Cardiac sarcoidosis can present with ventricular arrhythmias and sudden death, even in asymptomatic patients with normal cardiac function. In addition, the progression of cardiac sarcoidosis (CS) can be unpredictable, and there are no validated sudden death risk stratification methods for these patients. For these reasons, implantable cardioverter defibrillator (ICD) implantation has been advocated for all patients with CS, regardless of the extent of myocardial involvement.

The purpose of this study was to assess whether delayed enhancement (DE) on MRI is associated with ventricular tachycardia (VT)/ventricular fibrillation or death in patients with cardiac sarcoidosis and left ventricular ejection fraction >35%.

Methods—Fifty-one patients with cardiac sarcoidosis and left ventricular ejection fraction >35% underwent DE-MRI. DE was assessed by visual scoring and quantified with the full-width at half-maximum method. The patients were followed for 48.0±20.2 months. Twenty-two of 51 patients (63%) had DE. Forty patients had no prior history of VT (primary prevention cohort). Among those, 3 patients developed VT and 2 patients died. DE was associated with risk of VT/ventricular fibrillation or death ($P=0.0032$ for any DE and $P<0.0001$ for right ventricular DE). The positive predictive values of the presence of any DE, multifocal DE, and right ventricular DE for death or VT/ventricular fibrillation at mean follow-up of 48 months were 22%, 48%, and 100%, respectively. Among the 11 patients with a history of VT before the MRI, 10 patients had subsequent VTs, 1 of whom died.

Conclusions—RV DE in patients with cardiac sarcoidosis is associated with a risk of adverse events in patients with cardiac sarcoidosis and preserved ejection fraction in the absence of a prior history of VT. Patients with DE and a prior history of VT have a high VT recurrence rate. Patients without DE on MRI have a low risk of VT.

Key Words: delayed enhancement • implantable cardioverter-defibrillator • MRI • sarcoidosis • sudden cardiac death • ventricular tachycardia
approved by all institutional review boards with data use agreements in place. Using previously published criteria, patients who met diagnostic criteria for CS were identified. Patients from the University of Michigan, Henry Ford Hospital, University of Colorado, Johns Hopkins University, and Virginia Commonwealth University were included. Medical records were reviewed to identify patients who had cardiac MRIs, a left ventricular (LV) ejection fraction >35%, and ≥6 months of follow-up. Stored electrograms documenting arrhythmia episodes were reviewed to confirm appropriateness of ICD therapies (antitachycardia pacing or ICD discharge). Electrocardiograms and stored electrograms were analyzed, and ventricular arrhythmias were classified as monomorphic ventricular tachycardia (VT), polymorphic VT, or ventricular fibrillation (VF). Ventricular arrhythmia in the non-ICD group was defined as cardiac arrest, VT lasting ≥30 seconds or requiring defibrillation. VT/VF storm was defined as ≥3 episodes of VT/VF in a 24-hour period.

Cardiac MRI
All patients underwent cardiac MRI, including cine imaging of cardiac morphology and function and DE-MRI. All studies were performed on 1.5 Tesla scanners (Signa Excite CV/i; General Electric; Milwaukee, Wisconsin; Magnetom Sonata; Siemens Medical Solutions; Erlangen, Germany, Philips Healthcare, Best, The Netherlands). Cine imaging was performed in ventricular short- and long-axis planes using a segmented 2D steady-state-free-precession pulse sequence (repetition time, 2.78–4.10 ms; echo time, 1.0–1.72 ms; in plane resolution [phase; frequency] 256; 256–288; 288; field-of-view 320 to 440 mm; slice thickness, 5 to 8 mm). Fifteen minutes after administration of 0.20 mmol/kg of intravenous gadolinium contrast material (Gadopentetate dimeglumine [Magnevist®; Berlex Pharmaceuticals]; Gadoteridol [Prohance®, Bracco Diagnostics]; Gadobenate dimeglumine [Multihance®, Bracco Diagnostics]), DE-MRI was performed using an inversion recovery–prepared gradient echo sequence (repetition time, 3.82–6.98 ms; echo time, 1.2–3.36 ms; in plane resolution [phase; frequency] 256: 256; field-of-view, 320–420 mm; slice thickness, 8 mm) in ventricular short- and long-axis planes at matching cine image slice locations. Inversion times were chosen individually to null the signal of normal myocardium, using Look-Locker technique for Philips and Siemens and test scans for GE magnets. Typical inversion times were 250 to 360 ms.

