Detection and Monitoring of Acute Myocarditis Applying Quantitative Cardiovascular Magnetic Resonance

Florian von Knobelsdorff-Brenkenhoff, MD*; Johannes Schüller, MD*; Serkan Dogangüzel, MD; Matthias A. Dieringer, PhD; Andre Rudolph, MD; Andreas Greiser, PhD; Peter Kellman, PhD; Jeanette Schulz-Menger, MD

Background—Cardiovascular magnetic resonance based on the Lake Louise Criteria is used to make the diagnosis of acute myocarditis. Novel quantitative parametric mapping techniques promise to overcome some of its limitations. We aimed to evaluate quantitative cardiovascular magnetic resonance to detect and monitor acute myocarditis.

Methods and Results—Eighteen patients with clinical diagnosis of acute myocarditis (25 years [23–38 years]; 78% males) were prospectively enrolled and repeatedly underwent cardiovascular magnetic resonance at 1.5 T seven days (5–10 days) after symptom onset (FU0), after 5 weeks (FU1), and after 6 months (FU2). Eighteen age- and sex-matched healthy subjects served as controls. Cardiovascular magnetic resonance included imaging of edema, hyperemia, necrosis, and fibrosis using semiquantitative T2-weighted spin echo, T2 mapping, and T1 mapping before and 3 and 10 minutes after gadobutrol administration. Extracellular volume for diffuse and late gadolinium enhancement for focal fibrosis were assessed. Compared with controls, patients had significantly higher global T2 times at FU0 (55.1 ms [53.3–57.2 ms] versus 50.2 ms [49.2–52.0 ms]; P<0.001) and at FU1 (52.0 ms [52.0–53.2 ms]; P=0.007), which normalized at FU2 (50.9 ms [49.6–53.3 ms]; P=0.323). Global native T1 times in patients were elevated acutely (1004 ms [988–1048 ms] versus 975 ms [957–1004 ms]; P=0.002) and remained elevated throughout the follow-up (FU1: 998 ms [990–1027 ms]; P=0.014; FU2: 1000 ms [972–1027 ms]; P=0.044). Global extracellular volume fraction was statistically not different between patients and controls (P=0.057). 77.8% (14/18) of patients had focal late gadolinium enhancement. T2 ratio was significantly elevated in patients with myocarditis at FU0 (2.2 [2.0–2.3] versus 1.6 [1.5–1.7]; P<0.001). The difference decreased during follow-up (FU1: 1.9 [1.7–1.9]; P=0.001 and FU2: 1.7 [1.7–1.8]; P=0.053). The diagnostic accuracy to discriminate between patients with acute myocarditis and healthy controls was 86% for T2>52 ms, 78% for native T1>981 ms, 74% for extracellular volume fraction >0.24, and 100% for T2 ratio >1.9.

Conclusions—Although both T2 and T1 mapping reliably detected acute myocarditis, only T2 mapping discriminated between acute and healed stages, underlining the incremental value of T2 mapping.

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Key Words: edema • fibrosis • magnetic resonance • mapping • myocarditis

Myocarditis is a potentially life-threatening disease, causing 12% of sudden deaths in young adults and 9% of dilated cardiomyopathy.1 On the contrary, 50% of the patients recover completely.1 Early differentiation may impact the daily lifestyle significantly. Making the diagnosis of myocarditis and monitoring the disease stage is often a challenge.1,2 A current position statement of the European Society of Cardiology recommends assessing both clinical criteria like chest pain and dyspnea and diagnostic criteria based on ECG.

