Cardiomyopathies

Comprehensive Cardiovascular Magnetic Resonance Assessment in Patients With Sarcoidosis and Preserved Left Ventricular Ejection Fraction

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Background—Cardiac sarcoidosis (CS) may manifest as arrhythmia or even sudden cardiac death. Because patients with CS often present with nonspecific symptoms, normal electrocardiography, and preserved left ventricular ejection fraction, a reliable diagnostic tool for the work-up of CS is needed. Late gadolinium enhancement—cardiovascular magnetic resonance has proven diagnostic value in CS but has some limitations that may be overcome by adding newer cardiovascular magnetic resonance mapping techniques. The aim of our study was to evaluate a comprehensive cardiovascular magnetic resonance protocol, including late gadolinium enhancement and mapping sequences in sarcoid patients with no symptoms or unspecific symptoms and preserved left ventricular ejection fraction.

Methods and Results—Sixty-one sarcoid patients were prospectively enrolled and underwent comprehensive cardiovascular magnetic resonance imaging. Twenty-six healthy volunteers served as control group. Mean left ventricular ejection fraction was 65%; late gadolinium enhancement was only present in sarcoid patients (n=15). Sarcoid patients had a higher median native T1 (994 versus 960 ms; P<0.001), lower post contrast T1 (491 versus 526 ms; P=0.001), expanded extracellular volume (28 versus 25%; P=0.001), and higher T2 values (52 versus 49 ms; P<0.001) compared with controls. Among patients with values higher than the 95% percentile of healthy controls, most significant differences were observed for native T1 and T2 values. Most of these patients were late gadolinium enhancement negative.

Conclusions—Patients with sarcoidosis demonstrate higher T1, extracellular volume, and T2 values compared with healthy controls, with most significant differences for native T1 and T2. While promising, the clinical significance of the newer mapping techniques with respect to early diagnosis and therapy of CS will have to be determined in future studies.

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Key Words: cardiomyopathies ■ early diagnosis ■ gadolinium ■ healthy volunteers ■ sarcoidosis

Sarcoidosis is a systemic granulomatous inflammatory disease of unknown origin, which can affect the myocardium in addition or isolated. The incidence of sarcoidosis in the United States has been estimated at 10.9 per 100,000 in whites and at 35.5 per 100,000 in blacks every year.1

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Cardiac sarcoidosis (CS) may initially manifest as arrhythmia or even sudden cardiac death, which is a frequent cause of death in these often young to middle-aged patients.2,3 However, the diagnosis of CS remains challenging because many patients present with none or unspecific symptoms, no relevant electrocardiography (ECG) abnormalities, and preserved left ventricular ejection fraction (LVEF). Consequently, there is a need of a reliable diagnostic tool for the work-up of CS.

Cardiovascular magnetic resonance (CMR) is such a new tool, offering functional assessment, as well as tissue characterization without any radiation. Recent data suggest a prevalence of CS in the range of 20% to 26%, as detected by late gadolinium enhancement (LGE)-CMR.4–6 Moreover, LGE-CMR seems to offer both diagnostic and prognostic implications in patients with sarcoidosis because several studies revealed LGE as a prognostic parameter, especially valuable if the LVEF is normal.6,7 However, despite an excellent negative predictive value of LGE-CMR, the positive predictive value of this technique seems to be moderate only, performing best in detecting focal rather than diffuse processes.7,8

As a result of these limitations, there is gaining interest in newer CMR protocols including T1 and T2 mapping, which

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may add value for the detection of inflammation and diffuse myocardial processes.9,10

Consequently, the aim of our study was to evaluate a comprehensive CMR protocol, including established LGE and new T1- and T2-mapping techniques in sarcoid patients with no symptoms or unspecific symptoms and a preserved LVEF (≥50%) for potential cardiac involvement.

Methods

Patient Population

Sixty-four patients presenting at our institution between April 2014 and January 2016 were prospectively enrolled if they fulfilled the following criteria: (1) systemic sarcoidosis diagnosed by biopsy or clinical criteria; (2) no history of coronary artery disease, myocardial infarction, or previous revascularization; and (3) successfully underwent CMR imaging. Patients fulfilling the latter criteria were enrolled regardless of potential symptoms or ECG abnormalities as part of screening for cardiac involvement beside their routine clinical care; n=3 patients withdrew consent and were excluded. Overall, 61 patients could be included in the final report.

