Acute Myocarditis: Multiparametric Cardiac MR Imaging[1]

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Purpose: To evaluate the diagnostic value of cardiac magnetic resonance (MR) imaging at 3 T in patients suspected of having acute myocarditis by using a multiparametric cardiac MR imaging approach including T1 relaxation time as an additional tool for tissue characterization.

Materials and Methods: Ethics commission approval was obtained for this prospective study, and written informed consent was obtained from all subjects. Twenty four patients with acute myocarditis (mean age ± standard deviation, 34.7 years ± 15.1; 75% men) and 42 control subjects (mean age, 38.7 years ± 10.2; 64% men) were included. Cardiac MR imaging approaches included relative T2 short tau inversion-recovery signal intensity ratio (T2 ratio), early gadolinium enhancement ratio, late gadolinium enhancement, native T1 relaxation times, and extracellular volume fraction. Receiver operating characteristic analysis was performed to compare diagnostic performance. The reference standard was the clinical evidence for acute myocarditis.

Results: Native T1 relaxation times were significantly longer in patients with acute myocarditis than in control subjects (1185.3 msec ± 49.3 vs 1089.1 msec ± 44.9, respectively; $P < .001$). Areas under the curve of native T1 relaxation times (0.94) were higher compared with those of other cardiac MR parameters (late gadolinium enhancement, 0.90; T2 ratio, 0.79; extracellular volume fraction, 0.71; early gadolinium enhancement ratio, 0.63; $P = .390$, .018, .002, and < .001, respectively). Sensitivity (92%), specificity (91%), and diagnostic accuracy (91%) for native T1 relaxation times (cutoff, 1140 msec) were equivalent compared with those of the established combined Lake Louise criteria (sensitivity, 92%; specificity, 80%; diagnostic accuracy, 85%).

Conclusion: Diagnostic performance with native T1 mapping was superior to that with T2 ratio and early gadolinium enhancement ratio, and specificity was higher with native T1 mapping than that with Lake Louise criteria. This study underlines the potential of native T1 relaxation times to complement current cardiac MR approaches in patients suspected of having acute myocarditis.

Online supplemental material is available for this article.

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Acute myocarditis is the diagnosis in 75% of patients with acute chest pain and elevated serum troponin levels at presentation and who have unobstructed coronary arteries at invasive catheterization (1). At unselected routine necropsies, myocarditis is found in up to 0.6% of patients (2). Estimations are that myocarditis is the underlying cause for dilated cardiomyopathy previously classified as idiopathic in 9% of these patients (3). Clinically, myocarditis allegedly accounts for up to 20% of deaths in adults younger than 40 years (4) and U.S. Air Force personnel (5).

Cardiac magnetic resonance (MR) imaging is an established noninvasive diagnostic tool for detection of acute and chronic myocarditis (6–11). Diagnosis of myocarditis at 1.5 T is made on the basis of two of the three "Lake Louise" criteria: *(a)* regional or global myocardial signal intensity increase on T2-weighted images (increased T2 ratio ≥ 2.0), *(b)* increased global myocardial early gadolinium enhancement ratio (EGEr ≥ 4.0), and *(c)* at least one focal, nonischemic lesion at inversion-recovery late gadolinium enhancement (LGE) MR imaging (6). Although these criteria are accepted and used in clinical routine, they have several disadvantages: T2-weighted imaging is limited by signal intensity inhomogeneities and allows for qualitative visual assessment only. EGEr images are acquired during free breathing, and therefore, image quality is limited by respiratory motion artifacts (7,8). These disadvantages make a quantitative imaging technique that can be performed during breath hold to minimize respiratory motion artifacts desirable.

A technique for noninvasive tissue characterization based on calculation of myocardial T1 relaxation times and T1-derived extracellular volume fraction (ECV) has become available (12). However, to our knowledge, no comprehensive data for multiparametric cardiac MR imaging including T1 mapping at 3 T in patients suspected of having acute myocarditis exists to date. In this prospective study, we defined reference values to transfer the Lake Louise criteria to 3 T imaging. The null hypothesis of our study was that native T1 mapping does not offer additional diagnostic value in patients suspected of having acute myocarditis compared with that of the established Lake Louise criteria. The purpose of our study was to evaluate the diagnostic value of cardiac MR imaging at 3 T in patients suspected of having acute myocarditis by using a multiparametric cardiac MR imaging approach including T1 relaxation times as an additional tool for tissue characterization.

Advances in Knowledge

- Native myocardial T1 mapping allows excellent diagnostic performance (area under the curve, 0.94) in patients with acute myocarditis at 3-T MR imaging, with clinical evidence of acute myocarditis as the reference standard.
- Diagnostic performance with cardiac MR imaging that includes native myocardial T1 mapping in patients suspected of having acute myocarditis is equivalent to that with the established Lake Louise criteria (sensitivity, 92% vs 92%; specificity, 91% vs 80%; and diagnostic accuracy, 91% vs 85%, respectively).