Data Analysis
All DE-MRI images were analyzed off-line (QMASS 7.2.26, Medis, Leiden, the Netherlands) by 2 experienced reviewers (HP, GM) blinded to all clinical data. Differences were resolved by consensus. First, endocardial and epicardial borders were manually drawn in the short axis view (Figure 1). The left ventricle was divided into 17 anatomic segments and the right ventricle into 12 anatomic segments. The presence or absence of DE was determined for each segment by visual scoring. In addition, we quantified the extent of the left ventricular scar as percentage of the left ventricular mass, using a semiautomated threshold technique the full-width-half-maximum method (Figure 2): tissue with a signal intensity above 50% of the maximum signal of the enhanced myocardium was quantified as scar tissue.

Statistical Analysis
The analysis was performed with SPSS v. 19 (IBM, Armonk, New York), SAS 9.2 (SAS Institute Inc., Cary, NC), and R. Continuous variables were expressed as mean±1 SD. Student’s t test was used to compare means. Categorical variables were compared with the chi-square test or Fisher exact test, as appropriate.

Estimates of the positive predictive value, negative predictive value, sensitivity, and specificity at mean follow-up duration of 48 months were obtained from time-dependent receiver operating characteristic analysis using Kaplan–Meier estimator. To determine optimal cut-off values for the extent of DE that separated patients with ventricular arrhythmias from patients without ventricular arrhythmias during follow-up, sets of sensitivity and 1-specificity at month 48 were generated by varying number of segments with DE and later by varying percentages of LV mass with DE in a separate analysis. Receiver operating characteristic curves were then constructed using these values, and a cut-off was chosen to be optimal if it had the shortest Euclidean distance to the reference point (0, 1), which represents 100% sensitivity and 100% specificity. A P value <0.05 was considered statistically significant. VT/VF free survival was estimated with Kaplan–Meier analysis. Event-free survival was compared between groups using log-rank test. Hazard ratios were calculated with Cox regression. The primary end point was VT/VF-free survival in patients with no VT/VF before the MRI. The secondary end point was VT/VF free survival in all patients (primary and secondary prevention).

Results

Patient Characteristics
In a cohort of 176 patients with CS, 61 patients had both a cardiac MRI and an ejection fraction >35%. After excluding 5 patients because of uninterpretable MRIs, 3 patients because

Figure 1. Stack of manually drawn endocardial and epicardial borders in the left ventricular short axis and automated identification of delayed enhancement in a patient with incessant ventricular tachycardia.

Figure 2. Polar view of automated analysis displaying the extent of delayed enhancement (in percent) in the same patient illustrated in Figure 1.
of angiographic evidence of transmural infarction not appreciated before the MRI was performed, and 2 patients because of insufficient follow-up <6 months, 51 patients were included in the analysis. Forty patients underwent MRI before the first known occurrence of VT or ventricular fibrillation (VF) and comprised the primary cohort. Eleven patients underwent MRI after an episode of documented ventricular tachycardia (secondary cohort). Baseline characteristics of subjects are described in Table 1. Thirty-one patients underwent ICD implantation (20/40 patients in the primary and 11/11 patients in the secondary cohort). The recommendation for ICD implantation was at the discretion of the treating physician after discussion with the patient. Two patients underwent pacemaker implantation.

All patients had biopsy-proven extra-CS, and 5 patients also had pathology-proven CS (4 by endomyocardial biopsy and 1 after cardiac transplantation). Forty-one patients had biopsy-proven pulmonary involvement, 3 had a positive lymph node biopsy, 3 had a positive biopsy of the central nervous system, 2 had a positive skin biopsy, and 1 had a positive liver biopsy. The mean age at diagnosis of extra-CS was 45 years (range 30–65) and the mean age when cardiac involvement was diagnosed was 49 years (range 24–72).