Healthy volunteers (n=26) with no history of cardiac disease, no medication, and free of symptoms served as control group. Before CMR, all participants provided a blood sample for the measurement of hematocrit. Patients gave written informed consent, and the data collection has been approved by the ethics committee of the University of Tübingen, Germany.

CMR Protocol

ECG-gated CMR was performed in breath-hold using a 1.5-T MAGNETOM Aera (Siemens Healthcare, Erlangen, Germany) in line with current recommendations.11 Both cine and LGE short-axis images were prescribed every 10 mm (slice thickness 6 mm) from base to apex. In-plane resolution was typically 1.2×1.8 mm. Cine was performed using a steady state–free precession sequence. LGE images were acquired on an average of 5 to 10 minutes after contrast using a segmented inversion recovery gradient echo sequence,11 constantly adjusting inversion time to null normal myocardium.12,13 The contrast dose (gadopentetate) was 0.15 mmol/kg.

A modified Look-Locker inversion recovery prototype sequence was used for T1 mapping and performed in a single midventricular short-axis slice at mid-diastole, before and after 20 minutes of administration of gadodiamide, in line with current recommendations.14,15

Short-axis T2 mapping was performed in a matching midventricular short axis before the administration of contrast agent using an ECG-triggered T2-prepared single-shot balanced steady-state free precession prototype sequence with multiple T2 preparation times.16

More detailed information on CMR protocol is provided in the Table 1 in the Data Supplement.

CMR Analysis

Cine and LGE images were evaluated by experienced observers (S.G. and H.M.) as described elsewhere.6 In brief, endocardial and epicardial borders were outlined on the short-axis cine images. Volumes and ejection fraction were derived by the summation of endocardial and epicardial contours. Extent of LGE was assessed using QMass software (Medis, Leiden, The Netherlands), and the results were expressed as percentage of myocardial mass. The distribution of LGE was characterized as epicardial, intramural, transmural, or subendocardial.

Color-coded T1, extracellular volume (ECV), and T2 maps were generated based on inline-generated, motion corrected raw images using QMap software 1.0 (Medis) in a single matching midventricular short axis. Motion-corrected T1 maps were examined for quality of LGE was characterized as epicardial, intramural, transmural, or subendocardial.8

Using the anterior right ventricular insertion point as reference. Care was taken to avoid partial volume effects at the endocardial and epicardial borders for T1, ECV, and T2 maps. Global T1, ECV, and T2 values were calculated. T1 values were determined by fitting an exponential model to the measured data.17 Before CMR, the hematocrit was determined in all subjects, allowing with native and post contrast T1 measurements of the myocardium and blood pool the calculation of ECV, using a previously described equation.19 T2 results were obtained by fitting a 2 parameter intensity-weighted exponential model (no offset term).19

Statistical Analysis

Absolute numbers and percentages were computed to describe the patient population. All continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as means (with SD), and skewed variables were presented as medians (with quartiles). Comparisons between groups were made using the Mann–Whitney U test or the Fisher exact test, as appropriate. P values (2-tailed) of <0.05 were considered significant. All statistical analyses were performed using SPSS, version 22.0 (IBM Corp, Armonk, NY).

Results

Patient Characteristics

In total, n=87 subjects were included in the final analysis. Table 1: n=61 patients with systemic sarcoidosis, n=26 healthy individuals served as an age- and sex-matched control group. At inclusion, sarcoid patients were 50±10 years of age, predominantly male (59%), and did not differ from the control group (48±14 years of age, 50% males, P=0.50 and P=0.44, respectively).

Unspecific dyspnea and angina were the most frequently reported symptoms (62% and 30%, respectively). ECG abnormalities were detected in 16% of the patients only. The most common sites of sarcoid manifestation were lungs (92%), followed by lymph nodes (26%) and skin (11%).

The majority of the patients (43%) was diagnosed with sarcoidosis recently (within the last 12 months before CMR), 54% of the patients were on steroids during the time of CMR. Further patient characteristics can be viewed in Table 1.

CMR Findings

CMR findings are displayed in Table 2. The mean LVEF was 65% in our sarcoid patients and was, thus, not different to the control group (P=0.57). Furthermore, no significant differences in functional CMR parameters (LV size, mass, etc.) could be detected between sarcoid patients and controls.