Implications for Patient Care

- Cardiac MR imaging at 3 T in patients suspected of having acute myocarditis is feasible and yields an excellent diagnostic accuracy by using field strength–adapted Lake Louise criteria.
- Native myocardial T1 mapping used as an add-on parameter improves diagnostic accuracy with cardiac MR imaging in patients suspected of having acute myocarditis compared with that of the Lake Louise criteria (for T1 relaxation times and T2 ratio vs Lake Louise criteria, $P = .027$ and for T1 relaxation times and late gadolinium enhancement vs Lake Louise criteria, $P = .008$).
- In patients with contraindications for gadolinium-based contrast media, native myocardial T1 mapping may replace current Lake Louise criteria without sacrificing diagnostic accuracy.

Materials and Methods

Study Population

Written informed consent was obtained before cardiac MR imaging. The study was approved by the local ethics committee. C.S. and J.G. are employees of Philips Research (Hamburg, Germany). Philips Research developed a software imaging sequence, which was provided to the Department of Radiology of the University of Bonn free of charge and without financial support. Authors at the University of Bonn who are not employees of Philips Healthcare or Philips Research (J.A.L., J.D., D.K.T., D.D., A.M.S., R.F., R.H., J.O.S., H.S., and C.P.N.) designed the study and had exclusive control of patient recruitment, patient data, and data analysis. All authors approved the final manuscript.

In this prospective single-center study (*ClinicalTrials.gov* identifier: NCT01962584) patients were included

Published online before print
10.1148/radiol.14132540 **Content codes:** CA MR

Radiology 2014; 273:383–392

Abbreviations:
AUC = area under the curve
ECV = extracellular volume fraction
EGEr = early gadolinium enhancement ratio
LGE = late gadolinium enhancement

Author contributions:
Guarantors of integrity of entire study, J.A.L., J.D., H.S., C.P.N.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.A.L., J.D., D.K.T., D.D., J.G., A.M.S., C.P.N.; clinical studies, J.A.L., J.D., D.K.T., R.H., J.O.S., C.P.N.; experimental studies, J.G.; statistical analysis, J.A.L., J.D., A.M.S., R.F., C.P.N.; and manuscript editing, J.A.L., J.D., D.K.T., D.D., J.G., R.F., C.S., J.O.S., H.S., C.P.N.

Conflicts of interest are listed at the end of this article.

in the myocarditis group if they showed clinical evidence of having acute myocarditis. The clinical evidence was the reference standard against which the diagnostic performance of cardiac MR parameters was tested. All patients with acute myocarditis presented with acute chest pain, a history of viral infection during the last few weeks (flu-like illness with diarrhea and bronchitis or pneumonia), and elevated serum markers indicating infectious disease (C-reactive protein). All patients had evidence of myocardial injury (electrocardiographic changes such as ST segment changes, atrioventricular block, supraventricular tachycardia) and/or elevated troponin, and did not have a medical history of cardiac disease. Coronary artery disease was ruled out before cardiac MR imaging by means of invasive cardiac catheterization. Exclusion criteria included contraindications for cardiac MR imaging, previous myocardial infarction, previous myocarditis, or other acute or chronic cardiac disease. The diagnosis of acute myocarditis was made on the basis of clinical observation only, and cardiac MR imaging results were not taken into consideration. The control group consisted of healthy volunteers and outpatients referred for nonspecific thoracic pain who did not show structural abnormality at cardiac MR imaging. All control subjects had no medical history of cardiac or vascular disease, no cardiac risk factors, and normal electrocardiographic results. In outpatients referred for nonspecific thoracic pain, a detailed diagnostic workup was performed (including Holter electrocardiography, assessment of cardiac enzymes, echocardiography, and cardiac stress test) and clinical follow-up was unremarkable, without signs of cardiac disease.

Cardiac MR Imaging

All examinations were performed by using a 3-T MR imaging whole-body dual-transmission system (Ingenia 3T; Philips Healthcare, Best, the Netherlands) equipped with a 16-element receive coil with direct signal digitization in the coil and transfer by means of fiber optical cable. B_0 and B_1 volume shimming were applied.

Cardiac MR Protocol

Functional imaging.—Electrocardiographically gated steady-state free precession cine images were obtained in breath hold in the horizontal long axis, the vertical long axis, and the left ventricular outflow tract. A short axis stack view of the whole left ventricle was obtained for wall motion and functional analysis. Relevant sequence parameters are given in Table E1 (online).

Detection of inflammatory myocardial changes.—Edema-sensitive black blood T2-weighted short tau inversion-recovery sequences in the vertical long axis, short axis, and transverse orientation were used to visualize inflammatory changes in the myocardium (13). For detection of inflammation-induced hyperemia of the myocardium, transverse free-breathing unenhanced and contrast material–enhanced fast spin-echo T1-weighted images were obtained as previously described (7,8). For contrast enhancement, a cumulative double-dose bolus of 0.2 mmol per kilogram of body weight of gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) was administered intravenously (flow rate, 1.5 mL/sec) followed by a 25-mL saline flush.

LGE Imaging.—For detection of myocardial fibrosis and scarring, LGE imaging was performed by using segmented inversion-recovery gradient-echo sequences in the horizontal long axis, the vertical long axis, and the short axis (Fig 1) as previously described (14). Optimal inversion time was determined by using the Look-Locker technique (15).

