Cardiac MRI Texture Analysis of T1 and T2 Maps in Patients with Infarctlike Acute Myocarditis

Bettina Baessler, MD • Christian Luecke, MD • Julia Lurz, MD • Karin Klingel, MD • Maximilian von Roeder, MD • Suzanne de Waha, MD • Christian Besler, MD • David Maintz, MD • Matthias Gutberlet, MD • Holger Thiele, MD • Philipp Lurz, MD, PhD

From the Department of Radiology, University Hospital of Cologne, Kerpener Str 62, 50937 Cologne, Germany (B.B., D.M.); Department of Diagnostic and Interventional Radiology, Heart Center Leipzig, Leipzig, Germany (C.L., M.G.); Department of Internal Medicine/Cardiology, Heart Center Leipzig-University Hospital, Leipzig, Germany (J.L., M.v.R., C.B., H.T., P.L.); Department of Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tuebingen, Tuebingen, Germany (K.K.); Department of Cardiology, Angiology, and Intensive Care Medicine, University Heart Center Luebeck, Luebeck, Germany (S.d.W.); German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Luebeck, Luebeck, Germany (S.d.W.); and Leipzig Heart Institute, Leipzig, Germany (M.G., H.T., P.L.). Received February 16, 2018; revision requested March 14; final revision received June 5; accepted June 8. Address correspondence to B.B. (e-mail: bettina.baessler@uk-koeln.de).

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

Radiology 2018; 00:1–9 • https://doi.org/10.1148/radiol.2018180411 • Content code: CA

Purpose: To assess the diagnostic potential of texture analysis applied to T1 and T2 maps obtained with cardiac MRI for the diagnosis of acute infarctlike myocarditis.

Materials and Methods: This prospective study from August 2012 to May 2015 included 39 participants (overall mean age ± standard deviation, 34.7 years ± 12.2 [range, 18–63 years]; mean age of men, 29.8 years ± 9.2 [range, 18–56 years]) from the Magnetic Resonance Imaging in Myocarditis (MyoRacer) trial with clinical suspicion of acute myocarditis and infarctlike presentation. Participants underwent biventricular endomyocardial biopsy, cardiac catheterization, and cardiac MRI at 1.5 T, in which native T1 and T2 mapping as well as Lake Louise criteria (LLC) were assessed. Texture analysis was applied on T1 and T2 maps by using a freely available software package. Stepwise dimension reduction and texture feature selection was performed for selecting features enabling the diagnosis of myocarditis by using endomyocardial biopsy as the reference standard.

Results: Endomyocardial biopsy confirmed the diagnosis of acute myocarditis in 26 patients, whereas 13 participants had no signs of acute inflammation. Mean T1 and T2 values and LLC showed a low diagnostic performance, with area under the curve in receiver operating curve analyses as follows: 0.65 (95% confidence interval [CI]: 0.45, 0.85) for T1, 0.67 (95% CI: 0.49, 0.85) for T2, and 0.62 (95% CI: 0.42, 0.79) for LLC. Combining the texture features T2 run-length nonuniformity and gray-level non-uniformity resulted in higher diagnostic performance with an area under the curve of 0.88 (95% CI: 0.73, 1.00) ($P < .001$) and a sensitivity and specificity of 89% [95% CI: 81%, 93%] and 92% [95% CI: 77%, 93%], respectively.

Conclusion: Texture analysis of T2 maps shows high sensitivity and specificity for the diagnosis of acute infarctlike myocarditis.

©RSNA, 2018

Online supplemental material is available for this article.

Although a timely and correct diagnosis of myocarditis should represent the first step toward a tailored therapeutic strategy to reduce the risk of progression to chronic active inflammation and/or dilated cardiomyopathy (1,2), the diagnosis of myocarditis remains one of the most challenging in clinical cardiology (3).