LGE was present in 15 (25%) of the sarcoid patients, most commonly occurring in a nonischemic pattern (epicardial or intramural). No subject of the control group had evidence of LGE.

Looking at sarcoid patients with ECG abnormalities (n=10) revealed a higher frequency of LGE versus patients with no ECG abnormalities (n=51), P=0.001, Table 3.

T1 and ECV Results

We found higher native T1 values in our sarcoid patients: 994 (975–1039) ms versus 960 (942–986) ms in controls, P<0.001 (Table 2; Figure 1A). This holds true for LGE-positive sarcoid patients: 1004 (981–1103) ms, P=0.003 and for LGE-negative sarcoid patients: 989 (972–1036) ms, P=0.001. Conversely,
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sarcoid patients showed decreased post contrast T1 values in comparison to controls: 491 (470–517) ms versus 526 (509–552) ms, \( P=0.001 \). Again, this effect seems to be independent of the presence of LGE: 490 (425–506) ms in LGE-positive patients and 494 (475–523) ms in LGE-negative patients, \( P<0.001 \) and \( P=0.006 \), respectively (Table 2; Figure 1B).

For T1-derived ECV measures, sarcoid patients demonstrated significantly higher values: 28% (26%–30%) versus 25% (23%–27%) in the control group, \( P=0.001 \), regardless of their LGE status (Table 2; Figure 1C). Figure 2 displays a typical example for myocardial mapping in an LGE-positive sarcoid patient.

Native and post T1 values and ECV did not differ in sarcoid patients with ECG abnormalities versus sarcoid patients with no ECG abnormalities (\( P=0.38 \), \( P=0.13 \), and \( P=0.88 \); Table 3).

\section*{T2 Results}

Median myocardial T2 values were significantly higher in patients with sarcoidosis than in controls: 52 (50–55) ms versus 49 (48–50) ms, \( P<0.001 \) (Table 2; Figure 1D). This difference remains significant by dividing our sarcoid population in an LGE-positive and an LGE-negative group: 53 (51–60) ms and 52 (49–54) ms, \( P<0.001 \) for both. These findings are illustrated in Figure 3, in which an LGE-negative sarcoid patient demonstrated increased values for T2 and native T1 and decreased values for post contrast T1 in comparison to the median values in controls.

Patients with ECG abnormalities demonstrated significantly higher myocardial T2 values compared with patients with unremarkable ECG: 55 (53–61) ms versus 51 (49–53) ms, \( P=0.006 \) (Table 3).

\section*{Values Above the 95\% Percentile of Normal}

When using the 95\% percentile of our control group as a threshold for defining abnormal values, we found values above 1031 ms for native T1, below 455 ms for post contrast T1, above 32.8\% for ECV, and above 54.3 ms for T2 to be abnormal (Figure 4).
Among our sarcoid patients, n=17 demonstrated a native T1 value above the 95% percentile of our control group. In detail, n=12 patients were LGE negative and n=5 patients were LGE positive (Figure 4A). In n=10 patients, post contrast values were below 455 ms: n=4 of these were LGE negative and n=6 were LGE positive (Figure 4B).

Looking at ECV revealed that n=5 patients had values above the 95% percentile: n=3 were classified as LGE negative and n=2 as LGE positive (Figure 4C). Almost 25% (15 of 61 sarcoid patients) of patients showed increased T2 values above the 95% percentile of controls: n=10 LGE were negative and n=5 were LGE positive (Figure 4D).

Five of 10 patients (50%) with ECG abnormalities showed T2 values above the 95% percentile of healthy controls (>54 ms), 80% of them were LGE positive. However, 1 of 3 LGE-negative patients with ECG abnormalities demonstrated increased T2 value above the 95% percentile.