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See Clinical Perspective

blood tests, and imaging by echocardiography and cardiovascular magnetic resonance (CMR).2 In particular, CMR has evolved significantly during the last decade.3–5 Since 2009, the Lake Louise Criteria (LLC) recommended to combine different CMR techniques in patients with suspected myocarditis to determine myocardial edema (T2-weighted spin echo),...
hyperemia (T1-weighted spin-echo), and necrosis (late gadolinium enhancement [LGE]). The LLC allow the detection of focal and diffuse inflammatory reaction using a semiquantitative approach, and a pooled sensitivity and specificity of 67% and 91%, respectively, have been reported. This consensus document emphasized that images obtained by T1-weighted spin-echo sequences during free breathing may have limited diagnostic quality, and T2-weighted spin-echo images have an inherently low signal-to-noise ratio. Because the pattern of inflammation may change from focal injury to a diffuse reaction and vice versa, a quantitative approach is promising to detect the different stages. Parametric mapping has been introduced as a potential alternative and has reached the clinical arena: T2 mapping measures the T2 relaxation time. This has been reported to be elevated in voxels with acute myocardial damage, like in myocarditis or myocardial infarction, compared with remote myocardium or reference values. Recent studies demonstrated that the integration of T1 values significantly improved the diagnostic accuracy of CMR in subjects with acute myocarditis when compared with the conventional LLC approach. T2 times have been proposed as a good parameter to assess the activity of myocarditis. To date, clinical investigators have mostly focused on assessing either acute or chronic myocarditis, whereas preclinical studies have already covered both aspects. The exact temporal evolution of the range of myocarditis-related injuries over the course of myocarditis in the same group of patients has only been reported for the LLC some years ago, and recently for T1 mapping by Hinojar et al. In the present study, both T1 and T2 maps have been acquired repeatedly in subjects with clinically diagnosed myocarditis in the acute phase, in a short-term follow-up, and during reconvalescence.

### Methods

#### Study Design and Population

Between September 2013 and May 2015, 55 patients with clinically suspected acute myocarditis were prospectively screened and 18 patients met the inclusion criteria and agreed to participate (Table 1). Eight hospitals in Berlin helped to recruit patients. Inclusion criteria were chosen in accordance with a recent European Society of Cardiology position statement and with previous studies of our working group: (1) new onset of symptoms and signs suggestive of cardiac disease; (b) evidence for myocardial injury as defined by ECG changes and elevated serum markers; and (c) exclusion of coronary artery disease by invasive angiography (78%) or by clinical criteria if the probability was extremely low (22%). Fulfillment of any CMR criteria for myocarditis in a clinical CMR study did not influence the study inclusion. Exclusion criteria were previous myocardial infarction, previous myocarditis, and contraindications to CMR. All enrolled patients received a CMR study within 7 days (5–10 days) after symptom onset (FU 0), 40 days (39–44 days) thereafter (FU1), and after 189 days (182–194 days; FU2). CMR findings consistent with Takotsubo or any other cardiomyopathy, as well as myocardial infarction, led to exclusion of the subject. A group of 18 age- and sex-matched subjects underwent 1 CMR examination with the same protocol. The ethics committee approved the study, and all participants gave written informed consent.

### CMR Examination

All study CMR exams were performed at a single center (HELIOS Clinic Berlin-Buch) using a 1.5 T system (Magnetom Avanto; Siemens Healthcare, Germany). Image analysis was done by experienced CMR readers and supervised by 2 Society for Cardiovascular Magnetic Resonance level 3 experts using cvi42 5.0 (Circle Cardiovascular Imaging, Calgary, Canada). Acquisition parameters are shown in the appendix in the Data Supplement. Steady-state free-precession cine images were acquired in a long and in a stack of short axes covering the left ventricle (LV) to assess cardiac geometry and function. A breath-hold, black-blood, T2-weighted triple inversion-recovery sequence was acquired in 2 thick short-axis slices to assess edema. The T2 ratio was calculated as the ratio of the signal intensities of the myocardium and the skeletal muscle. Myocardium was delineated by contouring endocardium and epicardium; signal intensity of the skeletal muscle was assessed by drawing a region of interest in a representative part of the skeletal muscle, taking care for selecting a homogenous region to omit inclusion of artifacts. For T2 mapping, data were acquired in a basal and midventricular short axis plane. Three steady-state free-precession images with different T2 preparation times were acquired from which a pixel-wise myocardial map was calculated. The myocardium was manually delineated and the T2 relaxation times per segment noted. The apical slice was disregarded because of the known elevated error by partial volume. For T1 mapping, data were acquired in a basal and a midventricular short axis plane before and 1, 3, 5, 7, and 10 minutes after administration of gadobutrol (0.15 mmol per kg body weight iv; Gadovist; Bayer Healthcare, Germany). Data were obtained using a steady-state free-precession–based Modified Look-Locker Inversion Recovery technique with 5(3)3 pattern. The T1 relaxation times per segment were noted. The native and T1 values 10 minutes after contrast agent administration of myocardium and blood in combination with the actual hematocrit were used to calculate the ECV. The absolute amount of ECV and intracellular volume was calculated as ECV (in mL)=ECV (in %)×LV mass (in g)/1.05 g/mL, and intracellular volume =100%−ECV×LV mass×1.05 g/mL.

