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T_1 Mapping for the Diagnosis of Acute Myocarditis Using CMR

Comparison to T_2-Weighted and Late Gadolinium Enhanced Imaging

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OBJECTIVES This study sought to test the diagnostic performance of native T_1 mapping in acute myocarditis compared with cardiac magnetic resonance (CMR) techniques such as dark-blood T_2-weighted (T2W)-CMR, bright-blood T2W-CMR, and late gadolinium enhancement (LGE) imaging.

BACKGROUND The diagnosis of acute myocarditis on CMR often requires multiple techniques, including T2W, early gadolinium enhancement, and LGE imaging. Novel techniques such as T_1 mapping and bright-blood T2W-CMR are also sensitive to changes in free water content. We hypothesized that these techniques can serve as new and potentially superior diagnostic criteria for myocarditis.

METHODS We investigated 50 patients with suspected acute myocarditis (age 42 $\pm$ 16 years; 22% women) and 45 controls (age 42 $\pm$ 14 years; 22% women). CMR at 1.5-T (median 3 days from presentation) included: 1) dark-blood T2W-CMR (short-tau inversion recovery); 2) bright-blood T2W-CMR (acquisition for cardiac unified T_2 edema); 3) native T_1 mapping (shortened modified look-locker inversion recovery); and 4) LGE. Image analysis included: 1) global T_2 signal intensity ratio of myocardium compared with skeletal muscle; 2) myocardial T_1 relaxation times; and 3) areas of LGE.

RESULTS Compared with controls, patients had significantly higher global T_2 signal intensity ratios by dark-blood T2W-CMR (1.73 $\pm$ 0.27 vs. 1.56 $\pm$ 0.15, $p < 0.01$), bright-blood T2W-CMR (2.02 $\pm$ 0.33 vs. 1.84 $\pm$ 0.17, $p < 0.01$), and mean myocardial T_1 (1,010 $\pm$ 65 ms vs. 941 $\pm$ 18 ms, $p < 0.01$). Receiver-operating characteristic analysis showed clear differences in diagnostic performance. The areas under the curve for each method were: T_1 mapping (0.95), LGE (0.96), dark-blood T_2 (0.78), and bright-blood T_2 (0.76). A T_1 cutoff of 990 ms had a sensitivity, specificity, and diagnostic accuracy of 90%, 91%, and 91%, respectively.

CONCLUSIONS Native T_1 mapping as a novel criterion for the detection of acute myocarditis showed excellent and superior diagnostic performance compared with T2W-CMR. It also has a higher sensitivity compared with T2W and LGE techniques, which may be especially useful in detecting subtle focal disease and when gadolinium contrast imaging is not feasible. (J Am Coll Cardiol Img 2013;6:1048–58) © 2013 by the American College of Cardiology Foundation

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Acute myocarditis is common, accounting for up to 75% of patients presenting with chest pain, raised troponin, but nonobstructive coronary arteries (1–4); 12% of young adults presenting with sudden death (5); and 9% of patients who develop dilated cardiomyopathy (6). It is challenging to diagnose, often requiring a combination of clinical assessment and diagnostic tests. Cardiac magnetic resonance (CMR) is the imaging tool of choice because of its ability for multiparametric tissue characterization, as established in recent consensus guidelines (7).

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Currently, 3 CMR methods are available to assess different pathophysiological processes in acute myocarditis: dark-blood T_2-weighted (T2W) imaging for edema, T_1-weighted imaging pre- and post-contrast for hyperemia, and late gadolinium enhancement (LGE) to detect patterns of myocyte necrosis (7). Although CMR is a powerful tool, there are some recognized limitations related to technical factors, image analysis, and the mechanism of each method to detect myocarditis (7,8). Using a combined CMR approach with at least 2 of these 3 criteria can improve diagnostic accuracy (7).

Novel CMR techniques are constantly being developed, some of which may be suitable for the evaluation of myocarditis. For instance, bright-blood T2W has been shown to be superior to dark-blood T2W imaging for detecting the area at risk in acute myocardial infarction (8–10). Quantitative techniques such as T_1 mapping allow direct tissue characterization and have been shown to be superior to T2W techniques in detecting acute edema (11) and area at risk in acute myocardial infarction (12). These methods are promising but have not been systematically assessed in acute myocarditis.

In this prospective study, we performed multiparametric tissue characterization in patients with suspected acute myocarditis (7) using novel and conventional CMR techniques. We aimed to test the diagnostic performance of T_1 mapping and bright-blood T2W-CMR in acute myocarditis compared with dark-blood T2W-CMR and LGE imaging.