With its unique capability for tissue characterization, cardiac MRI has become the primary tool for noninvasive diagnosis of myocarditis for clinicians, if it is available to them. Current diagnostic Lake Louise criteria (LLC) aim to visualize the hallmarks of myocardial inflammation by means of T2-weighted edema imaging, assessment of vasodilatory response and/or capillary leak based on early gadolinium-enhanced imaging, and visualization of myocardial fibrosis and/or necrosis with late gadolinium-enhanced imaging (4). Nevertheless, many studies have reported considerable variations in sensitivity (66%–92%) and specificity (47%–80%) of LLC (5–7).

One potential explanation for this phenomenon is the existence of different types of myocarditis based on the predominant clinical presentation. Growing clinical evidence suggests that myocarditis with acute infarctlike presentation might need a different diagnostic approach than does myocarditis manifesting as new-onset heart failure or in its chronic stage (2,6–8).

Recently, T1 and T2 mapping techniques have been introduced as quantitative and thus more objective and reliable approaches to the detection of myocardial inflammation. However, the routine clinical use of mapping techniques is still hindered by several major limitations, the most important one being the large overlap of myocardial T1 and T2 times between health and disease (9–12). Recently proposed approaches that aim to detect inflammation-induced tissue changes by quantifying the heterogeneity of T2 relaxation times in the myocardium (10,13) require an elaborated off-line calculation of the derived parameters and thus cannot be easily applied during the mapping postprocessing workflow. Consequently, faster methods to assess inflammatory tissue changes that can be applied directly during the routine postprocessing of cardiac T1 and
Cardiac MRI Texture Analysis of T1 and T2 Maps in Infarctlike Acute Myocarditis

Implications for Patient Care

- In patients with biopsy-proven acute infarctlike myocarditis, the diagnostic performance of Lake Louise criteria, as well as global native T1 and T2, is only moderate when compared against endomyocardial biopsy as a reference standard.

- Two T2 mapping-derived texture features (T2 run-length nonuniformity and T2 gray-level nonuniformity), both representing measures of tissue inhomogeneity, yield superior diagnostic performance (sensitivity of 89% and specificity of 92%) for acute infarctlike myocarditis compared with Lake Louise criteria and native T1 and T2 mapping.

- Combination of texture features with blood parameters (troponin, creatine kinase-MB, N-terminal pro b-type Natriuretic Peptide) resulted in increased diagnostic performance (sensitivity and specificity of 100%) for detection of acute infarctlike myocarditis.

T2 maps are desirable for further improvement of diagnostic accuracy of cardiac MRI in myocarditis.

The increasing use of texture analysis (TA) allows the assessment of the underlying texture of a tissue. TA also detects tissue changes that remain imperceptible to the human eye (14) by quantifying gray-level patterns and pixel interrelationships in an image (14). Recently, applications of TA in cardiac MRI have been described in the setting of myocardial infarction, demonstrating the potential of TA for detecting small myocardial scars at cine imaging (15) and for differentiating acute versus chronic myocardial infarction (16).

The hypothesis for our study was that TA applied on myocardial T1 and T2 maps delivers diagnostic parameters reflecting inflammatory myocardial tissue changes with high diagnostic accuracy, especially when combined with clinical (blood) parameters. Thus, the purpose of our proof-of-principle study was to assess the diagnostic potential of TA applied to T1 and T2 maps obtained with cardiac MRI with and without combination of blood parameters for the diagnosis of biopsy-proven acute infarctlike myocarditis.

Materials and Methods

Our prospective single-center study represents a substudy from the Magnetic Resonance Imaging in Myocarditis (MyoRacer) trial (ClinicalTrials.gov registration no. NCT02177630), including 44 of 129 originally reported consecutive participants (7,17). This prior article evaluated patients with acute and chronic myocarditis by using LLC and T1 and T2 mapping, whereas the present article reports the application of TA on T1 and T2 mapping not reported previously. Our study had institutional review board and local ethics committee approval. All participants and healthy control participants gave written informed consent.

Study Design

Among all participants enrolled in the MyoRacer trial from August 2012 to May 2015, only participants with clinical suspicion of acute myocarditis and infarctlike presentation were included. Additionally, 10 healthy volunteers underwent cardiac MRI for comparison. Inclusion and exclusion criteria for participants and healthy control participants are illustrated in Figure 1.