**Discussion**

To the best of our knowledge, this is the first study evaluating cardiac involvement in patients with sarcoidosis and preserved LVEF by a comprehensive CMR approach, including LGE-CMR, as well as newer T1- and T2-mapping techniques. The main findings are (1) patients with sarcoidosis show increased

<table>
<thead>
<tr>
<th>Table 2. CMR Findings</th>
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<tbody>
<tr>
<td>Controls (n=26)</td>
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<tr>
<td>LVEF, %</td>
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<tr>
<td>LV-EDV, mL</td>
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<tr>
<td>LV-ESV, mL</td>
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<td>LV-SV</td>
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<tr>
<td>LV-EDD</td>
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<td>LA, cm²</td>
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<tr>
<td>IVS, mm</td>
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<td>PA, mm</td>
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<tr>
<td>LV mass, g</td>
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<tr>
<td>LGE</td>
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<tr>
<td>Epicardial</td>
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<tr>
<td>Intramural</td>
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<tr>
<td>Transmural</td>
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<tr>
<td>Subendocardial</td>
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<tr>
<td>% LV mass</td>
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<tr>
<td>Native T1 (ms)</td>
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<tr>
<td>Post contrast T1 (ms)</td>
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<tr>
<td>ECV</td>
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<tr>
<td>T2 (ms)</td>
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</table>

Patients divided by presence of LGE

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=26)</th>
<th>LGE-Negative Patients (n=46)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native T1, ms</td>
<td>960 (942–986)</td>
<td>989 (972–1036)</td>
<td>0.001</td>
</tr>
<tr>
<td>Post contrast T1, ms</td>
<td>526 (509–552)</td>
<td>491 (470–517)</td>
<td>0.006</td>
</tr>
<tr>
<td>ECV</td>
<td>25 (23–27)</td>
<td>28 (26–29)</td>
<td>0.002</td>
</tr>
<tr>
<td>T2, ms</td>
<td>49 (48–50)</td>
<td>52 (49–54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Controls (n=26)</td>
<td>LGE-Positive Patients (n=15)</td>
<td></td>
</tr>
<tr>
<td>Native T1, ms</td>
<td>960 (942–986)</td>
<td>1004 (981–1103)</td>
<td>0.003</td>
</tr>
<tr>
<td>Post contrast T1, ms</td>
<td>526 (509–552)</td>
<td>490 (425–506)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECV</td>
<td>25 (23–27)</td>
<td>29 (26–30)</td>
<td>0.01</td>
</tr>
<tr>
<td>T2, ms</td>
<td>49 (48–50)</td>
<td>53 (51–60)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

All values are mean±SD, or median with interquartile ranges. CMR indicates cardiac magnetic resonance; ECV, extracellular volume; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; IVS, interventricular septum; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; PA, pulmonary artery; and SV, stroke volume.
native T1, ECV, T2, and decreased post contrast T1 values compared with controls; (2) this holds true for LGE-positive patients (which is highly suggestive of CS by current guidelines) and LGE-negative patients; (3) abnormal values beyond the 95% percentile of healthy controls might help to detect CS even in the absence of standard signs of myocardial disease, such as LGE or impaired LVEF; and (4) beside LGE, native T1 mapping and T2 mapping seem to be the best parameters to separate between sarcoid patients and healthy controls.

### Patient Characteristics
The majority of patients were middle-aged and male, in line with previous reports. Usually, minor symptoms were reported, underscoring that the diagnosis of CS is challenging because of its unspecific clinical presentation. Furthermore, ECG abnormalities were detected in only 16%.

The most common sites of sarcoid manifestation were the lung (92%), followed by lymph node (26%) and skin (11%), which is in accordance with other studies. In contrast to another report, however, most of our patients (43%) were diagnosed having sarcoidosis within the past 12 months before CMR, reflecting a patient population presenting in an early stage of the disease. More than half of the patients (54%) were on steroids during the time of CMR, which is comparable to other reports.

### General CMR Results
The mean LVEF was preserved (65%) in our sarcoid population, and cardiac dimensions were similar to the healthy control group, reflecting the need of further tissue characterization to detect CS. In comparison to the control group, however, LGE was present in n=15 (25%) of the sarcoid patients, occurring in a nonischemic pattern in line with other reports.

### T1 and ECV Results
We found significantly higher native T1 values and expanded ECV in our sarcoid patients compared with controls (Table 2; Figure 1A and 1C). Of note, median native T1 values and median ECV values of our control group were completely in line with the native T1 values and ECV of a large population with more than 100 healthy subjects described previously, underscoring the validity of our mapping techniques. Native T1 was the best parameter (P<0.001) to separate between controls and sarcoid patients in the overall sarcoid population, confirming the results of a recent study in patients with systemic lupus erythematosus, who had also preserved LVEF.