The presenting symptoms leading to the screening for and subsequent diagnosis of CS were palpitations (19), dyspnea (17), syncope (1), cardiac arrest (2), chest pain (2), and fatigue (1). A seizure occurred in 1 patient who subsequently was diagnosed with both cardiac and neurosarcoidosis. Nine patients were devoid of any cardiac symptoms at the time of diagnosis. Thirty patients had functional New York Heart Association class I; 21 patients had a history of congestive heart failure and had a New York Heart Association functional class II or III. There were no patients with severe heart failure symptoms.

Standard electrocardiography (ECG) revealed complete atrioventricular block in 3 patients, 10 patients with right bundle branch block, 4 patients with left bundle branch block, and 2 with an interventricular conduction block pattern.

Overall, 33 patients were treated with ≥1 immunosuppressive medication: 24 patients were treated with steroids, 15 patients with methotrexate, 5 with hydrochloroquine, 3 with infliximab, 3 with mycophenolate mofetil, and 1 with cyclophosphamide. Eight patients were treated with antiarrhythmic medications: 2 patients with amiodarone, 3 with sotalol, 2 with flecainide, and 1 with dofetilide.

### MRI Analysis
Thirty-two of the 51 patients (63%) had DE. 21/40 primary prevention patients had DE on MRI and all 11 patients in the secondary prevention subgroup had DE \( (P=0.04) \). Twenty-four of 31 ICD patients had DE on MRI, whereas only 8/20 patients who did not undergo ICD implantation had DE on MRI \( (P=0.07) \).

DE was multifocal in 16 patients and unifocal in 16 patients. The delayed-enhanced tissue involved a mean of 9.3±12.0% of the LV mass (range <1%–36%). Figure I in the Data Supplement shows the distribution of scar burden among the study patients. In 12 patients, the burden of DE was 1% to 9%; in 13 patients, it was 10% to 19%; in 3 patients, it was 20% to 29%; in 2 patients, it was 30% to 39%; and in 2 patients, it was >40% of the LV mass.

DE was present in a mean of 5.2±5.3 segments in the 17-segment model of the LV and in a mean of 1.4±3.2 right ventricular (RV) segments in the 12-segment model of the right ventricle. DE was found in the septum in 29 patients, in the inferior wall in 25 patients, in the lateral wall in 24 patients, and in the apex in 2 patients. Thirteen patients had additional RV DE (RV DE did not occur in any patients without LV DE). Among the 13 patients, the RV base was involved in 8 patients, the RV midportion in 10 patients, and the RV apex in 7 patients. In patients with RV involvement, the LV scar burden was 23.7±16.5 g (15.0±11.2% LV mass), and in patients with no RV DE, the scar size was 2.7±6.0 g (7.1±11.5% LV mass; \( P=0.01 \)). Sixteen patients had multifocal left ventricular DE and the scar measured 19.6±15.1 g (14.4±10.6% LV mass), and in 16 patients with unifocal DE, the scar size was 1.0±0.62 g (0.7±2.6% LV mass; \( P<0.001 \)).

### Table 1. Patient Demographics

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COPD indicates chronic obstructive pulmonary disease; DE, delayed enhancement; EF, ejection fraction; HF, heart failure; LV, left ventricle; LVM, left ventricular mass; NYHA, New York Heart Association; and RV, right ventricle.
Delayed Enhancement and Adverse Outcomes

Primary Prevention Cohort

Among patients with no prior history of VT (primary cohort, n=40), 3 patients developed spontaneous VT requiring ICD therapy (antitachycardia pacing or ICD discharge) during follow-up and 2 patients died. The 3 VT patients all had DE observed on baseline MRI study (their LV ejection fractions were 55%, 66%, and 50%). Of the 2 patients who died, 1 patient did not have DE and the other did. The cause of death of the patient with DE was a traumatic fall resulting in massive internal hemorrhage. The cause of death of the patient without DE is unknown. One patient with DE <1% on MRI developed complete heart block and underwent a pacemaker implantation 15 months later. None of the patients without DE had VT during follow-up.