Biopsy and Immunohistochemistry

Biventricular endomyocardial biopsy (EMB) sampling was performed via femoral venous and arterial access by using myocardial biopsy forceps (Teleflex Medical Tuttlingen, Tuttlingen, Germany); six to seven EMB samples were taken from different locations within the left ventricle by using fluoroscopic guidance. Right ventricular biopsies (five to seven samples) were taken exclusively from the septal or apical regions.

Histologic, immunohistologic, and molecular pathologic analyses were performed by an experienced observer (K.K., with 15 years of experience in cardiovascular pathology) as previously described (6,7), in accordance with consensus recommendations (18). A detailed description of EMB analysis is provided in Appendix E1 (online).

In addition, standard blood parameters (troponin, creatine kinase-MB, N-terminal pro b-type Natriuretic Peptide) were recorded for each participant.

Cardiac MRI

Cardiac MRI was performed with a clinical 1.5-T system (Intera CV; Philips Healthcare, Best, the Netherlands) by using a dedicated five-element cardiac coil. For T2 short inversion time inversion-recovery and T1-weighted spin-echo sequences, a body coil was used. The entire cardiac MRI protocol is shown in Figure E1 (online). A detailed description of the protocol parameters and cardiac MRI data analysis is provided in Appendix E1 (Tables E1 and E2 [online]).

Image analysis of LLC was performed with a standard postprocessing platform (cmr42, version 5.1.0; Circle Cardiovascular Imaging, Calgary, Alberta, Canada) by two experienced observers (C.L. and B.B., with 8 years and 6 years of experience in cardiovascular imaging, respectively). The myocardium was evaluated visually for presence of myocardial edema at T2-weighted black-blood imaging, as well as by calculating the T2-ratio as previously described (4). Briefly, a myocardial region of interest and a skeletal muscle region of interest were drawn on one axial section before and after contrast material administration. Early gadolinium enhancement ratio was calculated as previously described and deemed pathologic when greater than or equal to 4 (4).

The myocardium was visually assessed on late gadolinium-enhanced images and considered suspicious for myocarditis in cases of focal signal intensity alterations with a subepicardial or...
Technical University of Lodz, Lodz, Poland) (21) as previously described (15,22). T1 and T2 maps (midventricular short axis and horizontal long axis) were exported as single Digital Imaging and Communications in Medicine images for further analysis, and regions of interest encompassing the entire left ventricular myocardium were drawn by an experienced observer (B.B.) who was blinded to participant data (Fig 2). The trabeculated layer and epicardial border were carefully excluded to avoid partial volume effects. Visually appreciable artifacts were excluded from the region of interest. Drawing of regions of interest and computation of the TA features by the software took about 30 seconds per participant.

For testing the reproducibility of texture features, region-of-interest delineation was repeated twice after a pause of 2 weeks in a subset of 20 participants by the same reader for intraobserver analysis and by another reader (C.L.) for interobserver analysis. Results of the first reading were blinded for both coreadings.

Gray-level normalization was performed with the TA software by rescaling the histogram data to fit within μ-gray-level mean ± 3σ (σ-gray-level standard deviation) to minimize the effect of brightness and contrast variations at TA (23). Five subset texture feature sets were extracted separately (Table E3 [online]), resulting in a total of 271 texture features.

**Texture Feature Selection and Dimension Reduction**

Because of the high number of texture features, a stepwise feature selection and dimension reduction was necessary to reduce the feature set to those that contributed most to accuracy of classification (24). The complete texture feature reduction and selection strategy is described in Appendix E1 (online).

**Statistical Analysis**

Statistical analysis was performed in R (version 3.4.0; R Foundation for Statistical Computing, Vienna, Austria) (25) with RStudio (version 1.0.136; RStudio, Boston, Mass) (26). R packages used for further statistical analyses are described in Appendix E1 (online). All continuous data are given as means ± standard deviations or medians with interquartile
Cardiac MRI Texture Analysis of T1 and T2 Maps in Infarctlike Acute Myocarditis