Furthermore, our sarcoid patient native T1 and ECV values were in the same range because the values reported in patients with suspected myocarditis. Significant differences in T1, ECV, and T2 values compared with controls were even detectable in LGE-negative patients, pointing toward a subclinical myocardial involvement of CS. This finding matches reports from patients with other inflammatory cardiomyopathies, for example, myocarditis, systemic lupus erythematosus, and rheumatoid arthritis.

To date, only scarce data are available for native T1 mapping in sarcoid patients. In a report of a patient with initially unknown nonischemic cardiomyopathy and extensive regions of LGE, native T1 values were increased (1064 ms) even in regions without LGE. The authors interpreted this finding as being from inflammatory origin. This finding, in addition to the peculiar LGE pattern, was highly suggestive of sarcoidosis, which could be confirmed by thoracic lymph node biopsy. Immunosuppressive therapy was started and 2 years later, native T1 decreased to 1008 ms, indicating the attenuation of the myocardial inflammation, pointing toward a potentially reversible state of the involved myocardium. Interestingly, LGE images were consistent in its distribution and extent compared with the examination 2 years before.

These findings support the potential role of T1 mapping for monitoring in patients with sarcoidosis because this technique seems to offer better characterization of disease activity and response to immunosuppressive medication than LGE alone, which cannot differentiate acute from chronic processes. However, as mentioned above, we have to keep in mind that increased native T1 and ECV values are nonspecific and might represent either myocardial inflammation or myocardial fibrosis.

### T2 Results
In contrast to the latter techniques, myocardial T2 values show a close correlation with free tissue water content, suggesting a possible diagnostic value for the detection of active myocardial inflammation. Recently developed T2 mapping seems to overcome the well-known limitations of previously

### Table 3. ECG Normal vs ECG Abnormal

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ECG Normal (n=51)</th>
<th>ECG Abnormal (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>66±6</td>
<td>57±6</td>
<td>0.13</td>
</tr>
<tr>
<td>LV-EDV, mL</td>
<td>118±27</td>
<td>132±40</td>
<td>0.28</td>
</tr>
<tr>
<td>LV-EVF, mL</td>
<td>40±13</td>
<td>53±25</td>
<td>0.10</td>
</tr>
<tr>
<td>LV-SV</td>
<td>76±16</td>
<td>78±23</td>
<td>0.85</td>
</tr>
<tr>
<td>LV-EDD</td>
<td>47±4</td>
<td>51±5</td>
<td>0.09</td>
</tr>
<tr>
<td>LA, cm²</td>
<td>20±4</td>
<td>23±6</td>
<td>0.16</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>10±2</td>
<td>12±2</td>
<td>0.005</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>89±23</td>
<td>116±56</td>
<td>0.25</td>
</tr>
<tr>
<td>LGE</td>
<td>8 (16%)</td>
<td>7 (70%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Epicardial</td>
<td>3 (6%)</td>
<td>3 (30%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intramural</td>
<td>6 (12%)</td>
<td>5 (50%)</td>
<td>0.001</td>
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<tr>
<td>Transmural</td>
<td>...</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>2 (4%)</td>
<td>3 (30%)</td>
<td>0.001</td>
</tr>
<tr>
<td>% LV mass</td>
<td>5</td>
<td>11.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Native T1 (ms)</td>
<td>1001 (976–1039)</td>
<td>988 (952–1024)</td>
<td>0.38</td>
</tr>
<tr>
<td>Post contrast T1 (ms)</td>
<td>495 (473–521)</td>
<td>489 (447–495)</td>
<td>0.13</td>
</tr>
<tr>
<td>ECV (%)</td>
<td>28 (26–29)</td>
<td>30 (24–31)</td>
<td>0.88</td>
</tr>
<tr>
<td>T2 (ms)</td>
<td>51 (49–53)</td>
<td>55 (53–61)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

All values are n or mean±SD or interquartile ranges. ECG indicates electrocardiography; ECV, extracellular volume; EDV, end-diastolic volume; ESV, end-systolic volume; IVS, interventricular septum; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricular; PA, pulmonary artery; and SV, stroke volume.
described T2-weighted sequences (eg, proneness to artifacts, heart rate dependence, etc.) and provide both a more objective and precise method for the detection of inflammatory conditions. Indeed, as sarcoidosis is a systemic granulomatous inflammatory disease, median myocardial T2 values were significantly higher in patients with sarcoidosis than in controls (Table 2; Figure 1D) and T2 performs as good as native T1 to separate controls from sarcoid patients (both \( P < 0.001 \)). This difference remains significant by dividing our sarcoid population in an LGE-positive and an LGE-negative group, under-scoring the benefit of T2 mapping compared with LGE-CMR alone.