T1 mapping and quantification of extracellular volume.—Before and 10 minutes after administration of contrast material, T1 maps were obtained in end-diastole in the short axis (basal, midventricular, and apical sections) and the horizontal long axis (one section) by using a steady-state free precession–based 3–3-5 modified Look-Locker inversion-recovery scheme (16). T1 relaxation maps were reconstructed directly on the imager console during image acquisition. Quality assessment was performed directly after image acquisition. When necessary, maps with motion artifacts were directly repeated until T1 maps with sufficient image quality were obtained. Hematocrit-corrected extracellular volume was calculated by using pre- and postcontrast T1 values for the myocardium and blood pool by using the following equation (17):

$$\mathrm{ECV}=\frac{\left(1/T1_{\mathrm{myo\ post}}-1/T1_{\mathrm{myo\ pre}}\right)}{\left(1/T1_{\mathrm{blood\ post}}-1/T1_{\mathrm{blood\ pre}}\right)}\times(1-H),$$

where ECV is extracellular volume, $T1_{\mathrm{myo\ post}}$ is the postcontrast myocardium T1 relaxation time, $T1_{\mathrm{myo\ pre}}$ is the precontrast myocardium T1 relaxation time, $T1_{\mathrm{blood\ post}}$ is the postcontrast blood pool relaxation time, and $T1_{\mathrm{blood\ pre}}$ is the precontrast blood pool T1 relaxation times, and H is hematocrit value.

Image Analysis

Images were evaluated by two radiologists (D.K.T., with 12 years of experience and C.P.N., with 9 years of experience) who are experienced in cardiac MR imaging. Cardiac function (left ventricular end systolic volume, left ventricular end diastolic volume, and left ventricular ejection fraction) was determined offline by using dedicated software (ViewForum, Philips Healthcare). Left ventricular end systolic volume and left ventricular end diastolic volume were quantified manually by tracing the endocardial borders. Papillary muscles were included in the left ventricular cavity volume. Native and postcontrast T1 relaxation times were extracted from T1 maps by using freely available software (Segment, version 1.9, R2783; *http://segment.heiberg.se*) (18). To exclude epicardial fat, pericardium, and blood from analysis, endocardial and epicardial borders were contoured. T1 maps were analyzed by using a segmental approach (19). In addition, interobserver reproducibility of T1 relaxation time measurements was evaluated (Appendix E1 [online]).