For selecting variables that allow classification of participants with positive findings for acute myocarditis at EMB from control participants and for participant subgroup analyses, multiple and multinomial logistic regression models were fitted and compared with the Akaike information criterion. The misclassification rate of these models was assessed by using 10-fold cross-validation (ie, data were split at random into 10 subsets, where each subset was used once as a test data set, with the remaining part being used for refitting the model). The presented proportions of correct classification were aggregated over the 10 subsets. To define optimal cutoff values for the current data, single classification trees (also known as recursive partitioning) were fitted by using the Gini index as a measure for impurity (27). The diagnostic accuracy of optimal predictive parameters was evaluated from the area under the curve (AUC) from receiver operating characteristic (ROC) analyses, and diagnostic sensitivity and specificity were calculated. Optimal diagnostic performance was chosen at the point where highest specificity was achieved. 95% confidence intervals (CIs) were calculated for all AUCs, sensitivities, and specificities. Again, misclassification rates were assessed by 10-fold cross-validation. ROC curves were compared according to the DeLong method. Intra- and interobserver agreement was tested by using intraclass correlation coefficients.

Results

Study Population

Our study flow and reasons for participant dropout for comparison of EMB results with cardiac MRI are illustrated in Figure 1. Participant characteristics are shown in Table E4 (online).

Results of EMB and Cardiac MRI

In two participants, only left ventricular specimens could be obtained during EMB. Among 39 participants included in our final study population, 26 had positive findings at EMB and 13 had negative findings. Diagnoses based on EMB findings are shown in Table E5 (online).

Similarly, edema ratio, early gadolinium enhancement, and presence of late gadolinium enhancement did not differ ranges, where appropriate. Testing for group differences was performed by using Wilcoxon sum-rank test or Welch independent $t$ test after assessing normality distribution of data by using the Shapiro-Wilk test. A two-tailed $P$ value of < .05 was regarded to indicate statistical significance.
between participants with positive findings at EMB and those with negative findings at EMB (Table 1). Consequently, the diagnosis of EMB-positive myocarditis was established with a sensitivity of 16 of 26 (63% [95% CI: 42%, 78%]) and a specificity of eight of 13 (62% [95% CI: 40%, 77%]) by using standard LLC (AUC in ROC analysis, 0.62 [95% CI: 0.42, 0.79]) compared with a sensitivity of 21 of 26 (80% [95% CI: 64%, 95%]) and specificity of seven of 10 (73% [95% CI: 53%, 86%]) for differentiating participants with positive findings at EMB from healthy control participants (AUC, 0.82 [95% CI: 0.68, 0.95]).

Similar observations were made for global myocardial T1 and T2, which showed a moderate and significant correlation (Pearson $r = 0.44$; $P < .001$). While demonstrating significant differences between participants with positive findings at EMB and control participants, no significant differences were observed for participants with positive findings at EMB versus those with negative findings (Table 1).

In logistic regression and ROC analysis, global T1 had a moderately significant AUC compared with global T2 (0.80 [95% CI: 0.65, 0.94] vs 0.80 [95% CI: 0.81, 0.99]; $P = .164$) for differentiating participants with positive findings at EMB from control participants, whereas their ability to differentiate participants with positive findings at EMB from those with negative findings was far inferior and similar to LLC with AUCs of 0.65 (95% CI: 0.45, 0.85) and 0.67 (95% CI: 0.49, 0.85) ($P = .877$), respectively.