METHODS

Study population. This was a prospective study enrolling consecutive patients (n = 50) with suspected myocarditis (7,13) from 2 hospitals (1 tertiary care center—The John Radcliffe Hospital, Oxford, United Kingdom—and 1 medium-sized district general hospital—Milton Keynes Hospital, Milton Keynes, United Kingdom). Patients underwent CMR scanning at the John Radcliffe Hospital between January 2010 and March 2012. All patients had: 1) acute chest pain; 2) elevation in cardiac troponin I level (>0.04 μg/l); and 3) history of recent systemic viral disease or absence of significant (>50%) obstructive coronary artery disease on coronary angiography or absence of risk factors for coronary artery disease or age <35 years. Exclusion criteria included contraindications to CMR, previous myocardial infarction, previous myocarditis, or any chronic cardiac conditions. Patients who demonstrated myocardial infarction as evidenced by an ischemic pattern of LGE (i.e., an isolated area involving the subendocardium) or an obvious alternative diagnosis on CMR (such as Takotsubo or hypertrophic cardiomyopathy) were also excluded. Healthy volunteers (n = 45) with no cardiac history or known cardiac risk factors, not on cardiovascular medications, and with a normal electrocardiogram underwent CMR as controls. All subjects gave written informed consent, and ethical approval was granted for all study procedures.

Cardiac magnetic resonance. CMR studies were performed within 14 days of symptoms using a single 1.5-T magnetic resonance system (Avanto, Siemens Healthcare, Erlangen, Germany). CMR included cine, T2W, T_1 mapping, and LGE imaging, with matching short-axis images. T_1 mapping was performed using the shortened modified look-locker inversion recovery (ShMOLLI) sequence (14);

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CMR = cardiac magnetic resonance
EGE = early gadolinium enhancement
EMB = endomyocardial biopsy
LGE = late gadolinium enhancement
PPV = positive predictive value
ROC = receiver-operating characteristic
ShMOLLI = shortened modified look-locker inversion recovery
SI = signal intensity
STIR = short-tau inversion recovery
T2W = T_2-weighted

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dark-blood and bright-blood T2W-CMR were performed with the short-tau inversion recovery (STIR) (7,15) and the acquisition for cardiac unified T_2 edema (9) sequences, respectively. All were acquired before administration of contrast agents. LGE imaging was acquired using a T_1-weighted phase-sensitive inversion recovery sequence (16) 8 to 10 min after intravenous administration of contrast agent (gadodiamide [Omniscan], GE Healthcare, Chalfont St. Giles, United Kingdom) (total 0.13 mmol/kg body weight at 6 ml/s). A 32-channel phased-array chest coil was used for all data acquisition, except for STIR imaging for which the body coil was used. Acquisition parameters are provided in the Online Appendix.

Image analysis. Matching short-axis slices were compared across cine, dark-blood T2W-CMR, bright-blood T2W-CMR, T_1 mapping, and LGE imaging. Analysis of left ventricular ejection fraction was performed using Argus software (Siemens Healthcare). Short-axis images from all methods were manually contoured using in-house software MC-ROI (programmed by S.K.P. in Interactive Data Language, version 6.1, Exelis Visual Information Solutions, Boulder, Colorado) to outline the endocardium and epicardium, and then divided into 6 segments per slice using the anterior right ventricular–left ventricular insertion point as reference and for comparing segments among sequences. Analysis of wall motion, T2W images, LGE images, and T_1 mapping was performed as previously published (7,11), with additional details provided in the Online Appendix. For all quantitative analysis of T2W, LGE, and T_1 map images, only regions of myocardium with a contiguous area of $\geq$40 mm^2 above the specified thresholds were considered relevant. This corresponds to 10 adjacent pixels for the STIR method, in accordance with currently proposed recommendations (7), to reduce the detection of noise as positive findings. To determine the sensitivity and specificity for each threshold, average involvement of at least 5% of at least 1 myocardial segment per subject above the specified threshold was considered a positive finding by each method.

Statistical analysis. Normality of data was tested using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD; nonparametric data are presented as medians with interquartile ranges. Unpaired samples between groups were assessed by the unpaired 2-tailed Student *t* test, or the Mann-Whitney *U* test for nonparametric data. Correlation was assessed using the Pearson r and Spearman rho coefficient as appropriate. Segmental data were averaged on a per-subject basis before any interindividual and group comparisons to control for clustering of segments within each subject. Receiver-operating characteristic (ROC) analysis was performed to compare the diagnostic performance of the CMR methods in detecting myocardial changes in patients compared with controls. Significance of the ROC analyses was assessed using the method of Delong et al. (17) (MedCalc, version 11.5.1.0, MedCalc Software, Mariakerke, Belgium). The McNemar test and Cochran's *Q* test were used for comparing combinations of CMR tissue characterization methods in the diagnosis of acute myocarditis. All statistical tests were 2-tailed, with p values <0.05 considered statistically significant. To determine the presence of significant differences in subject groups when using multiple CMR methodologies, analysis of variance was performed with Bonferroni-corrected post hoc comparisons for parametric data; for nonparametric data, the Kruskal-Wallis 1-way analysis of variance was performed with post hoc pairwise comparisons using the Mann-Whitney *U* test. The p value for significance was adjusted from $p < 0.05$ to $p < 0.01$ for multiple comparisons within groups where appropriate.