Our data are also supported by Crouser et al, who found in a retrospective analysis of 50 subjects with histologically proven sarcoidosis that 54% of the patients had significantly elevated T2 values compared with healthy controls. However, they used a threshold of >59 ms to indicate abnormal T2, which was exceeded only by \( n = 6 \) patients in our study. Reasons for this may be (1) different patient populations: (a) almost half of our sarcoid patient had been diagnosed with sarcoidosis within the past 12 months before CMR and (b) all patients of our study showed preserved LVEF versus 80% in the latter study, (2) different grades of inflammation because of different immunosuppressive treatment regimen, and (3) differences in the analysis of the T2 maps: measurement of global T2 in the entire slice (with the risk of averaging T2 values) in our study versus measurement of maximum (peak) myocardial T2 in a (subjective) region of interest.

However, in line with our results, T2 mapping seems to provide complementary information to detect CS beside the use of LGE-CMR because 41% of the LGE-negative patients demonstrated T2 abnormality, compared with 22% of the LGE-negative patients in our study. Another similarity with the study of Crouser et al are the findings that sarcoid patients with ECG abnormalities show significantly higher T2 values and a greater prevalence of LGE compared with patients with normal ECG, \( P = 0.006 \) and \( P = 0.001 \), respectively. Of note, T2 values of our control group were in line with the results of other groups. Because increased T2 values are thought to represent reversible processes, T2 mapping seems promising to serve as a novel quantitative biomarker during the clinical

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**Figure 1.** Box plots for median native T1 (A), post contrast T1 (B), extracellular volume (ECV) fraction (C), and T2 mapping (D) in controls, all sarcoid patients, late gadolinium enhancement (LGE)–negative sarcoid patients, and LGE-positive sarcoid patients; the center line in each box represents the median, whereas the lower and upper limits of each box represent the 25th and 75th percentiles, respectively. Sarcoid patients (all, LGE negative, and LGE positive) showed values which were significantly different to the values of the control group; */**/*** each \( P \leq 0.01 \).
course of the disease. Further head-to-head comparison studies will show, if T2 mapping (as long as there are no contraindications for CMR) might be comparable to positron emission tomography, which is nowadays the preferred method for the assessment of myocardial inflammation in patients with suspected CS. However, in contrast to positron emission tomography, T2 mapping has no need for ionizing radiation and careful metabolic patient preparation.

Values Above the 95% Percentile of Normal

Although differences in T1 and T2 values between sarcoid patients and controls turned out to be highly significant, there is some overlap in values, which make a reliable diagnosis of CS in individual sarcoid patients challenging (Figure 1). To address this point, we used the 95% percentile of our control group as a threshold for definite abnormal values in sarcoid patients. We found that the majority of abnormal values were reported for native T1 (n=17) and T2 (n=15), reflecting to be the most promising techniques for the potential detection of CS again. Interestingly, 70% of these patients with elevated T1 native values and two thirds of the patients with elevated T2 values were LGE-negative (Figure 4). As mentioned above, this underscores a rather synergistic than summative value of mapping techniques in concert with LGE.

Clinical Implications

Our data demonstrate the potential role of mapping sequences in addition to LGE-CMR for the detection of CS, since we found that patients with sarcoidosis demonstrate higher T1, ECV, and T2 values compared with healthy controls. Furthermore, our data reveal that native T1 mapping and T2 mapping are the best parameters to separate between normal subjects and sarcoid patients. These findings are independent of the presence of LGE, which would make CS probable because of a current statement. Among patients with values higher than the 95% percentile of healthy controls, most significant differences were observed for native T1 and T2 values.