The presence of any DE (LV or RV) was associated with risk of VT/VF or death (P=0.0032). The positive and negative predictive values of DE prediction of VT/VF or death at 48 months after MRI were 22% and 100%, respectively. The presence of RV DE had a sensitivity and specificity of 89% and 100% and the positive and negative predictive values were 100% and 67% for VT/VF prediction, respectively. Table 3 shows patient characteristics in the primary and secondary prevention cohorts.

Secondary Prevention Cohort

Among patients with a prior history of VT (secondary cohort, n=11), 10 patients had ≥1 episode of VT/VF and 1 of these patients subsequently died from recurrent VT/VF. One patient in this cohort did not have subsequent VT/VF or atrioventricular block. At 48 months after the MRI, the sensitivity and specificity for any DE to predict VT/VF or death were 100% and 0%, respectively, and the positive and negative predictive values were 100% and 0%. The presence of RV DE had a sensitivity and specificity of 89% and 100% and the positive and negative predictive values were 100% and 67% for VT/VF prediction, respectively. Table 3 shows patient characteristics in the primary and secondary prevention cohorts.

Qualitative MRI Data and Ventricular Arrhythmia in All Patients

Fourteen of 51 patients (29%) had VT (VT cycle length, 342±91 ms) or VF. All 14 of these patients with VT/VF had DE involving the left ventricle in 10.9±3.6 segments. Among them, 14 had septal, 12 had inferior, and 12 had lateral involvement. No specific anatomic location of DE in the LV was associated with VT/VF. Multifocal DE was present in 11/14 patients with CS and VT as compared with 5/37 patients with CS without VT (P value <0.001). Ten of 14 patients with VT/VF had RV involvement (5.1±4.2 RV affected segments); only 3 of the 37 patients without VT/VF had RV involvement (P<0.001).

Qualitative MRI Data and Adverse Events in All Patients

Table 4 indicates qualitative and quantitative measurements of DE with the predictive statistics for combined adverse events (VT/VF or death) at mean follow-up time of 48 months. The
presence of DE had a positive predictive value of 48% for future adverse events. The PPV was increased to 70% in the presence of multifocal DE involving the left ventricle, and in the presence of RV involvement, the PPV further increased to 100%.

Quantitative MRI Data and Adverse Events in All Patients
All patients with ≥9 involved segments had VT by 48 months after MRI; only 1 patient in whom <9 segments were involved had VT. In this patient, 5 segments were involved with DE. Table 5 shows MRI characteristics of patients with and without incident VT. By time-dependent receiver operating characteristic analysis, at 48 months, DE involving ≥9 segments on the combined left and right ventricular segmental analysis resulted in 92% sensitivity and 88% specificity for differentiating patients with VT/VF from those without VT/VF (area under the curve, 0.90). DE exceeding 6% of the LV mass was associated with 75% sensitivity and a specificity of 82% for identifying patients with VT/VF (AUC, 0.79).

LV and RV Function and Volumes
The mean LV ejection fraction was 0.53±0.10 in the primary prevention cohort and 0.46±0.09 in the secondary prevention cohort (P=0.04). The LV ejection fraction was similar in patients with DE and patients without DE (0.52±0.10 versus 0.52±0.09; P=0.93). The mean LV end-diastolic volume was 172 mL and tended to be larger in patients with DE compared with patients without DE (194±45 versus 143±73; P=0.11).

The mean RV ejection fraction was 0.46±0.07 in patients with DE and 0.45±0.07 in patients without DE (P=0.7). The LV ejection fraction tended to be lower in patients with VT than in patients without VT (48.7±10.1 versus 53.4±9.4; P=0.3). Patients with VT also had a lower RV EF than those without VT (39.8±12.9 versus 46.9±9.8; P=0.217).

Follow-Up Post MRI
The 51 patients were followed for 48.0±20.2 months after the DE-MRI. Thirty-one patients underwent ICD implantation (20 patients for primary and 11 patients for secondary prevention). Two patients underwent pacemaker implantation.