RESULTS

Detection of myocardial changes by CMR in acute myocarditis. Table 1 provides the study patient characteristics. Controls were sex-matched and of similar age distribution (22% women; age 42 ± 14 years). CMR findings are shown in Figure 1 and summarized in Table 2. Patients had significantly lower mean left ventricular ejection fractions compared with controls (ejection fraction 63 ± 12% vs. 72 ± 6%; $p < 0.01$). Patients had significantly higher T_2 signal intensity (SI) ratios, as measured by both dark-blood T2W and bright-blood T2W imaging, as well as significantly higher mean myocardial T_1 values and LGE SI ratios compared with controls. The pattern of LGE was predominantly subepicardial (95.6%) and midwall (84.4%), localized most frequently to the lateral wall (97.9%) and inferior wall (95.6%), as compared with the septum (60.0%) and anterior wall (35.6%). None of the 50 patients demonstrated an isolated ischemic (subendocardial) pattern of LGE to suggest myocardial infarction as the etiology of the presentation. Five of 50 patients (10%) had a subendocardial LGE pattern in conjunction with other patterns typical for myocarditis.

Relationship between myocardial T_1 and other measures of acute myocardial injury. Within the patient group, average myocardial T_1 values correlated well with

Table 1. Baseline Characteristics of the Patient Cohort (n = 50)

Age, yrs	42 ± 16
Female	11 (22)
Risk factors	
Hypertension	11 (22)
Diabetes	3 (6)
Hyperlipidemia	7 (14)
Smoking	16 (32)
Family history of premature CAD	5 (10)
Presenting characteristics	
Recent viral illness	41 (82)
Recent inflammatory illness	5 (10)
Troponin I, μg/l	5.15 [1.22 to 14.20]
C-reactive protein, mg/l	21 [4 to 89]
Coronary angiography	
Nonobstructive coronaries on angiography	36 (72)
Coronary angiogram not performed	14 (28)
Young age, <35 yrs	10
No risk factors for CAD, age >35 yrs	2
Recent viral/inflammatory illness, age >35 yrs	2
Time from symptoms to CMR, days	3 [1 to 6]

Values are n, n (%), or median [interquartile range].
CAD = coronary artery disease; CMR = cardiac magnetic resonance.

left ventricular ejection fraction ($r = -0.57$; $p < 0.0001$) and better than measures of global myocardial edema by dark-blood T2W ($r = -0.34$; $p < 0.02$) or bright-blood T2W imaging ($r = -0.44$; $p < 0.003$). Mean myocardial T_1 showed moderate correlations with relative T_2 SI changes by dark-blood T2W, bright-blood T2W, and LGE imaging ($r = 0.51$, 0.44, and 0.49, respectively; all $p < 0.003$). There were significant correlations between troponin I levels with focal areas of myocardial injury as measured by T_1 >990 ms ($\rho = 0.54$; $p < 0.0001$), LGE ($\rho = 0.43$; $p < 0.002$), dark-blood T2W ($\rho = 0.62$; $p < 0.0001$), and bright-blood T2W imaging ($\rho = 0.37$; $p = 0.01$). T_1 values were significantly higher in patient myocardial tissue characterized by an increased dark-blood T_2 SI ratio (1,055 ± 63 ms), increased bright-blood T_2 SI ratio (1,032 ± 70 ms), and LGE (1,045 ± 66 ms), compared with myocardial tissue of controls (941 ± 18 ms; all $p < 0.01$). For "CMR-negative" myocardial tissue in patients, that is, those without LGE and no significantly increased T_2 SI ratios on both dark-blood and bright-blood T2W imaging, T_1 values were also significantly higher compared with controls (978 ± 45 ms vs. 940 ± 28 ms; $p < 0.001$).

Diagnostic performance of CMR methods in the detection of acute myocarditis. To maximize the accuracy of the threshold values to detect acute myocarditis using these methods, each segment was strictly assessed for image quality before inclusion into the final ROC analysis, and only segments with no or minimal artifacts were included, as previously published (11). On cine imaging, 3.5% of segments corresponding to the left ventricular outflow tract were rejected; on dark-blood STIR imaging, 8.6% were rejected because of artifacts, signal dropout, or breathing motion; and on bright-blood acquisition for cardiac unified T_2 edema imaging, 3.7% of segments were rejected because of off-resonance or patient movement artifacts. T_1 maps were assessed for quality in 3 ways: examination of the T_1 maps, the raw T_1 images, and R^2 maps; 11.2% of the segments were excluded because of off-resonance artifacts, poor T_1 fit on the R^2 maps, patient movement, or a low signal-to-noise ratio (11). On LGE imaging, 2% were rejected because of artifacts caused by patient movement or poor image quality. No subject was excluded from the final analysis owing to image quality.