Figure 1

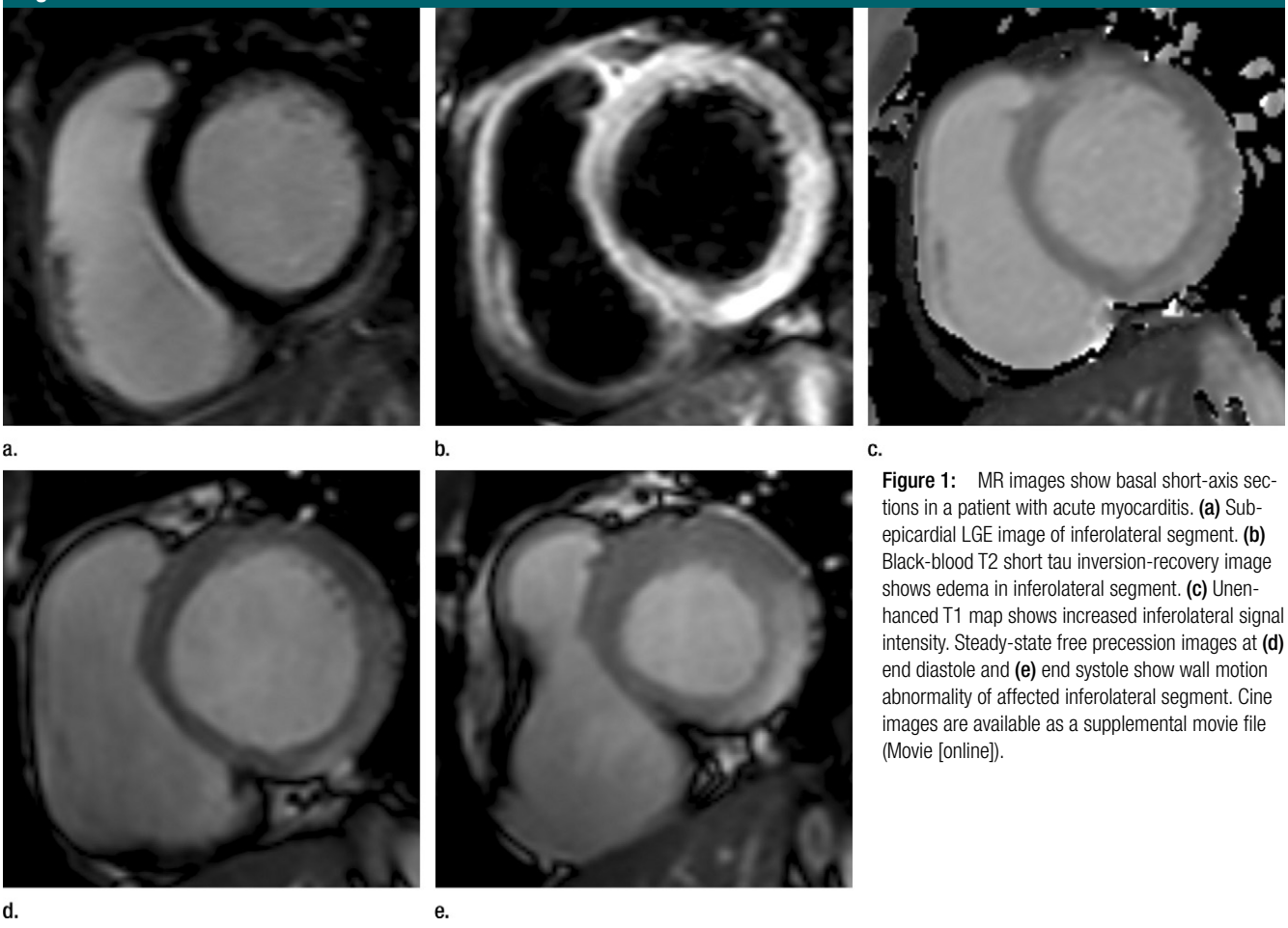

Figure 1: MR images show basal short-axis sections in a patient with acute myocarditis. **(a)** Subepicardial LGE image of inferolateral segment. **(b)** Black-blood T2 short tau inversion-recovery image shows edema in inferolateral segment. **(c)** Unenhanced T1 map shows increased inferolateral signal intensity. Steady-state free precession images at **(d)** end diastole and **(e)** end systole show wall motion abnormality of affected inferolateral segment. Cine images are available as a supplemental movie file (Movie [online]).

Wall motion abnormalities (steady-state free precession cine), myocardial edema (black blood T2-weighted short tau inversion recovery), and myocardial fibrosis and scaring (LGE) were assessed visually and considered positive (ie, indicating myocarditis) in cases of focal signal intensity alterations with a pattern typical for myocarditis (6) (Fig 2). In accordance with previously published recommendations (6) T2-weighted short tau inversion-recovery imaging was quantitatively evaluated for presence of global myocardial edema by calculating the T2 ratio of the myocardium and the skeletal muscle (8). EGEr for assessment of inflammation-induced hyperemia was calculated as previously described (7). For both T2 ratio and EGEr, the mean value of three measurements was used for statistical analysis.

Statistical Analysis

Statistical analysis was performed by using software (SAS 9.2; SAS Institute, Cary, NC). Patient characteristics were presented as mean ± standard deviation or as absolute frequency. The unpaired Student *t* test was used for comparison of continuous variables between groups. Diagnostic performance of single continuous variables (including qualitative LGE) and derived quantitative combination scores of continuous variables was primarily analyzed by plotting receiver operating characteristics and comparing the area under the curve (AUC). AUCs were compared by using the method proposed by DeLong et al (20). Cutoff values were chosen by maximizing the reclassification accuracy for the single predictive variables and scores, and (reclassification) sensitivity, specificity, and accuracy were calculated. For the combination of single predictive variables, scores were derived on the basis of logistic regression analysis. Because of the limited sample size, these analyses were restricted to the pair-wise combinations of relevant variables. A *P* value of less than .050 was considered indicative of a significant difference.

Results

Population Characteristics

A total of 66 subjects were enrolled in this study (24 patients with acute

myocarditis and 42 control subjects). The control group consisted of 32 (76.2%) healthy volunteers and 10 (23.8%) outpatients. Mean time between admission and cardiac MR imaging was 2.63 days ± 2.22. Baseline patient characteristics are summarized in Table 1. Mean age in the control group was 38.7 years ± 10.2 (men: 36.8 years ± 14.7; range, 18–66 years; women: 42.1 years ± 15.4; range, 19–71 years; P = .293). Mean age in the myocarditis group was 34.7 years ± 15.1 (men: 31.2 years ± 7.7; range, 20–48 years; women: 45.2 years ± 9.7; range, 32–56 years; P = .002). Age (P = .257), sex (P = .422), and left ventricular function (P = .077) did not differ significantly between the groups. Troponin I and C-reactive protein were significantly higher in the myocarditis group.

During image acquisition, 41 (15.5%) of 264 modified Look-Locker inversion-recovery examinations were repeated because of motion artifacts. In addition, 229 of 2244 (10.2%) segments were excluded from the segmental analysis because of off-resonance or motion artifacts.

Myocardial T1 relaxation times were significantly longer in the myocarditis group compared with those of healthy control subjects (1185.3 msec ± 49.3 vs 1089.1 msec ± 44.9; $P < .001$). ECV was significantly higher in myocarditis patients than in control subjects (30.3% ± 12.4% vs 23.6% ± 4.1%; P = .005). The T2 ratio of the myocarditis group was higher compared with that of healthy control subjects (1.8 ± 0.4 vs 1.4 ± 0.3; $P < .001$) (Fig E1 [online]). Segmental pre- and postcontrast T1 relaxation times data and segmental ECV data are given in Table E2 (online). EGEr was significantly higher in the myocarditis group than that in the healthy control subjects (4.4 ± 4.7 vs 2.6 ± 1.1, P = .048). All cardiac MR parameters evaluated are presented in Table 2.