On the basis of these data, it may be safe to propose the following diagnostic algorithm for a comprehensive CMR protocol in patients with suspected CS: (1) LGE-CMR: (a) if positive, CS is probable and (b) if negative, further mapping

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**Figure 2.** Cardiac magnetic resonance of a 44-year-old female presenting with palpitations and right bundle-branch block. Cine images revealed a preserved left ventricular ejection fraction (51%) with hypokinesia in the anterior wall. Late gadolinium enhancement (LGE) demonstrated a diffuse pattern of epicardial, intramural, and transmural enhancement in the anterior wall (black arrows), suggestive of cardiac sarcoidosis (CS). Native T1 map showed an increased T1 with 1040 ms (normal median range 960 [942–988] ms), expanded extracellular volume (ECV) of 36% (normal median range 25 [23–27] %), and decreased postcontrast T1 with 452 ms (normal median range 526 [509–552] ms). Coronary artery disease could be ruled out by coronary angiography, and endomyocardial biopsy confirmed CS.
techniques are warranted and (2) T1 native and T2 values above the 95% percentile, as the best discriminators to controls, would make CS probable, even in the absence of LGE.

This approach may be of future clinical importance because CS may otherwise be missed in those patients because of non-specific symptoms, normal ECG, and preserved LVEF and might result in sudden cardiac death as the first clinical manifestation. However, the absence of LGE in combination with normal T1 and T2 values would significantly decrease the likelihood of CS. Nevertheless, additional evaluation is required before this algorithm can be used for the clinical routine.

Important to mention that current AHA guidelines for device-based therapy of cardiac rhythm abnormalities do not acknowledge current CMR-based myocardial characterization techniques or other imaging modalities. Consideration should rather be given to clinical symptoms, LV function, and arrhythmia at electrophysiological studies in combination with the treating physicians experience and available literature to make individualized decisions about defibrillator placement for the primary prevention of sudden cardiac death. Therefore, large randomized trials or prospective registries focusing on myocardial imaging techniques (including comprehensive CMR protocols) are warranted to strengthen the role of imaging modalities in patients with CS about defibrillator implant.

Limitations
This is a single-center study, so potential center-specific bias cannot be excluded. However, as most mapping sequences are vendor- and center specific, this setting seems even favorable. Moreover, there is still a lack of established normal values and thresholds, so centers are encouraged to establish their own normal values and thresholds on healthy controls, as we did, and which is suggested by current recommendations.

It might be criticized that measuring global myocardial T1 or T2 values in a single midventricular slice might tend to miss a focal process because of averaged values. However, this standardized approach is a common practice less subjective than just drawing individualized regions of interest,

Figure 3. Cardiac magnetic resonance (CMR) of a 27-year-old female with a history of pulmonary sarcoidosis since 2 mo. She was experiencing recurrent anginal pain. CMR revealed a preserved LVEF (64%) with normal cardiac dimensions. Late gadolinium enhancement (LGE) images revealed no LGE. However, native T1 (1004 ms), extracellular volume (ECV, 26%), and T2 (53 ms) were increased, and post contrast T1 (483 ms) decreased compared with our control group (median native T1 960 ms, ECV 25%, post contrast T1 526 ms, and T2 49 ms).
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and might be even better comparable to a potential follow-up examination, for example, for the evaluation of response to treatment. Furthermore, for a comprehensive CMR approach, which compares the power of different techniques (native T1, post contrast T1, ECV, and T2), it is crucial that these measurements are made in matching locations, which would be hard to achieve for individualized drawn regions of interest. Although controls did not differ significantly to our sarcoid population by age and sex, healthy controls introduce a potential bias and are not equal to patients with sarcoidosis who do not have cardiac involvement. Furthermore, the 95th percentile is specific to this set of controls, which is small in size. Endomyocardial biopsy was not routinely performed. However, it is well known that endomyocardial biopsy has several limitations, for example, invasiveness, sampling error, and lowering its diagnostic benefit. Furthermore, in oligosymptomatic patients with preserved LVEF, this would be a rather unethical approach and not in line with the current guidelines.