The quality of the T2 and T1 maps was approved by assessing each single raw image regarding artifacts and motion, evaluating the plausibility of the curve fit and considering the goodness of fit in parametric maps. To test observer dependency, n=25 T1 maps were analyzed twice by one observer with >3 months latency and by a second reader. LGE imaging was performed in the same planes as the steady-state free-precession cine images using a segmented

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Myocarditis</th>
<th>Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>24.5 (23–38)</td>
<td>26.5 (24–35)</td>
<td></td>
</tr>
<tr>
<td>Sex (males/females)</td>
<td>14/4</td>
<td>14/4</td>
<td></td>
</tr>
<tr>
<td>NYHA (I, II, III, IV)</td>
<td>4, 8, 4, 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS (I, II, III, IV)</td>
<td>5, 5, 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tropinin*</td>
<td>45.0 (14.2–63.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak creatine kinase, U/L</td>
<td>241 (48–699)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>60 (57–63)</td>
<td>61 (60–63)</td>
<td>0.223</td>
</tr>
<tr>
<td>LVEDV-I, mL/cm</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.7–1.0)</td>
<td>0.195</td>
</tr>
<tr>
<td>LVM-I, g/cm</td>
<td>0.8 (0.7–0.9)</td>
<td>0.7 (0.6–0.7)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Results are expressed as median and interquartile range or as frequencies. CCS indicates Canadian Cardiovascular Society; EDV-I, end-diastolic volume index; EF, ejection fraction; LV, left ventricle; LVM-I, left ventricular mass index; and NYHA, New York Heart Association.

*Troponin is expressed as the median of the multiple of the upper normal limit because different kits and cutoffs have been used in the recruiting hospitals.
inversion-recovery gradient-echo sequence beginning 15 minutes after contrast administration.

Statistical Analysis

Results are shown as median and interquartile range or absolute frequencies. Groups were compared using the Mann–Whitney U test in case of >2 groups after testing with the Kruskal–Wallis method. Intra- and interobserver dependency was assessed by Bland–Altman analysis and intraclass correlation coefficient (ICC) with 2-way mixed model for absolute agreement. Receiver-operating characteristic curves were used based on logistic regression to assess the diagnostic performance of the modalities. The Youden index was used to define the optimal cutoff value to assess accuracy, sensitivity, and specificity of the diagnostic parameters. 95% confidence intervals were calculated for these parameters. A P value of <0.05 was regarded as statistically significant. All analyses are regarded exploratory, including all hypothesis tests. Therefore, analyses with significance at a 5% level are regarded as strong trend, and promising candidates for setting up a confirmatory study and adjustments for multiple comparisons were dispensed. Calculations were performed using SPSS Statistics version 23.0 (IBM, Armonk), SAS Version 9.4 (SAS Institute Inc, Cary, NC), and PRISM 6 (Graphpad Software Inc). The receiver-operating characteristic curve figures were prepared using R Version 3.2.1 with packages ROC R Version 1.0.7.23

Results

All patients completed the follow-up. Figure 1 provides an example of the various techniques in 1 subject acutely and during follow-up.

T2-Weighted Imaging

The T2 ratio was significantly elevated in subjects with myocarditis compared with controls at FU0 (2.2 [2.0–2.3] versus 1.6 [1.5–1.7]; P<0.001). At FU1, the difference was lower, but statistically still significant (1.9 [1.7–1.9]; P=0.001), while at FU2, there was no significant difference (1.7 [1.7–1.8]; P=0.053). Under consideration that in one subject, no T2-weighted images with diagnostic quality could be obtained, the cutoff of 1.9 for the T2 ratio provided a sensitivity and a specificity of 100% to discriminate subjects with acute myocarditis from controls (Table 2 and Figure 2).

