) and troponin (23 IU). Coronary angiography was normal. During the acute phase, focal lateral and anterior T2 signal elevation was seen and was confirmed after post-processing the images with a special software that automatically delineates areas of high signal intensity (apparently normal myocardium + 2 SD) in **red**. This apparently corresponds to the lateral and anterior intramural late enhancement lesions **(circles)** in the LGE images. At follow-up, the focal T2 abnormality has obviously disappeared but late enhancement lesions persisted. Endocardial and epicardial contours in T2 images highlighted in **red** and **green**, respectively. The **blue** region of interest shows normal myocardium.

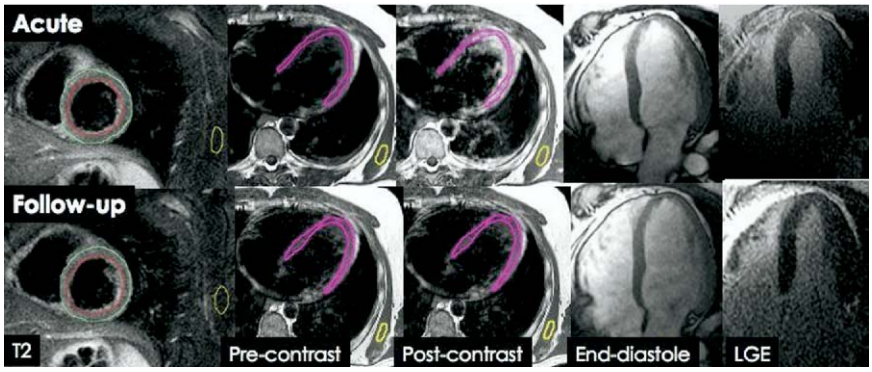

Figure 2. Normalization of T2 and gRE in the Absence of any LGE Over the Course of Myocarditis

Representative T2-weighted, pre-contrast, and early post-contrast enhancement, still end-diastolic frame, and late gadolinium enhancement (LGE) during the acute phase as well as at 16 months' follow-up from Patient #4. This male 36-year-old patient presented with acute chest pain and dyspnea after acute respiratory tract infection. Both creatine kinase (407 IU) and troponin (8.5 IU) were elevated with normal coronary angiography. During the acute phase, both T2 ratio (2.2) and global relative enhancement (gRE) (6.3) were elevated without evidence of LGE (only the 4-chamber view is shown). These values normalized at follow-up (T2, 1.7; gRE, 2).

acute phase did not correlate with delta-EDV ($p = 0.376$). The acute phase T2 ratio, however, correlated significantly with delta-EDV (beta = 0.47, $p = 0.008$). This relation remained significant in a stepwise regression analysis model including T2 ratio, gRE, LGE extent, baseline EF, age, and CK, in which only T2 emerged as an independent predictor of delta-EDV (beta = 0.47, $p = 0.012$).

DISCUSSION

To the best of our knowledge, this is the first study documenting the value of a comprehensive CMR approach to differentiate reversible from irreversible injuries in myocarditis. We then exploited this concept to show that reversible injuries, namely, myocardial edema (T2-weighted) and increased capillary leakage (gRE), differentiate acute from healed myocarditis whereas necrosis/fibrosis imaging (LGE) alone cannot.

Reversible injuries in myocarditis. Both T2 and gRE consistently decreased over the course of myocarditis, and this was associated with improvement both in clinical and LV function parameters. These findings extend the recently reported observations of Gutberlet et al. (9), who observed persistent elevation of T2 in chronic myocarditis patients with evidence of persistent inflammation and depressed LV function. Accordingly, one may postulate that complete recovery of myocarditis is associated with reduction in CMR parameters of inflammation (which we showed in this study) and the development of chronic myocarditis can be detected with good diagnostic accuracy using CMR, as shown by

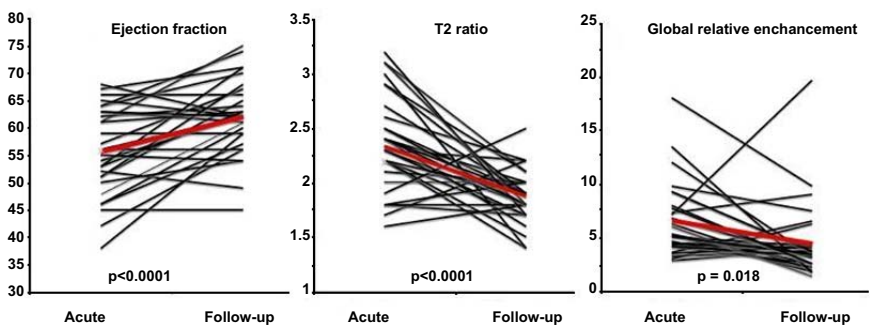

Figure 3. Concordant Normalization of LV Global Function and Tissue Parameters of Acute Myocardial Injury in Myocarditis

Line graphs demonstrating the change in left ventricular (LV) ejection fraction, T2, and global relative enhancement over the course of myocarditis. The significant improvement in ejection fraction paralleled a simultaneous normalization of T2 and global relative enhancement (**red line** indicates mean value of the entire group).