Whether abnormalities by T1 and T2 mapping in patients with sarcoidosis represent CS remains elusive. However, 3 successive histological stages are described for CS: (1) edema, (2) granulomatous inflammation, and (3) fibrosis yielding to postinflammatory scar. T1 and T2 mapping seem to be superior to LGE in the detection of inflammation and diffuse myocardial processes, which could be shown for various other cardiac diseases (eg, myocarditis and systemic lupus erythematosus), with some of them even confirmed by endomyocardial biopsy. These potentially reversible changes in myocardial condition detected by mapping techniques might precede irreversible fibrosis (detected by LGE) in currently LGE-negative sarcoid patients. However, as LGE-negative sarcoid patients yield excellent prognosis, abnormal T1- and T2-mapping results, even if they represent early disease, carry uncertain clinical significance. To date, treatment of such abnormalities is not warranted, but significance of these findings should be evaluated by future longitudinal studies, preferably including a combination of clinical and comprehensive CMR follow-up studies in patients with sarcoidosis.

Conclusions

In our population of patients with extra-CS and preserved LVEF, we found increased values for native T1, ECV, and T2 compared with controls, irrespective of the presence of LGE. Native T1 and T2 were the best discriminators from controls. Although promising, the clinical significance of the newer mapping techniques with respect to early diagnosis and therapy of CS will have to be determined in future studies.

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References
Our data demonstrate the potential role of mapping sequences in addition to late gadolinium enhancement (LGE)–cardiovascular magnetic resonance for the detection of cardiac sarcoidosis (CS) in patients with sarcoidosis, since we found that patients with sarcoidosis demonstrate higher T1, extracellular volume, and T2 values compared with healthy controls. Furthermore, our data reveal that native T1 mapping and T2 mapping are the best parameters to separate between normal subjects and sarcoid patients. These findings are independent of the presence of LGE, which would make CS probable according to the current guidelines. Patients with values higher than the 95% percentile of healthy controls showed the most significant differences for native T1 and T2 values. On the basis of these data, the following approach for a comprehensive cardiovascular magnetic resonance protocol in patients with suspected CS might be appropriate: (1) LGE-cardiovascular magnetic resonance: (a) if positive, CS is probable and (b) if negative, further mapping techniques are reasonable and (2) T1 native and T2 values above the 95% percentile, as the best discriminators to controls, would make CS more probable, even in the absence of LGE. This approach may have clinical impact, as CS may otherwise be missed in those patients because of nonspecific symptoms, normal ECG, and preserved LVEF and might result in sudden cardiac death as the initial clinical manifestation. However, negative LGE and normal T1 and T2 values would make CS unlikely. Although promising, the clinical significance of the newer mapping techniques with respect to early diagnosis and therapy of CS will have to be determined in future studies.
Comprehensive Cardiovascular Magnetic Resonance Assessment in Patients With Sarcoidosis and Preserved Left Ventricular Ejection Fraction


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**Supplemental Material**

*CMR protocol*

**T2 Mapping**

T2 mapping was performed in short axis orientation before administration of contrast media using a T2-prepared single-shot bSSFP prototype sequence. T2-weighted images were obtained using ECG gating to diastole in a single breath-hold with 0, 25, and 55 ms T2 preparation times. Motion correction based on elastic registration was performed allowing generation of T2 pixel maps. After each single image acquisition, 4 heartbeats were used for signal recovery.

Typical imaging parameters were TE/TR 1.1/2.5 ms, acquisition time per heartbeat 150 ms, flip angle 70°, bandwidth 1445 Hz/pixel, matrix 192 × 116 pixels, measured in-plane spatial resolution 1.9 × 2.3 mm² and slice thickness 8 mm, PAT acceleration R=2.

**T1 Mapping**

T1 mapping was performed in short axis orientation using a modified Look-Locker inversion recovery (MOLLI) sequence before and 20 minutes after contrast media administration.

Three inversion episodes were employed, where in the first episode 3 images were acquired, followed by 3 recovery heartbeats, then 3 images in the second episode and another image in the 3rd episode (3(3)3(0)1 MOLLI acquisition scheme), resulting in 7 images in total and a scan duration of 10 heartbeats.

Inversion times (TI) were 120, 200, 280 ms respectively in the initial images after inversion, Typical imaging parameters were TE/TR 1.0/2.4 ms, acquisition time per heartbeat 168 ms, flip angle 35°, bandwidth 1371 Hz/pixel, matrix 192 × 136 pixels, measured in-plane spatial resolution 1.9 × 2.0 mm² and slice thickness 8 mm, PAT acceleration R=2.