Both T_1 mapping and LGE imaging demonstrated excellent and equivalent diagnostic performance, with areas under the curve (AUC) of 0.96 and 0.95, respectively (p = ns). T_1 mapping significantly outperformed dark-blood T2W (AUC: 0.78) and bright-blood T2W imaging (AUC: 0.76; both $p < 0.001$). To check for bias against any of the methods, ROC analysis was repeated using all data including segments affected by artifacts. All of the aforementioned relative relationships were preserved, with no significant change in the AUC for each method (all AUC: ≤0.02).

The diagnostic performance of each CMR tissue characterization method and their combinations are summarized in Table 3. T_1 mapping, using a cutoff of T_1 ≥990 ms as established in our previous study for detecting acute edema (11), demonstrated very good performance, with a sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), and negative predictive value of ~90% across the board. The T2W methods showed good diagnostic performance within ranges published in the literature (7), whereas LGE had a high specificity (97%) and PPV (97%) with a lower sensitivity (74%) compared with T_1 mapping.

The combination approach represents a tradeoff between sensitivity and specificity. Combining the T2W methods with LGE significantly improved specificity and PPV, with some loss in sensitivity, thus LGE aided T2W imaging in arriving at a

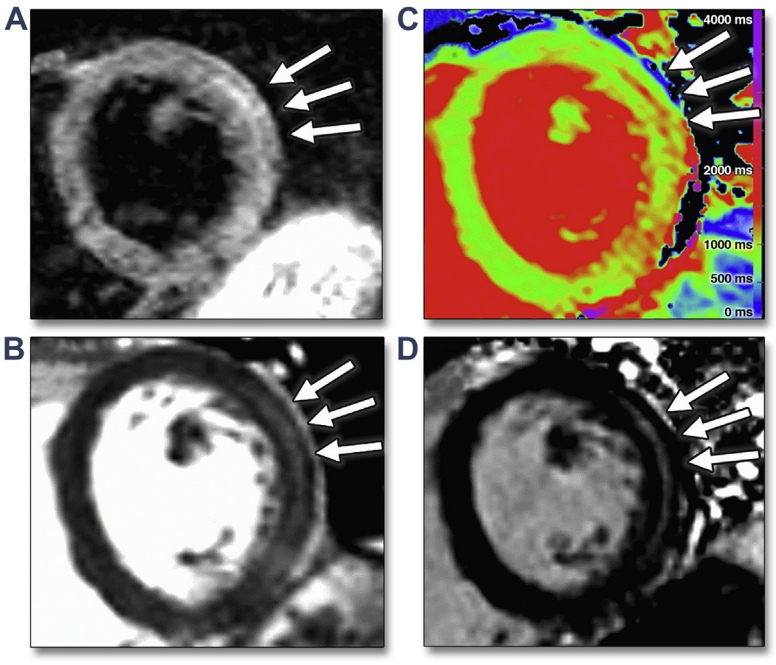

Figure 1. Acute Myocarditis

(A) Dark-blood T_2-weighted (T2W) imaging demonstrating increased signal intensity in the mid lateral wall **(arrows)**. **(B)** Bright-blood T2W imaging demonstrating increased signal intensity in the mid lateral wall **(arrows)**. **(C)** Shortened modified look-locker inversion recovery (ShMOLLI) T_1 map demonstrating increased T_1 values (1,100 to 1,200 ms) in the lateral wall **(arrows)**. **(D)** Late gadolinium enhancement (LGE) imaging demonstrating mid-wall enhancement in the lateral wall **(arrows)**.

positive diagnosis of myocarditis. On the other hand, compared with T_1 mapping alone, combining T_1 mapping with LGE only improved specificity slightly (from 91% to 97%), but at the expense of lower sensitivity (dropping from 90% to 70%), and this combination was not better than LGE alone (not surprising, given the 2 methods had a very similar ROC curve, as shown in Fig. 2). However, the overall diagnostic performance of the T_1 + LGE combination fared better than any of the T2W + LGE combinations. In fact, T_1 mapping showed a better diagnostic performance than the T2W methods, either alone or in combination with LGE.

Table 2. CMR Findings in Patients With Acute Myocarditis Compared With Controls

CMR Measures	Controls	Patients
Ejection fraction, %	72 ± 6	63 ± 12*
Dark-blood T_2 SI ratio	1.56 ± 0.15	1.73 ± 0.27*
Bright-blood T_2 SI ratio	1.84 ± 0.17	2.02 ± 0.33*
Myocardial T_1, ms	941 ± 18	1,010 ± 65*
LGE, % myocardium	0% [0% to 2%]	11% [5% to 21%]*

Values are mean ± SD or median [interquartile range]. Dark-blood T_2 SI ratio and bright-blood T_2 SI ratio = $SI_{myocardium}/SI_{skeletal\ muscle}$; LGE (%) = median volume fraction of late gadolinium enhancement (LGE) per subject. *$p < 0.01$.
CMR = cardiac magnetic resonance; SI = signal intensity.