Diagnostic Performance of Multiparametric Cardiac MR Imaging

Native T1 relaxation time yielded an excellent diagnostic performance with an AUC of 0.94. Compared with other

Figure 2

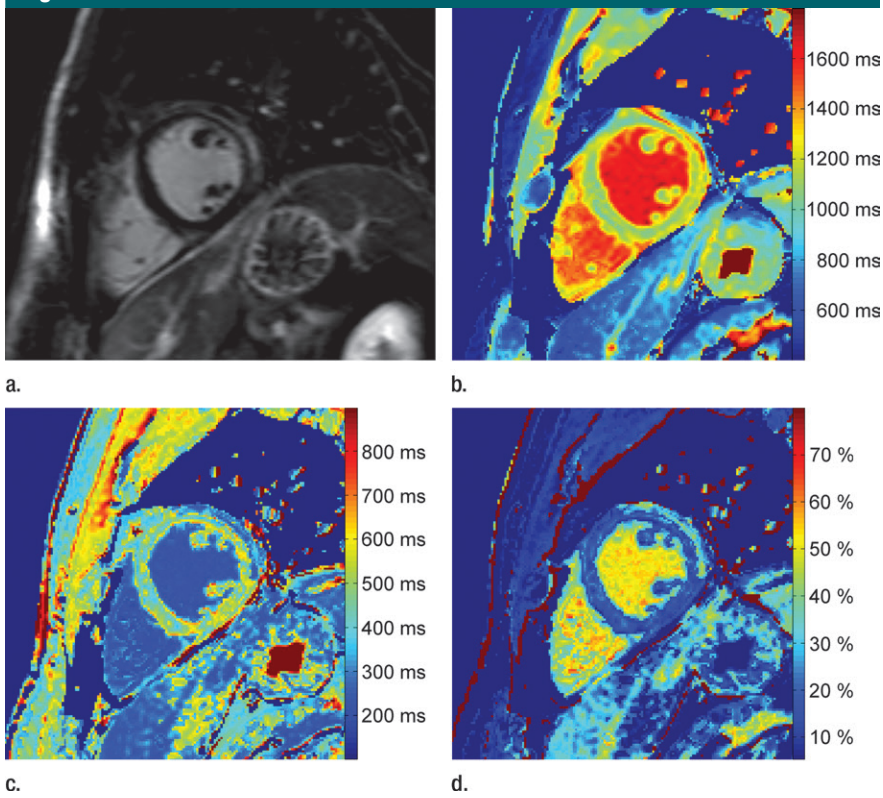

Figure 2: Midventricular short-axis sections in a patient with acute myocarditis. **(a)** Subepicardial LGE image of lateral myocardial wall. **(b)** Corresponding native T1 map shows increased T1 values in affected area. **(c)** Postcontrast T1 map indicates increased contrast enhancement in affected area. **(d)** ECV map shows increased extracellular volume in myocarditis-affected lateral wall. ECV map was calculated with in-house software written in Matlab (MathWorks, Natick, Mass).

Table 1

Patient Characteristics

Parameter	Control Group (n = 42)	Myocarditis Group (n = 24)	P Value
Age (y)	38.7 ± 10.2	34.7 ± 15.1	.257
No. of male patients	27 (64)*	18 (75)*	.422
Heart rate (beats/min)	65.3 ± 11.6	68.4 ± 10.7	.305
Sinus rhythm	42 (100)*	24 (100)*	.999
Body mass index (kg/m^2)	24.6 ± 3.2	26.6 ± 3.7	.030
Left ventricular ejection fraction (%)	63.2 ± 6.5	59.8 ± 8.9	.077
Left ventricular end diastolic volume/body surface area [mL/m^2]	127.7 ± 31.7	128.4 ± 38.8	.424
Interventricular septal thickness [mm]	9.4 ± 1.9	10.1 ± 1.3	.145
Troponin I [ng/mL]	NA†	7.2 ± 7.9	
White blood cell count [10^3/μL]	6.21 ± 1.9	7.9 ± 2.2	.004
C-reactive protein [mg/L]	1.6 ± 1.3	37.2 ± 33.2	.014
Hematocrit [%]	40.8 ± 4.4	41.5 ± 3.5	.489

Note.—Unless otherwise indicated, data are mean ± standard deviation for continuous variables.

* Categorical variables are given as absolute frequency, with percentages in parentheses.

† Below the detection limit.

Table 2

Myocarditis-specific Cardiac MR Results

Parameter	Control Group ($n = 42$)	Myocarditis Group ($n = 24$)	*P* Value
T2 ratio	1.4 ± 0.3	1.8 ± 0.4	<.001
EGEr	2.6 ± 1.1	4.4 ± 4.7	.048
No. of subjects with LGE typical for myocarditis	0 (0)*	18 (75)*	<.001
Subjects with regional myocardial edema	0 (0)*	18 (75)*	<.001
Myocardial native T1 relaxation times (msec)	1089.1 ± 44.9	1185.3 ± 49.3	<.001
ECV (%)	23.6 ± 4.1	30.3 ± 12.4	.005
T1 skeletal muscle (msec)	1003.15 ± 49.8	1005.9 ± 50.1	.835

Note.—Unless otherwise indicated, data are mean ± standard deviation for continuous variables.

* Categorical variables are given as absolute frequency, with percentages in parentheses.