T2 Mapping

Seven (0.8%) of 864 segments were excluded because of off-resonance or motion artifacts. No complete slice or subject was excluded. The global T2 relaxation time (composite of the basal and the midventricular slice) was significantly elevated in myocarditis patients compared with that in controls at FU0 (55.1 ms [53.3–57.2 ms] versus 50.2 ms [49.2–52.0 ms]; P<0.001) and at FU1 (52.0 ms [52.0–53.2 ms]; P=0.007), whereas at FU2, no statistical difference was observed (50.9 ms [49.6–53.3 ms]; P=0.323; Figure 3). Figure 4 shows the course of the T2 times during follow-up for every single subject. The segmental analysis showed that almost all myocardial segments were abnormal at FU0, with regression at FU1 and no abnormal segment at FU2 (Figure 5). The cutoff of >52.3 ms for the global T2 value provided a sensitivity of

![Figure 1. A case of a patient with myocarditis. The various imaging techniques during the acute presentation (FU0; Top row); during short-term follow-up (FU1; middle row), and during late follow-up (FU2; bottom row). FU indicates follow-up; LGE, late gadolinium enhancement; and TIRM, triple inversion recovery magnitude.](http://circimaging.ahajournals.org/)
83.3% and a specificity of 88.9% to discriminate subjects with acute myocarditis from controls (Table 2 and Figure 2).

T1 Mapping

The postcontrast T1 maps of 1 examination at FU0 and FU2 were excluded because of technical problems. Out of the remaining 5064 myocardial segments, 221 (4.4%) were excluded because of off-resonance or motion artifacts. Interobserver/intraobserver dependency regarding the T1 quantification was low (native T1: mean difference −4.8±25.7, ICC=0.92; 1.7±15.6, ICC=0.98; postcontrast T1: 0.6±9.7, ICC=0.98; 1.89±8.6, ICC=0.99).

The global native T1 relaxation time was significantly elevated in myocarditis patients compared with that in controls at FU0 (1004 ms [988–1048 ms] versus 975 ms [957–1004 ms]; P=0.002). This was true for subjects with and without LGE (P=0.010 and P=0.026). At FU1 (998 ms [990–1027 ms]; P=0.007) and at FU2 (1000 ms [972–1027 ms]; P=0.004), a statistical difference between patients and controls remained (Figure 3). The T1 elevation was distributed mainly in the inferolateral region (Figure 5).

Figure 4 shows the course of the native T1 values during follow-up for every single subject. The cutoff of 980.7 ms for the native T1 value provided a sensitivity of 88.9% and a specificity of 66.7% to discriminate subjects with acute myocarditis from controls (Table 2 and Figure 2).

The postcontrast T1 times after 1, 3, 5, 7, and 10 minutes showed that the clearest difference between subjects with myocarditis at FU0 and controls was evident after 3 minutes. Therefore, the results from the 3-minute time point were used as postcontrast T1 times. Postcontrast T1 values were significantly reduced in myocarditis patients compared with the controls at FU0 (306 ms [292–334 ms] versus 351 ms [336–399 ms]; P<0.001), FU1 (325 ms [309–346 ms]; P=0.007), and FU2 (326 ms [316–341 ms]; P=0.005; Figure 3). Figure 4 shows the course of the postcontrast T1 values during follow-up for every single subject. The T1 reduction was globally distributed (Figure 5). The cutoff to discriminate patients with acute

Table 2. Diagnostic Accuracy of CMR Parameters to Detect Acute Myocarditis

<table>
<thead>
<tr>
<th>Parameter (Cutoff)</th>
<th>Diagnostic Accuracy (Confidence Interval), %</th>
<th>Sensitivity (Confidence Interval), %</th>
<th>Specificity (Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 ratio (&gt;1.9 m)</td>
<td>100 (90.3–100)</td>
<td>100 (81.5–100)</td>
<td>100 (81.5–100)</td>
</tr>
<tr>
<td>Presence of LGE</td>
<td>88.9 (73.9–96.9)</td>
<td>77.8 (52.4–93.6)</td>
<td>100 (81.5–100)</td>
</tr>
<tr>
<td>T2 (&gt;52.3 ms)</td>
<td>86.1 (70.5–95.3)</td>
<td>83.3 (58.6–96.4)</td>
<td>88.9 (65.3–98.6)</td>
</tr>
<tr>
<td>Native T1, ms (&gt;980.7 ms)</td>
<td>77.8 (60.8–89.9)</td>
<td>88.9 (65.3–98.6)</td>
<td>66.7 (41.0–86.7)</td>
</tr>
<tr>
<td>Postcontrast T1 (t&lt;sub&gt;1&lt;/sub&gt;ms (&gt;308.5 ms)</td>
<td>82.4 (65.4–93.2)</td>
<td>62.5 (35.4–84.8)</td>
<td>100 (81.5–100)</td>
</tr>
<tr>
<td>ECV (&gt;0.241)</td>
<td>74.3 (56.7–87.5)</td>
<td>94.1 (71.3–99.9)</td>
<td>55.6 (30.8–78.5)</td>
</tr>
<tr>
<td>Combined approach</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T2 ratio and LGE</td>
<td>88.9 (73.9–96.9)</td>
<td>77.8 (52.4–93.6)</td>
<td>100 (81.5–100)</td>
</tr>
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<td>72.2 (46.5–90.3)</td>
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<td>88.6 (73.3–96.8)</td>
<td>82.4 (56.6–96.2)</td>
<td>94.4 (72.7–99.9)</td>
</tr>
<tr>
<td>Native T1 and postcontrast T1 (t&lt;sub&gt;1&lt;/sub&gt;ms)</td>
<td>80.6 (64.9–90.8)</td>
<td>61.1 (35.7–82.7)</td>
<td>100 (81.5–100)</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