**Table 1: Results of Cardiac MRI and Texture Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Control Participants ($n = 10$)</th>
<th>Participants with Positive Findings at EMB ($n = 26$)</th>
<th>Participants with Negative Findings at EMB ($n = 13$)</th>
<th>$P$ Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$P$ Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema ratio</td>
<td>...</td>
<td>1.9 ± 0.5</td>
<td>...</td>
<td>1.8 ± 0.5</td>
<td>.48</td>
</tr>
<tr>
<td>Early enhancement</td>
<td>...</td>
<td>4.7 ± 2.5</td>
<td>...</td>
<td>5.7 ± 4.2</td>
<td>.73</td>
</tr>
<tr>
<td>Presence of late gadolinium</td>
<td>...</td>
<td>20 (74)</td>
<td>...</td>
<td>7 (54)</td>
<td>.43</td>
</tr>
<tr>
<td>enhancement</td>
<td>Lake Louise criteria</td>
<td>...</td>
<td>17 (63)</td>
<td>...</td>
<td>.26</td>
</tr>
<tr>
<td>Mean T1 (msec)</td>
<td>962 ± 80</td>
<td>1053 ± 76</td>
<td>1012 ± 75</td>
<td>.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.14</td>
</tr>
<tr>
<td>Mean T2 (msec)</td>
<td>55.8 ± 1.8</td>
<td>62.1 ± 4.8</td>
<td>59.0 ± 4.4</td>
<td>&lt;.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.09</td>
</tr>
<tr>
<td>T2 run-length nonuniformity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>737 ± 132</td>
<td>1024 ± 230</td>
<td>739 ± 236</td>
<td>&lt;.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.09</td>
</tr>
<tr>
<td>T2 gray-level nonuniformity</td>
<td>142 ± 38</td>
<td>233 ± 49</td>
<td>161 ± 48</td>
<td>&lt;.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.09</td>
</tr>
<tr>
<td>T2 sum average</td>
<td>16.5 ± 0.2</td>
<td>16.8 ± 0.2</td>
<td>16.8 ± 0.2</td>
<td>&lt;.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.78</td>
</tr>
<tr>
<td>T2 sum entropy</td>
<td>1.17 ± 0.03</td>
<td>1.19 ± 0.03</td>
<td>1.15 ± 0.04</td>
<td>.002&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.002&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2 invasive different moment</td>
<td>0.44 ± 0.05</td>
<td>0.49 ± 0.05</td>
<td>0.48 ± 0.10</td>
<td>.003&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.05&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>T1 angular second moment</td>
<td>0.014 ± 0.004</td>
<td>0.023 ± 0.006</td>
<td>0.036 ± 0.001</td>
<td>.53</td>
<td>.01&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2 short run emphasis</td>
<td>0.83 ± 0.04</td>
<td>0.76 ± 0.05</td>
<td>0.79 ± 0.07</td>
<td>&lt;.001&lt;sup&gt;†&lt;/sup&gt;</td>
<td>.02&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>T1 sigma</td>
<td>0.44 ± 0.11</td>
<td>0.57 ± 0.17</td>
<td>0.59 ± 0.15</td>
<td>.02&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>.75</td>
</tr>
</tbody>
</table>

Note.—Data are means ± standard deviations. Whereas mean T1 and T2 relaxation times show significant differences (positive findings at EMB = 6.0 ± 2.2 months, control participants = 7.9 ± 3.6 months; $P = .002$), lake Louise criteria showed no significant differences for control participants versus participants with positive findings at EMB.

<sup>a</sup> Control participants versus participants with positive findings at EMB.

<sup>b</sup> Participants with positive findings at EMB versus those with negative findings.

<sup>c</sup> Indicates significant $P$ values.

<sup>†</sup> Texture features are dimensionless.

**TA for Differentiating Participants with Positive Findings for Acute Myocarditis at EMB from Healthy Control Participants**

At the end of the multistep dimension reduction and texture feature selection process described in Appendix E1 (online), the six most important and independent texture features derived from T1 and T2 mapping were selected for further statistical analyses, including three second-order features from the co-occurrence matrix (T2 sum average, T2 invasive different moment, and T1 angular second moment), two second-order features from the run-length matrix (T2 run-length nonuniformity [T2_RLNonUni] and T2 short run emphasis), and one higher-order feature from the autoregressive model (T1 sigma).