Figure 3

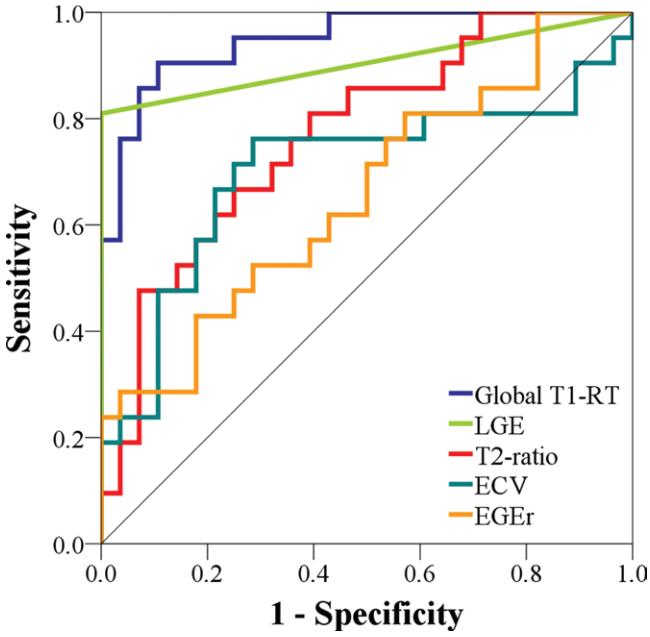

Figure 3: Graph shows receiver operating characteristic curves for global native T1 relaxation times (*T1-RT*; AUC, 0.94), LGE (AUC, 0.90), T2 ratio (AUC, 0.79), ECV (AUC, 0.71), and EGEr (AUC, 0.63).

cardiac MR parameters, only LGE showed an equivalent diagnostic performance (AUC, 0.90; $P = .390$). AUCs of ECV (0.71), T2 ratio (0.79), and EGEr (0.63) were considerably lower ($P = .002$, .018, and < .001 respectively; Fig 3). Native T1 relaxation times showed an equivalent diagnostic performance to that with combined Lake Louise criteria (AUC = 0.86, $P = .076$).

With a cutoff value of 1140 msec, native T1 relaxation times showed excellent diagnostic performance, with a sensitivity of 92%, specificity of 91%, positive predictive value of 85%, negative predictive value of 95%, and a diagnostic accuracy of 91%. From the Lake Louise criteria, LGE and T2 ratio yielded the best diagnostic performance, with sensitivity of 75% and 79%, specificity of 100% and 61%, diagnostic accuracy of 91% and 68%, positive predictive value of 100% and 58%, and negative predictive value of 88% and 82%, respectively. Diagnostic performance and cutoff values for all cardiac MR parameters are given in Table 3.

When we used the Lake Louise criteria (positive for myocarditis if positive for any two of the three criteria: increased EGEr, increased T2 ratio, and presence of LGE pattern typical of myocarditis) our results yielded sensitivity of 92%, specificity of 80%, diagnostic accuracy of 85%, positive predictive value of 79%, and negative predictive value of 92%. When we combined native T1 relaxation times with the two best-performing Lake Louise criteria, AUC for native T1 relaxation times plus T2 ratio was 0.97, and for native T1 relaxation times plus LGE, 0.99 (see Fig 4). Those scores were superior to those yielded by using Lake Louise criteria alone (AUC = 0.86; $P = .027$ and $P = .008$, respectively). Sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value for native T1 relaxation times plus T2 ratio were 92%, 97%, 95%, 96%, and 95%, respectively. For T1 relaxation times plus LGE, scores for sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value were 96%, 95%, 96%, 92%, and 98%, respectively (Table 3).

Discussion

In this prospective study, established MR parameters of myocardial inflammation (Lake Louise criteria: T2 ratio, EGEr, and LGE) and T1 relaxation times were obtained in control subjects and in patients suspected of having acute myocarditis. The main finding was that quantitative native T1 relaxation time alone allows equivalent diagnostic performance to that of the Lake Louise criteria and improves diagnostic performance significantly when used in addition to the Lake Louise Criteria.

Black Blood T2-weighted Imaging

Currently, black blood T2-weighted imaging is the recommended technique

Table 3

Diagnostic Performance with Different Cardiac MR Parameters and Scores for Diagnosis of Acute Myocarditis

Parameter	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Single parameter					
EGEr	83	42	53	77	60
T2 ratio	79	61	58	82	68
LGE	75	100	100	88	91
Native T1 relaxation times	92	91	85	95	91
ECV	67	81	67	81	75
Combined parameter					
Lake Louise criteria*	92	80	79	92	85
Lake Louise criteria*+ native T1 relaxation times	88	100	100	91	94
Native T1 relaxation times + T2 ratio	92	97	96	95	95
Native T1 relaxation times + LGE	96	95	92	98	96

Note.—Data are percentages. Cutoff values for EGEr, 2.09; T2 ratio, 1.52; native T1 relaxation time, 1140 msec; ECV, 26.3%.

* Positive for myocarditis if positive for any two of the three Lake Louise criteria (increased EGEr, increased T2 ratio, presence of LGE pattern typical of myocarditis).