CMR indicates cardiovascular magnetic resonance; ECV, extracellular volume; and LGE, late gadolinium enhancement.

83.3% and a specificity of 88.9% to discriminate subjects with acute myocarditis from controls (Table 2 and Figure 2).

Figure 2. Diagnostic performance of T2 ratio, late gadolinium enhancement (LGE), T2-, native T1-, and postcontrast T1 relaxation times, as well as extracellular volume (ECV) to detect acute myocarditis. The graph shows the receiver-operating characteristic curves (ROC) analysis. MOLLI indicates Modified Look-Locker Inversion Recovery.
myocarditis from controls was <308.5 ms to achieve a sensitivity of 62.5% and a specificity of 100% (Table 2 and Figure 2).

**Extracellular Volume Fraction**

Even though patients with myocarditis had higher global ECV than controls (FU0: 0.26 [0.25–0.28] versus 0.24 [0.24–0.25]; FU1: 0.26 [0.25–0.27]; FU2: 0.24 [0.23–0.28]), the difference was not significant ($P=0.057$; Figure 3). The segmental analysis revealed regional ECV elevation in the lateral wall (Figure 5). This was true in subjects with LGE (elevation in segments 5 [$P=0.006$], 6 [$P=0.009$], 11 [$P<0.001$], and 12 [$P=0.004$]) and without LGE (elevation in segments 6 [$P=0.047$], 11 [$P<0.001$], and 12 [$P=0.004$]). The cutoff to discriminate patients with acute myocarditis from controls was 0.24 to achieve a sensitivity of 94.1% and a specificity of 55.6% (Table 2 and Figure 2).

The total ECV was significantly elevated in acute myocarditis patients (33.2 mL [29.2–41.2 mL]) compared with controls (27.1 mL [21.0–29.6 mL]; $P=0.001$) and persisted elevated throughout the follow-up (FU1: 32.7 mL [27.4–35.4 mL]; $P=0.004$; FU2: 32.0 mL [28.0–36.6 mL]; $P=0.004$). The total cellular volume was not different between the various myocarditis states and controls ($P=0.094$).

**Late Enhancement**

In FU0, 14/18 subjects had evidence of subepicardial or intramural LGE, mainly inferolateral (Figure 5). During follow-up, LGE was evident in 14 (FU1) and 13 (FU2) patients. The presence of LGE provided a sensitivity and specificity of 77.8% and 100% to detect acute myocarditis (Table 2 and Figure 2).

**Detection of Myocarditis: Combined Approach**

The diagnostic value of combinations of the diverse techniques is shown in Table 2. The highest diagnostic accuracy was achieved by the combination of T2 ratio with LGE (88.9%) and for the quantitative approaches: T2 times+native T1 times (86.1%), native T1 times+LGE (86.1%), and T2 times and LGE (83.3%).

**Discussion**

This study documents the value of a comprehensive quantitative CMR approach to make the diagnosis of acute myocarditis and to monitor the course of disease. We demonstrate that multiparametric mapping identifies myocardial injury in patients with high clinical suspicion of acute myocarditis and preserved LV ejection fraction. T2 mapping allowed the differentiation between acute and healed myocarditis, indicating myocardial edema as a reversible injury. Assessment of T1 mapping and ECV identified diseased patients, and the parameters represent both reversible (edema) and predominantly irreversible injury, that is, necrosis and fibrosis. The myocardial changes remained elevated during follow-up. LGE is known to reflect focal necrosis/fibrosis, usually indicating an irreversible injury, and
was also identifiable during the whole study period, if present. The advantage of the parametric techniques is its robustness in comparison to the established techniques.\textsuperscript{6,8}