All six texture features showed significant differences between participants with positive findings for myocarditis at EMB and healthy control participants, except for T1 angular second moment (Table 1). In single and multiple logistic regression analyses, the five significantly different texture features showed a similar diagnostic performance when used as a single parameter in a model according to their Akaike information criterion with AUCs in ROC analyses ranging from 0.78 to 0.90, except for T1 sigma with an AUC of 0.72 (95% CI: 0.57, 0.88) (Table 2). The combination of global myocardial T2 and T2_RLNonUni in a model finally resulted in highest diagnostic performance with an AUC of 1.00 (95% CI: 0.77, 1.00), a sensitivity of 26 of 26 (100% [95% CI: 87%, 100%]), and a specificity of 10 of 10 (96% [95% CI: 82%, 100%]), respectively (Fig 3, Table 2). Ten-fold cross-validation resulted in robust models with an AUC ranging from 0.69 to 0.82, demonstrating a stable calculation of diagnostic performance.
TA for Differentiating Participants with Positive Findings for Acute Myocarditis at EMB from Participants with Negative Findings at EMB

By repeating the stepwise dimension reduction and feature selection process, a similar set of three texture features was identified as important for the differentiation of participants with positive and negative findings. Again, T2_RLNonUni was identified as a most important variable. In addition, another second-order feature from the T2 co-occurrence matrix (T2 sum entropy) and one additional feature from the T2 run-length matrix (T2 gray-level nonuniformity [T2_GLevNonU]) were deemed important.

All three texture features showed significant differences between participants with positive findings at EMB and those with negative findings (Table 1). The selected texture features showed a superior diagnostic performance compared with LLC as well as global T1 and T2 when used as single parameters in a model, with AUCs ranging from 0.80 to 0.86 (Table 2). Combining the two run-length matrix features (T2_RL NonUni and T2_GLevNonU) in the model finally showed the best diagnostic performance, with an AUC of 0.88 (95% CI: 0.73, 1.00), a sensitivity of 23 of 26 (89% [95% CI: 81%, 93%]), and a specificity of 12 of 13 (92% [95% CI: 77%, 93%]), respectively (Fig 4a, Table 2). Ten-fold cross-validation resulted in an internal estimate of accuracy of 0.80 and a cross-validation estimate of accuracy of 0.80.

When combining blood parameters (tropinin, creatinine kinase-MB, N-terminal pro b-type Natriuretic Peptide) with the two texture features in a model, diagnostic performance was even better and superior to a combination of blood parameters with LLC (AUC, 1.00 [95% CI: 0.80, 1.00] vs 0.78 [95% CI: 0.57, 0.89]; \( P < .001 \); sensitivity, 26 of 26 [100%; 95% CI: 90%, 100%] vs 16 of 26 [60%; 95% CI: 43%, 75%]; and specificity, 13 of 13 [100%; 95% CI: 83%, 100%] vs 13 of 13 [100%; 95% CI: 79%, 100%]) (Fig 4b).

Discussion

In our study, we assessed the potential of TA for confirming or rejecting the clinical diagnosis of myocarditis while comparing the results of cardiac MRI to EMB, rather than to those of healthy control participants. The main findings of our study can be summarized as follows:

---

**Table 2: Diagnostic Performance of Conventional Cardiac MRI and Texture Features**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lake Louise criteria</td>
<td>0.82</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
<tr>
<td>Mean T1</td>
<td>0.80</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
<tr>
<td>Mean T2</td>
<td>0.87</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
<tr>
<td>T2 run-length nonuniformity</td>
<td>0.89</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
<tr>
<td>T2 gray-level nonuniformity</td>
<td>0.87</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
<tr>
<td>T2 short run emphasis</td>
<td>0.85</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
<tr>
<td>T2 gray-level nonuniformity + T2 mean</td>
<td>0.92</td>
<td>21/26 (80)</td>
<td>10/13 (77)</td>
</tr>
</tbody>
</table>

Note—Unless otherwise specified, data are numbers of participants with positive findings, numbers of participants with negative findings, and numbers of participants with positive findings and negative findings. For participants with positive findings, the combination of T2 run-length nonuniformity and mean T2 resulted in superior diagnostic performance compared with conventional cardiac MRI parameters when used as single parameters in receiver operating curve analysis. Combining T2 run-length nonuniformity and T2 mean in a model finally results in superior diagnostic performance compared with conventional cardiac MRI parameters when used as single parameters in receiver operating curve analysis.
In a selected participant cohort with biopsy-proven acute infarctlike myocarditis, the diagnostic performance of LLC and global myocardial T1 and T2 is only moderate when compared against EMB as the reference standard. In addition, TA parameters yield better diagnostic performance compared with conventional LLC as well as to global myocardial T1 and T2, especially when adding clinical (blood) parameters to the model.