Figure 4

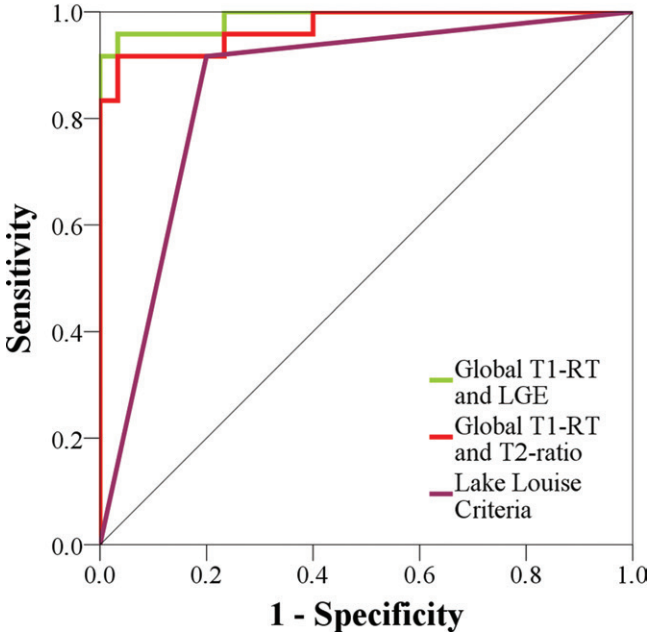

Figure 4: Graph shows receiver operating characteristic curves for combined score global native T1 relaxation time *(T1-RT)* and LGE (AUC, 0.99), global T1 relaxation times and T2 ratio (AUC, 0.97), and Lake Louise Criteria (AUC = 0.86).

for detection of myocardial edema (6). However, several challenges exist in obtaining black blood T2-weighted images, even with implementation of recommended sequence parameters (6). First, image quality depends on a regular, nontachycardic heart rhythm. The presence of arrhythmia (such as premature ventricular contractions or atrial fibrillation), which is common in patients with acute myocarditis, may degrade image quality. Also, respiratory artifacts in patients with a limited ability to hold their breath long enough can degrade image quality to a variable extent. Second, several sequence-specific challenges exist. For most myocardial segments, the inversion-recovery sequences used for black blood T2-weighted imaging provide good contrast between the left ventricular blood pool and the myocardium. However, in areas with slow left ventricular cavity blood flow (eg, the apex and the intertrabecular space) nulling of the left ventricular blood pool signal often is imperfect and impairs the image contrast in these areas (21). In addition, black blood T2-weighted images often show signal intensity inhomogeneities, which can obscure myocardial edema. Third, image interpretation can be hindered further in cases of global myocardial edema, (ie, when no normal signal from healthy myocardium is present), or in cases of coexisting myositis, when the T2 ratio may be incorrectly low (22). All of these reasons may be responsible for the fact that the diagnostic accuracy of black blood T2-weighted imaging was only 68% in our study, a value that correlates well with previously published results (6–9,22).

Myocardial EGEr

Inflammation-induced hyperemia causes an increased normalized accumulation of gadopentatate dimeglumine in the myocardium during the early washout

period that is indicative of myocardial inflammation or hyperemia. Although visual identification may be possible, quantitative evaluation of myocardial EGEr is mandatory. However, two major trade-offs exist. First, EGEr involves a global approach, and depending on the section orientation chosen for cardiac MR imaging, some myocardial segments may not be available for image analysis and interpretation. Second, respiratory motion artifacts can severely degrade image quality to a nondiagnostic degree. Third, normalization of the signal intensity on T1-weighted images to that of skeletal muscle may be hampered by coexisting myositis. Although no difference in skeletal muscle T1 relaxation times between the groups was found, which indicates that coexisting myositis was not present, EGEr was the weakest cardiac MR imaging parameter for acute myocarditis, with an AUC of 0.63 and a diagnostic accuracy of 60%. This is true especially when it is compared with results of previously published studies (6–9,22) in which EGEr yielded a diagnostic accuracy of 78%.

LGE Imaging

LGE imaging has an excellent contrast-to-noise ratio, making it one of the most robust cardiac MR imaging methods for visualization of myocardial lesions, even in cases of only focal disease (23). In our study, LGE alone yielded an excellent diagnostic accuracy of 91%, which is substantially higher than those in previously published studies at 1.5 T (6,8–11,24). A possible explanation may be the increase in signal-to-noise-ratio and contrast-to-noise-ratio for LGE at 3 T compared with that at 1.5 T (25), which may translate into an improved diagnostic performance. In comparison to those in a previous study at 1.5 T (26), LGE and T1 relaxation times yielded comparable diagnostic accuracy of 91%. However, although LGE showed a specificity of 100% in our study population, sensitivity was only 75%. In comparison, T1 relaxation times yielded a specificity of 91% and a sensitivity of 92%. Although intracellular edema, which occurs before myocyte necrosis, already prolongs T1 relaxation times, it does not increase extracellular space (which is necessary for gadolinium accumulation in LGE). Therefore, LGE might be inferior to T1 mapping for detection of acute myocarditis, although it offers excellent sensitivity.