The T2 relaxation times were significantly elevated in acute myocarditis, confirming recent other studies.\textsuperscript{8,9} The unique observation of this study is the gradual degradation of the T2 relaxation times during the follow-up until there was no statistical difference to controls left after 6 months. The T2 ratio took the same course as the T2 relaxation time did. Hence, one might argue that there is no added value for T2 mapping versus the conventional T2 ratio. Yet, the diagnostic accuracy of the T2 ratio was unexpectedly high in this study with 100%. Previous publications reported lower values of 70\% or 76\%.\textsuperscript{6,16}

The higher than expected success rate of the T2 ratio can be related to several factors. First, all CMR exams were done in a center with large experience with T2-weighted imaging, and the translation of this technical success rate to less experienced centers is questionable. Second, the study population mainly included subjects with high clinical suspicion of myocarditis because they predominantly presented acutely at an emergency department with infarct-like myocarditis. This group of patients is suspected to have a high prevalence of myocardial edema detectable by T2-weighted imaging, whereas less acute cases may be below the detectable threshold. Third, our population was characterized by a preserved ejection fraction and stable heart rhythm. T2-weighted imaging is usually more challenging in sick patients with high or irregular heart rate or pericardial effusion.\textsuperscript{5} Fourth, CMR imaging generally became more robust as hardware and software recently underwent various developments. Despite the evidence of superiority of the conventional T2-weighted imaging versus the novel T2 mapping, the latter offers some potential advantages: (1) all T2 maps were of diagnostic quality, confirming the high robustness of previous studies using the same technique\textsuperscript{8,20}; (2) the T2 quantification is independent from the skeletal muscle as a reference, which can be involved in the inflammatory process during myocarditis; (3) the segmental analysis of T2 maps enables detecting a heterogeneous distribution of T2 values throughout the myocardium. This provides insights into the pathogenesis of myocarditis as shown in this study and allows the identification of focal abnormalities. A recent study demonstrated that the variation of segmental T2 values and pixel standard deviation was much larger in patients with acute myocarditis compared with that in healthy controls.\textsuperscript{24} For these reasons, we and others anticipate that T2 mapping adds to or even replaces the T2 ratio to assess reversible myocardial injury in subjects with myocarditis.\textsuperscript{25}

The LLC include the global relative enhancement, which measures the early distribution and washout of the contrast agent within the first minutes after its administration, as a marker of inflammation and reversible myocardial damage in acute myocarditis.\textsuperscript{6} In this study, global relative enhancement was not a part of the study protocol. Instead, T1 maps were obtained repeatedly early after contrast agent administration. The postcontrast T1 times were significantly reduced in myocarditis subjects compared with those in the controls, which may be an indicator for capillary leakage and hyperemia as it has been suggested for global relative enhancement.\textsuperscript{6} Between the acute CMR and the subsequent follow-up, the mean postcontrast T1 value increased. However, its level still remained below that of the healthy controls. The constant reduction in postcontrast T1 is possibly induced by a chronic expansion of the ECV representing interstitial fibrosis. Therefore, reduced postcontrast T1 values are highly specific for diseased myocardium but are no perfect biomarker to differentiate between acute or healed myocarditis. In addition, absolute postcontrast T1 values are limited by being dependent from contrast agent dosage, renal function, or cardiac output and are, therefore, not recommended.\textsuperscript{12}

![Figure 4. Course of the T2-, native T1-, and postcontrast T1\textsubscript{rc} relaxation times, as well as extracellular volume (ECV) for each individual myocarditis patient during the follow-up. Red line indicates median value. FU indicates follow-up.](http://circimaging.ahajournals.org/doi/fig/10.1161/CIRCIMAGING.116.004703)
Figure 5. T2-, native T1-, and postcontrast T1 relaxation times, extracellular volume (ECV), and the presence of late gadolinium enhancement (LGE) per myocardial segment for myocarditis patients and controls. The outer ring represents the basal segments, the inner ring the midventricular segments. Segments with abnormal values compared with controls are highlighted in red and by asterisk. Results are presented as median and interquartile range or as frequency regarding LGE. FU indicates follow-up.
Focal LGE with myocarditis pattern was present in 77.8% of the myocarditis patients and persisted in all but one over the entire course of the follow-up. This observation emphasizes the high specificity of LGE to irreversible injury and is in concordance with previous reports. Sensitivity, however, remains a controversial issue because 22.2% of the patients had elevated troponin in the absence of any focal necrosis as assessed by LGE. Already, many years ago, this finding has been interpreted as an important confounder of LGE imaging in myocarditis, attributable to the inability to detect diffuse necrosis. In the meantime, T1 mapping has been introduced and histologically validated to detect diffuse myocardial damage. Several studies have already reported the additive value of elevated native T1 relaxation times in subjects with acute myocarditis, achieving a diagnostic accuracy of 61% to 99%, and the present study came to a result in between this range (78%). The cutoff, which discriminated best acute myocarditis subjects from healthy controls, was 980 ms, which is in the range of the 990 ms reported by Ferreira et al, and 992 ms by Hinojar et al, and 1000 ms by Luettekens et al.