Gutberlet et al. (9). As such, CMR may offer a novel tool to noninvasively monitor disease progression or regression as well as its response to therapy. We have previously validated this latter concept in different settings of inflammatory heart disease, including sarcoid heart disease (13) and systemic lupus erythematosus-related myocardial inflammation (14). In both reports, we showed that CMR parameters of tissue inflammation decrease in response to steroid therapy, confirming earlier reports (15). These findings extend previous observations.

Tissue edema (16–18) and increased capillary leakage (19) are the most likely pathological correlates to these 2 CMR parameters. The fact that these pathological injuries are reversible, transient features of the active inflammatory response could thus explain our CMR findings. Using histopathology, Uchida et al. (20) found that myocardial edema and hyperemia were consistent features of acute but not of healed myocarditis, and a recent CMR study found that T2 changes are rather rare in the chronic myocarditis setting (7). Furthermore, we (21) and others (22) have also previously shown that T2 changes reflecting myocardial edema are features of the acute but not of the chronic injury in myocardial infarction, lending further support to our current findings.

Irreversible injuries in myocarditis. Apart from 1 patient, LGE persisted over the entire course of myocarditis. This finding is in agreement with previous reports (8,23) and highlights the specificity of this LGE pattern to irreversible injury. Sensitivity, however, remains a controversial issue because 39% of the patients had markedly elevated troponin in the absence of any LGE (Fig. 2), and troponin levels were not significantly different among patients with or without LGE. This finding underlines an important confounder of LGE imaging in myocarditis, namely, the inability to detect diffuse necrosis. In fact, LGE imaging was designed to visualize "focal" irreversible injury in myocardial infarction, assuming the presence of healthy or "remote" myocardium (24), which explains the lower sensitivity others also observed (9,25). This assumption does not hold true in pathological entities, which may be characterized by diffuse necrosis, as it is the case with myocarditis.

In this context, the significant correlation we observed between global T2 ratio and troponin may be explained by innumerous minute foci of necrosis accompanied by edema (global) and troponin release while LGE fails to identify a healthy myocardium to suppress or a specific lesion to highlight. Mahrholdt et al. (23) recently observed a novel association between the pattern of LGE and LV remodeling in myocarditis. The patient population we investigated is different from that of Mahrholdt et al. (23) in terms of homogeneity and severity of heart failure. Specifically, a significant fraction (≈50%) of patients in that study presented with LV dilatation and impaired EF in which initial EDV emerged as a strong independent predictor of later LV dilatation. That comes in clear contrast to our population, who presented with almost normal LV function and dimensions. Interestingly, however, the population we studied (young, predominantly male, infarct-like clinical presentation, almost normal LV function, and mostly posterolateral LGE) seems to match well to the parvovirus subgroup of the study by Mahrholdt et al. (23), in which—similar to our findings—recovery was the rule.

Differentiating acute from convalescent myocarditis. We have previously shown the specificity of CMR to distinguish myocarditis patients from healthy volunteers (12). We now extend these observations to address another clinically important issue, namely, the differentiation of acute from healed myocarditis. Similar to myocardial infarction (21), a comprehensive approach combining CMR parameters of reversible and irreversible injuries was able to estimate the age of the injury. This observation has a special relevance in the myocarditis setting. The insidious onset as well as the diverse clinical presentations of myocarditis would mean that a significant fraction of patients may present after serum markers and electrocardiographic changes of acute injury have already subsided. Furthermore, the clinical presentations of acute and chronic myocarditis frequently overlap, and this diagnostic gap appears to be well addressed by the comprehensive CMR approach we present. The differentiation between acute and chronic myocarditis affects the clinical management of the patients, because physical exercise within the acute phase of myocarditis is known to have detrimental effects on the severity of myocardial injury and may even lead to sudden cardiac death (26–28). Accordingly, recent guidelines recommend that physical exertion should be restricted for patients with acute myocarditis (29).

Clinical implications. The unique ability of CMR to monitor myocarditis-related tissue injuries noninvasively has the potential to guide decision making, for example, reinstitution of normal physical exertion if parameters of acute tissue injury have already subsided. Although speculative, CMR parameters of injury may emerge as end points to assess the efficacy

of novel interventions. Indeed, some of these interventions target myocarditis injuries such as myocardial edema (30), readily quantifiable using CMR.

Study limitations. This study was an extension of our previous study in which endomyocardial biopsy and immunohistochemistry were not performed and as such would suffer from this same limitation. Accordingly, we cannot determine the histopathological fate of myocarditis in our population. However, the lack of symptoms and the uneventful recovery, as well as the significant improvement of EF at follow-up, seem to reflect healing in most of the patients. Myocarditis is a complex disease with diverse presentations, perpetrators, and prognostic profiles. Therefore, our data may only apply to patient subgroups similar to the population we investigated. One-third of the patients did not undergo coronary angiography to exclude coronary artery disease. These patients were very young and had a low pre-test probability of coronary artery disease, but even more important, none of our patients exhibited an infarct-like pattern of LGE, rendering the possibility of coronary artery disease highly unlikely. Finally, the time to follow-up was variable, reflecting in part the retrospective nature of this analysis.

CONCLUSIONS

We have demonstrated the ability of a comprehensive CMR approach to differentiate reversible from irreversible injuries over the course of myocarditis. The findings suggest that this approach may serve as a useful noninvasive tool to monitor myocarditis patients.

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Key Words: myocarditis ■ cardiovascular magnetic resonance ■ cardiomyopathy ■ T2-weighted ■ edema ■ late gadolinium enhancement.