Only a small set of previous studies (5,28–30) focused in a similar fashion on a homogeneous participant cohort with acute infarctlike symptoms. In most of these studies, the diagnostic sensitivity and specificity of LLC was in the range of 80%–92% and 80%–100%, respectively (5,28–30). Notably, all these studies compared the diagnostic potential of LLC to a group of healthy control participants by using the clinical suspicion of myocarditis as the reference standard. The diagnostic performance of LLC for differentiating between participants with positive findings for myocarditis at EMB and healthy control participants in our study is in line with these previous results. The lower diagnostic
performance of LLC and global myocardial T1 and T2 for differentiating participants with positive findings at EMB from those with negative findings in our study compared with previous reports (4,6,7,28,29) needs further explanation. One important difference between acute infarctlike myocarditis and other clinical presentations of myocarditis could be the focal versus diffuse nature of the pathologic condition. Although difficult to prove, myocarditis at an early stage is believed to cause more patchy and inhomogeneous myocardial pathologic condition than participants with heart failure–like presentation and chronic symptoms, resulting in a homogeneously diffuse myocardial pathologic condition. T1 or T2 time averaged over the entire myocardium might miss focal spots of disease and thus lead to false-negative results, reducing sensitivity (10,13). The problem of high interindividual variability of myocardial T1 and T2 times can further reduce sensitivity and—even more so—specificity when using an averaging approach alone (9,10).

Although previous reports have shown a high sensitivity and specificity for native T1 in detecting myocardial edema (5,28,31), no parameter derived from T1 mapping was among the most powerful discriminators when assessing predictive models and a significant correlation was observed between mean T1 and T2. Thus, our results show that no significant additional effect can be achieved by combining T1 and T2 parameters, including those derived from TA in a multiparametric imaging approach for detecting acute infarctlike myocarditis.

Both texture features (T2_RLNonUni and T2_GLevNonU) are derived from the higher-order run-length feature matrix, which is based on computing the number of gray-level runs of various lengths. A gray-level run represents a set of linearly adjacent picture points having the same gray-level value (14), and the length of the run is the number of picture points within it. The run-length matrix elements define how often a particular gray-level value is met in a particular run length (14). Thus, the two features T2_RLNonUni and T2_GLevNonU are a measure for the homogeneity of the pixel gray-level distribution of the underlying tissue, where higher values represent more inhomogeneity within the gray-levels of the run-length matrix. Although the two features were highly collinear in our study, they showed a significant additive value when used in combination.

We acknowledge several limitations of our study. Although EMB is widely accepted as the reference standard for diagnosing myocarditis, a sampling error leading to false-negative results cannot be excluded. We performed biventricular EMB acquiring a high number of samples as suggested previously (32) to acquire a reliable reference standard, but some minor uncertainty remains. The mapping techniques used in our study represented the methodology available in mid-2012. In the meantime, techniques with potentially more robust estimation of T1 and T2 relaxation times have been reported (33). Thus, additional studies using these techniques should be performed to further elucidate the application of TA on T1 and T2 mapping and the influence of technical factors, such as field strength or sequence type, on derived markers for tissue inhomogeneity.

In conclusion, our findings show that the utility of global T1 or T2 times in participants suspected of having infarctlike myocarditis is limited because signal averaging over the entire myocardium might miss focal spots of disease and thus reduce sensitivity. In contrast, combining two parameters derived from T2 mapping (T2_RLNonUni and T2_GLevNonU) in a predictive model resulted in excellent diagnostic performance and detected participants with positive findings for myocarditis at EMB with high sensitivity and specificity.

Author contributions: Guarantors of integrity of entire study, B.B., C.B.; 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; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, B.B., C.B., D.M., M.G., H.T., P.L.; clinical studies, J.L., K.K., M.v.R., S.d.W., C.B., D.M., M.G., H.T., P.L.; statistical analysis, B.B., C.B. and manuscript editing, B.B., C.L., J.L., C.B., D.M., M.G., H.T., P.L.


References