T1 Mapping

In acute myocarditis, two mechanisms are the main causes of prolongation of T1 relaxation times. First, animal studies have demonstrated that myocardial T1 is prolonged in the ischemic myocardium because of an increase in water content (27). More recently, human in vivo studies have confirmed these findings (26,28), and it was postulated that T1 prolongation is caused by an increase in both the total water content and the relative amounts of water in intracellular and extracellular space (27). Second, it was hypothesized that the motional freedom of protons is affected by the altered electrolyte distribution in ischemic tissue, which further enhances T1 prolongation. All of these (cellular edema, increased extracellular space and water, inflammation, and myocyte necrosis) commonly occur in patients with acute myocarditis (6,29) and may therefore cause prolongation of T1 relaxation times already in an early stage of the disease.

In the present study, use of T1 mapping showed excellent diagnostic performance with a cutoff value of 1140 msec, with a diagnostic accuracy of 91%, which is comparable to that in a previous study performed at 1.5 T (26). T1 relaxation times alone exceeded the diagnostic performance of the established Lake Louise criteria (diagnostic accuracy: 91% vs 85%).

ECV has been inferior to T1 relaxation times, with a diagnostic accuracy of 75% compared with 91% in the present study. However, we recommend routine calculation of ECV, because, unlike T1 relaxation times, it is independent of MR imaging field strength, and may allow for performance of follow-up examinations on both 1.5-T and 3-T systems (12).

Multiparametric Analysis

Currently, cardiac MR imaging–based diagnosis relies on a combination approach known as the Lake Louise criteria (6). Groupwise comparison of cardiac MR imaging parameters of myocardial inflammation (T2 ratio, EGEr, and T1 relaxation times) already showed distinct differences between the groups, with increased T2 ratio, increased EGEr, and prolonged T1 relaxation times. These results for healthy control subjects are in good agreement with those of previous studies performed at 3 T (30), indicating the robustness of the technique.

Although global T1 relaxation time alone already yields excellent diagnostic accuracy, this can be improved by combining T1 relaxation time assessment with assessment of either T2 ratio or LGE. When combining native T1 relaxation times with LGE, diagnostic accuracy increases from 91% for T1 relaxation times alone to 96%, and in combination with T2 ratio, to 95%. This may be of great importance because the recommended cardiac MR protocol for evaluation of myocarditis is restricted to patients without contraindications for the use of gadolinium-based contrast agents.

Study Limitations

Our study had several limitations. This study was performed by using clinical validation for patients suspected of having acute myocarditis only. Endomyocardial biopsy as a reference standard was not performed because it has a low sensitivity for excluding myocarditis (31,32) and is not routinely performed in clinical practice. Instead, an accepted standard used previously in multiple cardiac MR validation studies was used (6–8). The accuracy of T1 relaxation time measurement depends on inversion pulse efficiency, platform, and field strength (33). In addition, T1 relaxation time measurement errors in patients with tachycardia may be a problem in clinical routine diagnostics (34). To date, several sequences and timing schemes for myocardial T1 relaxation time measurement exist, but to our knowledge, no method has

been demonstrated to be superior to another.

In our study, we chose the 3–3-5 modified Look-Locker inversion-recovery scheme because it offers a good compromise among imaging time, accuracy, and reproducibility throughout a wide range of T1 relaxation times and field strengths (34). Consequently, our data suggest that T1 mapping at 3 T in patients with acute myocarditis by using the 3–3-5 modified Look-Locker inversion-recovery scheme is clinically feasible with an equivalent diagnostic accuracy compared with that obtained at 1.5 T (26). Native myocardial T1 relaxation time prolongation is nonspecific and may also be seen in other myocardial diseases such as cardiac amyloidosis (35), hypertrophic and dilated cardiomyopathy (36), and diffuse fibrosis (37). Therefore, T1 relaxation times should only be used in the clinical context. Because of the small sample size and the use of reclassification methods, further prospective studies are necessary to confirm our findings.

In conclusion, our study results showed that native T1 mapping has high accuracy for the diagnosis of acute myocarditis at 3 T. In the future, acute myocarditis may be evaluated by using T1 relaxation time assessment in combination with T2 ratio without reducing diagnostic accuracy. However, further prospective studies are necessary to confirm our findings. Therefore, although it seems possible that T1 relaxation time assessment may be the only approach necessary in daily clinical routine to assess all changes that occur in patients with acute myocarditis (edema, hyperemia, and necrosis or scarring), we recommend assessing T2 ratio and LGE, unless contraindications to gadolinium-based contrast agents exist, to take advantage of the increased diagnostic performance of these combined parameters.

Disclosures of Conflicts of Interest: J.A.L. No relevant conflicts of interest to disclose. **J.D.** No relevant conflicts of interest to disclose. **D.K.T.** No relevant conflicts of interest to disclose. **D.D.** No relevant conflicts of interest to disclose. **J.G.** No relevant conflicts of interest to disclose. **A.M.S.** No relevant conflicts of interest to disclose. **R.F.** No relevant conflicts of interest to disclose. **C.S.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: Author is an employee of Philips Healthcare. Other relationships: none to disclose. **R.H.** No relevant conflicts of interest to disclose. **J.O.S.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: personal fees from SJM, Medtronic, and Biotronik. Other relationships: none to disclose. **H.S.** No relevant conflicts of interest to disclose. **C.P.N.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: personal fees from Medtronic. Other relationships: none to disclose.

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