Thirteen patients sustained ≥1 episode of ventricular tachycardia (cycle length 342±91 ms) or ventricular fibrillation after the MRI. The mean length of follow-up after ICD implantation was 31 months (range 6–80). Appropriate ICD therapy occurred in 13/32 patients with DE on MRI. In these 13 patients, the number of appropriate ICD therapies ranged from 1 to 81 (mean 13.4±23.4) during the follow-up period. Among those, 5 patients had ≥1 episode of VT/VF storm (median 4, mean 13). Monomorphic VT occurred in 12 out of 13 patients. Two patients had ≥1 episode of polymorphic VT or VF. In 1 patient, all 5 episodes of arrhythmia were polymorphic VT. None of the patients who did not undergo ICD implantation experienced syncope during follow-up. There were no ventricular high rate episodes in the 2 patients with pacemakers.

Immunosuppressive medication was used in all 13 of patients with VT post MRI, but only in 28/38 patients with no VT (P=0.048). None of the patients without DE had documented ventricular tachycardia during follow-up.

Discussion

Main Findings
Patients with CS are at risk for VT/VF, despite normal or near normal left ventricular ejection fraction (LVEF). RV multifocal
DE is associated with a combined end point of VT/VF or death. However, the presence of a low scar burden determined by DE was not associated with adverse outcomes. In particular, lack of DE was associated with a low risk of VT. These findings may help to improve risk stratification in patients with CS.

Risk Stratification of Patients With Cardiac Sarcoidosis

The diagnosis of CS is a class IIa indication for ICD implantation according to expert consensus as part of the ACC/AHA/HRS guidelines for prevention of sudden cardiac death. In a multicenter study of patients with primary and secondary prevention ICDs, most patients receiving appropriate therapies had an LVEF >35%. However, ICD implantation is associated with life-long device-related morbidity and may not be required in most patients. In addition, the criteria for the diagnosis of CS remain controversial. Therefore, because the presence of DE is associated with VT even in the setting of preserved left ventricular function, cardiac MRI may be a useful tool for ICD patient selection.

A recent study by Mehta et al evaluated electrophysiological testing for risk stratification in patients with asymptomatic CS. In that study, most of patients with inducible VT had a reduced LVEF, and therefore, the patient population at risk was different than in the present study. The incremental value of electrophysiological testing compared with LVEF is unclear and is not evaluated in the present study. The present study indicates that DE-MRI might help to improve risk stratification of patients with the clinical diagnosis of CS who have preserved or mildly reduced left ventricular function. In our study, the severity of heart failure did not predict ventricular arrhythmia, although the sample size is too small to draw definitive conclusions.

Late Gadolinium Enhancement in Patients With Cardiac Sarcoidosis

Granulomatous infiltration of the myocardium leads to postinflammatory scarring, and similar to postinfarction patients, reentry may be facilitated. Both inflammation and scarring can be identified by MRI. In the 2006 revision of the Japanese Ministry of Health criteria for CS, DE-MRI was included as a diagnostic imaging technique. Patel et al showed that MRI identified cardiac involvement in 21 out of 81 patients with extra-CS. In the latter study, the rate of major adverse events (death, defibrillator shock, or pacemaker requirement) was 9-fold higher in DE-MRI–positive patients than in DE-MRI–negative patients. The majority of these patients, however, had an ejection fraction of <35%, and therefore, these patients already met criteria for ICD implantation based on prior guidelines. Because patients with an ejection fraction <35% were excluded from the present study, the patient population substantially differs from the patients described by Patel et al. Unlike in the study by Patel et al, patients with and without prior VT were included in this study. Because the MRI findings were predictive for future adverse events in both patient groups, they were considered together. Combining both groups is further justified because a large report indicates that secondary prevention patients with CS have a similar prevalence of VA compared with primary prevention patients with CS.