At acute presentation, the elevated native T1 less probably represents fibrosis, but edema, hyperemia, and myocardial necrosis. This study demonstrated that the native T1 slightly decreased during early follow-up. As this occurs parallel to the reduction of the T2 ratio and the T2 times, it may represent the resolution of myocardial edema. Yet, when compared with controls, native T1 remained elevated throughout the follow-up even in the healed stage. Therefore, it transits to be a marker of interstitial fibrosis as it has been demonstrated in several disease groups like chronic ischemic cardiomyopathy, dilated cardiomyopathy, or valvular heart disease.

This observation is in concordance with a recent study that reported no difference of the myocardial T1 between patients with clinically suspected myocarditis and ongoing activity in myocardial biopsy, compared with patients with clinically suspected myocarditis and no ongoing activity. Hence, even though elevated native T1 occurs in the acute phase of myocarditis and serves as a discriminator toward healthy controls at that time, it remains elevated and can then be regarded as a marker of irreversible myocardial injury. Hinojar et al have recently published similar results. They performed a follow-up CMR in a subgroup of patients initially presenting with acute myocarditis. Thereby, native T1 values were found to be significantly lower in the follow-up scan, but still higher compared with those of control patients. Both studies revealed a steady decline in native T1 values from acute disease to chronic convalescence. Longer follow-ups are required to analyze whether the T1 values finally reach normal levels.

The ECV takes a similar course as native T1 and post-contrast T1. Even though statistically not significant, an ECV elevation was detectable in acute myocarditis that persisted during follow-up. The absence of statistical significance may be attributed to the small sample size, the variance of ECV, and the applied statistics. In addition, averaging ECV over the entire myocardium may be not sensitive enough to detect regional abnormalities, as underlined by the segmental analysis in this study that demonstrated significant differences between myocarditis and controls for several myocardial segments. Hence, even though global values seem easier to handle, postprocessing that facilitates the use of segmental or pixel-wise evaluations is required in the future. Moreover, the general level of ECV was lower in this study as compared with that in other studies. Although in the present study an ECV of 0.24 achieved the best results, this cutoff was 0.29 in the studies by Luettekens et al and by Radunski et al. This discrepancy may be explained by differences in the T1 techniques, timing of the postcontrast T1 maps, as well in the patient samples. For example, the population of the present study was younger as the one by Radunski et al. and had a higher ejection fraction (60% vs. 42%).

We know from previous experiences with CMR in myocarditis that the combination of CMR techniques might be superior to single techniques. In the present study sample, some single techniques (like T2 ratio and T2 mapping) have already shown to achieve high diagnostic accuracies, so the combination with a weaker partner does not automatically strengthen its value. From a practical point of view, the presence of elevated T2 ratio or T2 times in a subject with clinically suspected acute myocarditis is highly accurate to make the diagnosis of acute myocarditis. If the combinations T2 ratio or T2 times+LGE with myocarditis pattern or T2 ratio or T2 times+native T1 times are abnormal, the diagnosis of acute myocarditis is even more secure because it is based on 2 parameters. Taking all the current knowledge together, one could assume that during a follow-up in known myocarditis or in severe renal failure, if only disease activity has to be investigated, a contrast media-free approach may be adequate.

In conclusion, we demonstrated for a group of patients with high clinical suspicion of myocarditis and preserved LV ejection fraction that edema assessment by quantitative T2 mapping reliably discriminated between acute myocarditis and controls and provided insight into the stage of disease. The discrimination between healthy and diseased was reliable based on the quantification of native T1 and postcontrast T1, but it was less helpful to differentiate between acute and convalescent myocarditis. Therefore, T2 mapping and native T1 mapping seem to be valuable additions of the still important conventional techniques, that is, edema evaluation by T2-weighted imaging and focal fibrosis imaging by LGE to make the diagnosis of acute myocarditis and to monitor the disease activity. CMR is able to differentiate patients with acute, active myocarditis from more chronic stages, but larger trials including different stages of myocarditis are needed.