DISCUSSION

In this work, we have demonstrated for the first time to our knowledge that quantitative CMR by T_1 mapping had an excellent diagnostic performance in detecting changes in acute myocarditis. Further, T_1 mapping outperformed both dark-blood and bright-blood T2W techniques, either alone or in combination with LGE, in the diagnosis of acute myocarditis, with superior sensitivity and excellent specificity and diagnostic accuracy.

The CMR methods tested in this study all have advantages and limitations. From the technical standpoint, factors that lead to the failure of a method to diagnose acute myocarditis may be categorized into: 1) compromised image quality during acquisition (patient movement, poor breath-holding, tachyarrhythmia); 2) suboptimal post-processing techniques; and 3) noise and the selection of thresholds.

Table 3. Diagnostic Performance of CMR Tissue Characterization Methods in the Detection of Suspected Acute Myocarditis

	Sensitivity	Specificity	Accuracy	PPV	NPV
Individual					
T_1 mapping*	90	91	91	92	89
Dark-blood T_2†	52	84	67	79	61
Bright-blood T_2‡	67	55	64	78	42
LGE§	74	97	83	97	69
Combination					
T_1 mapping and LGE‖	70	97	80	97	66
Dark-blood T_2 and LGE	48	97	66	96	53
Bright-blood T_2 and LGE	50	100	55	100	18

Values are %. *Myocardial injury is detected when T_1 is ≥990 ms; †edema is diagnosed when the T_2 SI ratio (T_2 $SI_{myocardium:skeletal\ muscle}$) is ≥2.0; ‡edema is diagnosed when the T_2 SI ratio (T_2 $SI_{myocardium:skeletal\ muscle}$) is ≥2.2 (equivalent to >2 SD of normal; see Table 2); §LGE is detected when myocardial SI is ≥2 SD above mean SI of normal myocardium. ‖The combination of T_1 mapping and LGE was significantly better in performance than dark-blood T_2 + LGE and bright-blood T_2 + LGE (all $p < 0.005$). For each technique, only contiguous areas of myocardium ≥40 mm^2 above the stated threshold were considered relevant; involvement of ≥5% of any segment on a per-subject basis was the threshold used for comparison of methods.
NPV = negative predictive value; PPV = positive predictive value; T2W = T_2-weighted; other abbreviations as in Table 2.

Dark-blood T2W imaging. Dark-blood T2W-CMR is widely used for clinical edema imaging. In addition to following recommended parameters (7), optimal image quality relies on a regular heart rhythm with a ventricular rate within a relatively normal range, appropriate selection of the repetition time tailored to the patient's heart rate, and the ability of the patient to breath-hold. Excessive tachycardia and irregular rhythms, such as atrial fibrillation, and poor breath-holding render dark-blood T2W images nondiagnostic most of the time. Dark-blood T2W images are known for signal dropout, especially in the basal inferolateral wall, where myocarditis typically manifests. When myocarditis is global, the use of "normal remote" myocardium as a reference, which may not be available, leads to significant underestimation of the extent of myocardial injury (Fig. 3). The use of skeletal muscle circumvents this problem unless skeletal muscle is also inflamed, which occurs in some cases of myocarditis (18) and also in this work (Fig. 4). This is supported by the findings that patients with myocarditis demonstrated significantly higher T_1 values in skeletal muscle and with greater variability (822 ± 55 ms) compared with controls (803 ± 32 ms; $p = 0.04$). In this cohort of 50 patients, there were 3 cases in which the dark-blood T_2 edema ratio relative to skeletal muscle was <2.0 (1.78 ± 0.11) despite reasonable image quality, but the average myocardial T_1 was significantly increased (1,158 ± 11 ms) (Fig. 4). This can be explained by skeletal muscle inflammation, supported by significantly increased T_1 values in the skeletal muscle regions in these 3 patients (941 ± 104 ms, more than 4 SD above the values of the normal cohort). The finding of increased T_1 values in skeletal muscle on T_1 mapping is consistent with skeletal muscle inflammation demonstrated in patients presenting with acute myocarditis using pre-and post-contrast T_1-weighted imaging (18). Thus, in some of our patients, conventional T2W imaging was unable to diagnose edema in myocarditis even when using skeletal muscle as a reference, with the remainder of the patients potentially affected by the same mechanism, only to a lesser degree, as supported by the