In contradistinction to the study by Patel et al, the mere presence of DE was not associated with adverse outcomes. The positive predictive value of any DE in the present study for VT/VF was only 22%, but the predictive value of the MRI increased to 48% in the presence of multifocal DE. Multifocal DE is seen in patients with larger amounts of scar tissue, and therefore, it is not surprising that patients with VT more often had DE involving multiple left and right ventricular segments. A cut-off value of ≥9 involved segments separated patients with and without future VTs, suggesting that a threshold effect may be present. Right ventricular involvement seems to be particularly important for arrhythmogenesis; it was predictive of adverse events in primary prevention patients and for the group as a whole. The positive predictive value for future adverse events (VT/VF or death) was 100% in the presence of right ventricular involvement. Schuller et al reported that right ventricular dysfunction in particular was associated with appropriate ICD therapy.

Limitations

This was a retrospective analysis in a small number of patients with CS that were drawn from a multicenter registry. Limitations inherent to registry patients apply to this study. Arrhythmic events were more frequent in the secondary prevention group than in the primary prevention group. Receiver operating characteristic cut-off values were determined from both patient groups to distinguish patients with ventricular arrhythmias from patients without ventricular arrhythmias. It is unclear whether the MRI data from both secondary and primary prevention populations can be extrapolated to primary prevention patients.

Not all patients underwent ICD implantation. It is possible that the VF/VF occurrences in those patients are underestimated because these arrhythmias can terminate spontaneously.

Because all patients with VT/VF underwent ICD implantation, serial MRIs could not be performed, and therefore, we cannot comment on dynamic changes of the areas of DE over time. Likewise, patients without ICDs did not undergo serial MRIs, which may have shown changes over time. Because of difficulty with nulling of the RV, it is possible that involvement of the right ventricle may have been underestimated. In the presence of DE, Patel et al reported a 2-fold increase of sensitivity for CS compared with the Japanese Health and Welfare criteria. Not all patients meeting criteria for CS based on published criteria had DE. Inclusion in this study was based on the updated diagnostic criteria from 2006, which may explain why significant myocardial scarring determined by the presence of DE was not observed in every patient diagnosed with CS. Because the MRIs were performed at various stages of the work-up for the diagnosis of CS, there may be a bias related to the timing of the test. Given the limited timeframe of follow up, patients with lesser degree of DE might have had events occurring late and not captured within the study period.

Misclassification bias is also a potential limitation of this study. However, if patients with artifact were included, then this misclassification of myocardial scarring would bias our results toward no relationship between the presence of DE and subsequent VT/VF.

Conclusions

Patients with CS can have VT/VF, despite a normal or near normal LVEF. The presence of DE, especially multifocal or in
the right ventricle, is predictive of adverse events in patients with CS and preserved left ventricular function. Lack of DE is associated with a low risk of VT/VF. Further investigation is needed to determine the value of DE-MRI for sudden death risk stratification with the use of other testing in patients with CS.

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Disclosures

None.

References


Clinical Perspective

Patients with cardiac sarcoidosis are at risk of ventricular arrhythmias and death, leading to a class IIa indication for implantable cardioverter defibrillator implantation according to expert consensus in the ACC/AHA/HRS guidelines for prevention of sudden cardiac death. However, implantable cardioverter defibrillators are associated with life-long device-related morbidity and may not be beneficial in many patients, especially those with relatively preserved left ventricular function. The relation of scar burden assessed from delayed gadolinium enhancement (DE) on cardiac MRI to ventricular tachycardia (VT) and mortality was studied in 51 patients with cardiac sarcoidosis and left ventricular ejection fraction of >35%. Among 40 patients with no prior history of VT, 3 developed VT and 2 died; all but 1 had DE, and the extent and right ventricular DE appeared to be associated with greatest risk. All patients with a history of VT had DE and 10 of 11 had recurrent VT. The presence of a low scar burden determined by DE was not associated with adverse outcomes. These findings suggest that DE-MRI may be useful for risk stratification in patients with cardiac sarcoidosis.
Magnetic Resonance Imaging for Identifying Patients With Cardiac Sarcoidosis and Preserved or Mildly Reduced Left Ventricular Function at Risk of Ventricular Arrhythmias


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Supplemental Figure 1: Bar graph showing distribution of scar burden in the patient cohort.