Limitations of the Study

A debatable limitation of this study is that disease definition was based on clinical validation of suspected myocarditis rather than endomyocardial biopsy as a reference standard. The selection of the study population may be regarded as a confounder because only subjects with a strong clinical suspicion of myocarditis were included. The performance of the tested methods in subjects with less clear clinical presentation has to be determined in future, larger, ideally multicenter studies. Another limitation of the present study is its focus on the analysis of the diagnostic accuracy to differentiate acute myocarditis from healthy controls. The capability of CMR to detect and discriminate chronic phases of myocarditis during the longitudinal follow-up of the study was not addressed in detail because the definition of the type of chronic phase (eg,
active versus healed) is generally challenged by the absence of a clear reference and because other indirect markers of ongoing inflammation (eg, troponin, B-type natriuretic peptide) were not assessed systematically. Furthermore, the sample sizes of such subgroup analyses would be inappropriate. This aspect may also be elucidated in a larger longitudinal study. The authors focus on the use of CMR to discriminate diseased patients from controls. However, the differentiation of patients with acute, active myocarditis from more chronic stages is also an important target and should be addressed in this longitudinal study.

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References
Making the diagnosis of myocarditis is a frequent clinical challenge, with significant impact on the individual subject’s life. Cardiovascular magnetic resonance contributes important information in this clinical scenario, but currently applied techniques have known limitations. This study evaluated quantitative cardiovascular magnetic resonance, including T1 and T2 mapping, to detect and monitor acute myocarditis in 18 patients with a clinical diagnosis of acute myocarditis compared with 18 controls. Patients had significantly higher myocardial T2 times acutely compared with controls that decreased during follow-up, representing the course of myocardial inflammation/edema. Myocardial T1 times were also elevated, but remained abnormally high during follow-up, potentially representing both acute myocardial injury and myocardial remodeling during convalescence. In conclusion, both T2 and T1 mapping reliably detected acute myocarditis, but only T2 mapping discriminated between acute and healed stages, underlining the incremental value of T2 mapping. Hence, this study adds to the current evolution that quantitative cardiovascular magnetic resonance with T1 and T2 mapping may become essential components of a comprehensive cardiovascular magnetic resonance assessment of myocarditis.
Detection and Monitoring of Acute Myocarditis Applying Quantitative Cardiovascular Magnetic Resonance
Florian von Knobelsdorff-Brenkenhoff, Johannes Schüler, Serkan Dogangüzel, Matthias A. Dieringer, Andre Rudolph, Andreas Greiser, Peter Kellman and Jeanette Schulz-Menger

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SUPPLEMENTAL MATERIAL

Supplemental Methods

CMR image acquisition parameters

**SSFP cine imaging:** ECG triggered with retrogating, repetition time (TR) 34.7 ms, 30 reconstructed phases, echo time (TE) 1.2 ms, field of view (FOV) 340x276 mm², matrix 256x146, slice thickness (ST) 7 mm, flip angle (FA) 70°, GRAPPA acceleration factor 2.

**T2-weighted imaging:** ECG triggered, Turbo factor 25, shot time 200 ms, TE 60 ms, inversion time (TI) 170 ms, FOV 340x309 mm², matrix 256x256, ST 20 mm, FA 180°.

**T2 mapping:** T2 prep times 0, 25 and 55 ms, 3 recovery heartbeats, shot time 190 ms, TR 2.4 ms, TE 1.1 ms, FA 70°, FOV 340x288 mm², matrix 224x190, ST 6 mm, GRAPPA acceleration factor 2, motion corrected.

**T1 mapping:** 5(3)3 MOLLI acquisition scheme, TI(min) 120 ms, TR 2.4 ms, TE 1.1 ms, shot time 190 ms, FA 35°, FOV 360x270 mm², matrix 224x168, ST 6 mm, GRAPPA acceleration factor 2, motion corrected.

**Late enhancement (LGE):** echo spacing 10.4 ms, shot time 261 ms, TI 300 ms, TE 5.4 ms, FA 30°, FOV 350x263 mm², matrix 256x197, ST 7 mm, PSIR reconstruction.