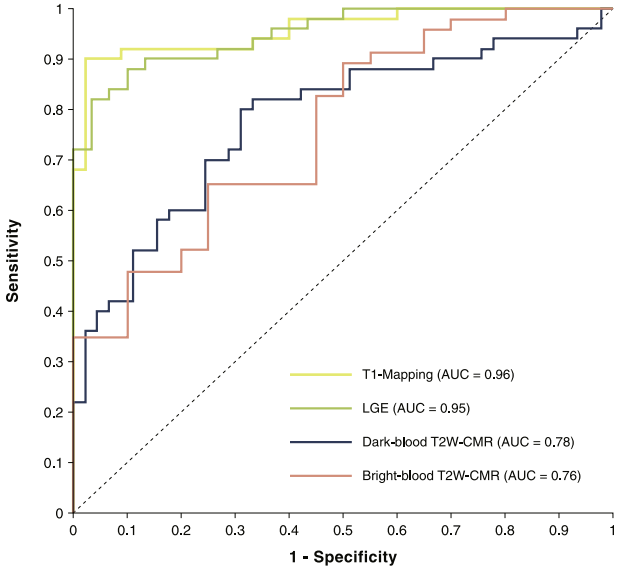

Figure 2. Diagnostic Performance of T_1 Mapping Compared With T2W and LGE Imaging in the Detection of Acute Myocarditis

T_1 mapping is similar to LGE and both significantly outperformed T2W imaging. AUC = area under the curve; CMR = cardiac magnetic resonance; other abbreviations as in Figure 1.

overall increase in T_1 values in patient skeletal muscle. All of these factors contribute to the underperformance of dark-blood T2W imaging in the detection of edema in a systemic disease such as acute myocarditis.

Bright-blood T2W imaging. Newer bright-blood T2W imaging offers some practical advantages: breath-holds are shorter (typically under 10 s), and the method is more forgiving in cases of tachyarrhythmias or patient movement. Better signal- and contrast-to-noise ratios seemed to improve visualization of focal signal changes, especially in large acute lesions such as ST-segment elevation myocardial infarction (10); however, the detection of small, focal patchy edema in acute myocarditis was more challenging. When normal unaffected myocardium could be reliably identified, bright-blood T2W imaging tended to display these changes well. Visual detection of global edema, on the other hand, was less obvious to the eye on bright-blood T2W images, and the use of skeletal muscle as the reference region of interest can often be limited by artifacts and noise over the region of the muscle, in addition to the same issue surrounding skeletal muscle inflammation as with dark-blood T2W imaging discussed earlier in the text (11). As previously demonstrated, for cases of global edema, dark-blood T2W imaging had a superior diagnostic performance over bright-blood T2W imaging (11,19).

LGE imaging. LGE imaging has an excellent contrast-to-noise ratio, making it one of the most robust CMR methods for visualizing myocardial lesions, including small focal disease. Acute myocarditis can sometimes demonstrate little LGE and/or predominantly global edema, which tends to be inconspicuous on LGE imaging, such as in the cases shown in Figure 3, hence the improved diagnostic yield by combining any 2 of 3 CMR methods for diagnosing the disease (7). It is also conceivable that sometimes the lesions are so small, they are beyond the resolution of even LGE contrast imaging. As shown in Table 3, combining LGE with T_1 mapping did not significantly improve the diagnostic performance of LGE alone, but worsened the overall diagnostic performance of T_1 mapping alone; this may be related to the fact that T_1 mapping is able to detect changes caused by both edema and myocyte necrosis, and thus can serve to function as a "LGE + T2W" combination, only with much better sensitivity, diagnostic accuracy, and negative predictive value than any of the LGE + T2W combination set out in Table 3. From a practical point of view, it may be possible for a T_1 mapping sequence to be the only one required to assess for all the criteria of acute myocarditis (edema, hyperemia, and necrosis/scarring), serving as the major component of a CMR myocarditis protocol; this is worth exploring in future studies.

T_1 mapping. T_1 mapping using ShMOLLI circumvents most of the issues suffered by conventional T2W and LGE imaging. It provides a direct, quantitative means for myocardial characterization without the need for contrast agents or reference regions of interest to detect changes within the myocardium. It has short breath-holds, is heart rate independent, and is robust to even tachyarrhythmias, making it highly suitable for scanning acutely ill patients. These advantages confer on ShMOLLI T_1 mapping its superior diagnostic performance compared with the T2W and LGE methods tested.

There may be a number of mechanisms that prolong myocardial T1 in acute myocarditis. Earlier work had shown that myocardial T1 increased in ischemic myocardium in canine models, which largely, but not entirely, reflected the increase in water content (20). It was postulated that T1 prolongation may be due to changes in both total water content as well as the relative amounts of water in intracellular and extracellular space (20); in addition, it was also hypothesized that changes in sodium and potassium distribution may affect the motional freedom of protons, contributing to prolongation of T1 values in ischemic tissue. More recently, it has also been demonstrated that T1 is significantly increased in acute myocardial edema in animal (21) and human (11) studies. Cellular edema, increased extracellular space and water, inflammation, and myocyte necrosis are common features of acute myocarditis (7,22), and all of these pathophysiological processes may prolong T1 values in the early stage.

T1 mapping had an excellent diagnostic performance, with an ~90% overall sensitivity, specificity, and diagnostic accuracy for detecting changes in myocarditis using a T1 cutoff of 990 ms. The selection of diagnostic thresholds depends on the amount of noise in the technique and represents an exchange between sensitivity and specificity. Historically, 2 SD above the normal mean is accepted as a cutoff for identifying abnormally high values. This was used, for example, in the original validation of dark-blood T2W imaging in detecting acute myocarditis (13) and is commonly used in LGE imaging to identify fibrosis in ischemic and nonischemic heart disease (12,13,23). However, as shown in Table 3, the threshold of 2 SD above the normal mean SI for dark-blood T2W imaging is actually a relatively high

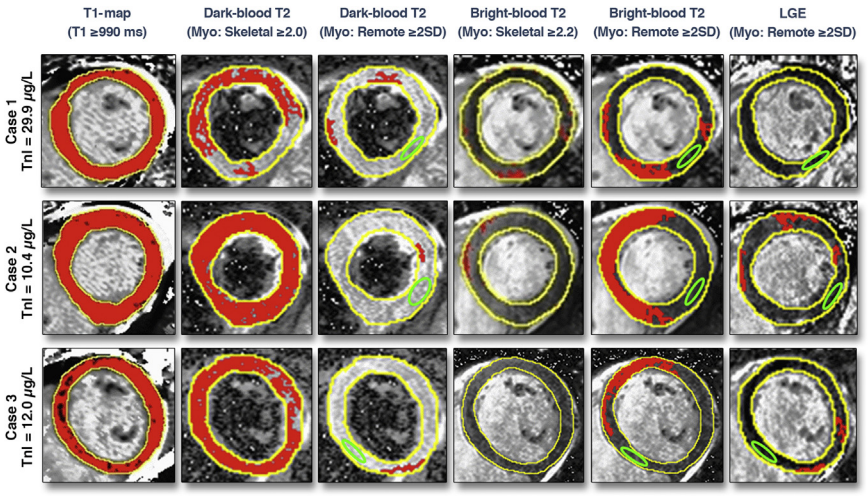

Figure 3. Three Cases of Acute Myocarditis With Global Edema but Only Mild LGE

CMR methods based on reference regions of interest (ROIs) significantly underestimate the areas of myocardial injury. **Red** indicates areas of myocardium (myo) with values above the standard threshold for each CMR method. **Green contour** marks the positioning of myocardial reference ROI. Myocardial contours are outlined in **yellow**. Skeletal muscle ROI not shown. TnI = troponin I (μg/l); other abbreviations as in Figures 1 and 2.

threshold with good specificity but low sensitivity, meaning that low-grade disease would easily be missed. Interestingly, for T1 mapping, although the threshold of T1 ≥ 990 ms is a sensitive threshold, it simultaneously represents an even more stringent >2.7 SD above normal T_1 values. This is directly due to the fact that normal myocardial T_1 values have a tight normal range with small variability in the normal population (24), contributing to its good diagnostic performance.

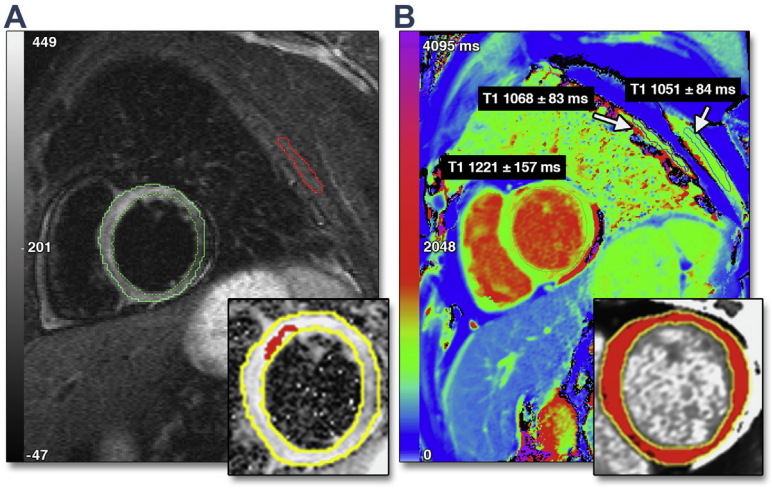

Figure 4. A Case of Acute Severe Myocarditis Demonstrating the Effect of Skeletal Muscle Inflammation on Dark-Blood T2W-CMR Using Skeletal Muscle as a Reference Region to Detect Global Edema in the Myocardium

This patient had an initial ejection fraction of 37%, elevated C-reactive protein level of 94.6 mg/l (normal 0 to 8 mg/l), and a white blood cell count 17.9 × 10^9/l, with recurrent ventricular tachycardia in hospital. **(A)** Dark-blood T2W imaging showed a visible increase in myocardial T_2 SI. Inset: computer-aided analysis of the T2W image using skeletal muscle as a reference **(red contour)** failed to adequately detect a significant increase in T_2 SI ratio ≥2.0 relative to skeletal muscle within the myocardium **(green contour)**. **(B)** T_1 map of the corresponding slice in the same patient. Purple contour **(top right)** outlines skeletal muscle (T_1 = 1,068 ± 83 ms, **arrow**) corresponding to that on the T2W image; an adjacent region of skeletal muscle **(blue contour)** also showed high T_1 values (1,051 ± 84 ms, **arrow**). Inset: computer-aided analysis of the T_1 map, demonstrating global increase in the myocardial T_1 value (1,221 ± 157 ms). Abbreviations as in Figure 1.

Combination approach. In agreement with published literature (7), a combination approach can improve specificity to detect disease. On the basis of the results of this study, T_1 mapping has a superior overall diagnostic performance over the T2W techniques in the detection of acute myocarditis, either alone or in combination with LGE; one may argue that T_1 mapping may be performed in place of T2W imaging in select cases, although this approach should be tested in larger studies, perhaps comparing all currently available techniques in the assessment of acute myocarditis. Although the combination of T_1 + LGE was not significantly better than LGE alone, on a practical level, the main benefit of performing both T_1 mapping and LGE (rather than just LGE) would be to take advantage of the superior sensitivity of T_1 mapping (90%) compared with LGE (and T2W imaging). This may be especially useful when LGE is nonrevealing, when the predominant process is edema, and in detecting subtle, small focal disease. It may also be helpful if LGE imaging were not achieved for reasons commonly encountered in the early clinical setting (such as when the patient does not tolerate the full protocol, has contraindications to gadolinium, or lacks intravenous access).

Study limitations. This study was performed using clinical validation for suspected myocarditis rather than endomyocardial biopsy (EMB) as a reference standard, and as such, lacks direct histopathological confirmation of the diagnosis. However, in view of the well-documented low sensitivity of EMB for ruling out myocarditis (25–28) to serve as a reliable gold standard and the fact that EMB is not routine clinical practice in both hospitals, we had chosen to validate the CMR methods using an internationally accepted standard (7), as performed in multiple previous CMR validation studies (7,13,18,29). Although none of our patients underwent EMB, the majority of the patients (92%) had a preceding systemic viral or inflammatory illness, which, together with their CMR findings, would be consistent with a diagnosis of myocarditis; a few patients (n = 4) did not have a clear infectious or inflammatory precipitant, but none of the 50 patients in the patient cohort had an isolated ischemic pattern of LGE suggestive of myocardial infarction as the presenting diagnosis. Other obvious diagnoses, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, or Takotsubo cardiomyopathy, were not included in this study, as outlined in the Methods section.

Early gadolinium enhancement (EGE) was not performed for practical reasons because our protocol was already extensive. Therefore, of 3 available conventional sequences, we selected dark-blood T2W and LGE imaging because EGE is more time consuming and its image quality often affected by the irregular breathing patterns or arrhythmias (7) commonly encountered in acutely ill patients. Because the goal of the study was to validate novel CMR techniques in a cohort defined by clinical features, none of the Lake Louise imaging criteria were used as inclusion criteria when enrolling subjects. T_2 mapping is another quantitative CMR technique that has been shown to be useful in the diagnosis of acute myocarditis (30) but was not studied in this work. Future and larger studies may directly compare all available CMR methods, such as dark-blood T_2, bright-blood T_2, T_2 mapping, T_1 mapping, EGE, LGE, post-contrast T_1, and extracellular volume fraction mapping in order to test method performance against each other and to fully assess the utility of novel techniques in routine clinical settings.

Because the accuracy of myocardial T_1 measurement remains to be established, no currently available T_1 mapping method can claim to accurately measure T_1. For T_1 mapping methods based on inversion recovery pulses, there may be systematic errors in T_1 measurements related to inversion pulse efficiency and other factors (31), and thus, T_1 thresholds established may be platform specific. Currently, ShMOLLI appears to be an attractive method for T_1 mapping because its known 4% underestimation of T_1 remains consistent over a wide range of native tissue T_1 (13); it also has a stable, narrow range of normal myocardial T_1 values (24), making it highly suitable for detecting disease states (11,12,32–34).

Increase in native myocardial T_1 values is nonspecific and is seen in a number of myocardial diseases other than acute myocardial injury, including cardiac amyloidosis (32), hypertrophic and dilated cardiomyopathy (34), diffuse fibrosis (33), and chronic infarct scars (12,35), and thus, as with all other diagnostic tools, must be interpreted within the clinical context. The exact mechanism(s) leading to prolonged T_1 values in different cardiac diseases remain to be established.

CONCLUSIONS

T_1 mapping and bright-blood T2W-CMR are novel methods sensitive to the detection of acute myocarditis. T_1 mapping showed excellent and superior diagnostic performance compared with T2W-CMR, with a high sensitivity compared with T2W and LGE techniques, which may be especially

useful in detecting subtle focal disease and in cases where gadolinium contrast imaging is not feasible.

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Key Words: cardiac magnetic resonance ■ myocarditis ■ ShMOLLI ■ T_1 mapping ■ T_2-weighted CMR.

▶ APPENDIX

For an expanded Methods section, please see the online version of this paper.