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CMR Imaging Predicts Death and Other Adverse Events in Suspected Cardiac Sarcoidosis

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OBJECTIVES This study aimed to demonstrate that the presence of late gadolinium enhancement (LGE) is a predictor of death and other adverse events in patients with suspected cardiac sarcoidosis.

BACKGROUND Cardiac sarcoidosis is the most important cause of patient mortality in systemic sarcoidosis, yielding a 5-year mortality rate between 25% and 66% despite immunosuppressive treatment. Other groups have shown that LGE may hold promise in predicting future adverse events in this patient group.

METHODS We included 155 consecutive patients with systemic sarcoidosis who underwent cardiac magnetic resonance (CMR) for workup of suspected cardiac sarcoid involvement. The median follow-up time was 2.6 years. Primary endpoints were death, aborted sudden cardiac death, and appropriate implantable cardioverter-defibrillator (ICD) discharge. Secondary endpoints were ventricular tachycardia (VT) and nonsustained VT.

RESULTS LGE was present in 39 patients (25.5%). The presence of LGE yields a Cox hazard ratio (HR) of 31.6 for death, aborted sudden cardiac death, or appropriate ICD discharge, and of 33.9 for any event. This is superior to functional or clinical parameters such as left ventricular (LV) ejection fraction (EF), LV end-diastolic volume, or presentation as heart failure, yielding HRs between 0.99 (per % increase LVEF) and 1.004 (presentation as heart failure), and between 0.94 and 1.2 for potentially lethal or other adverse events, respectively. Except for 1 patient dying from pulmonary infection, no patient without LGE died or experienced any event during follow-up, even if the LV was enlarged and the LVEF severely impaired.

CONCLUSIONS Among our population of sarcoid patients with nonspecific symptoms, the presence of myocardial scar indicated by LGE was the best independent predictor of potentially lethal events, as well as other adverse events, yielding a Cox HR of 31.6 and of 33.9, respectively. These data support the necessity for future large, longitudinal follow-up studies to definitely establish LGE as an independent predictor of cardiac death in sarcoidosis, as well as to evaluate the incremental prognostic value of additional parameters. (J Am Coll Cardiol Img 2013;6:501–11) © 2013 by the American College of Cardiology Foundation

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Cardiac involvement is the most important cause of death in sarcoidosis patients, yielding a 5-year mortality rate between 25% and 66% despite immunosuppressive treatment (1–3). Because ventricular tachyarrhythmias resulting from myocardial granulomas causing electric instability have been identified as the underlying mechanism of death (2,3), some patients may benefit from implantable cardioverter-defibrillator (ICD) placement (4), yet risk stratification and clinical management remain difficult (5).

Several groups recently determined that cardiac magnetic resonance (CMR) using late gadolinium enhancement (LGE), not only can improve the detection of cardiac sarcoidosis in comparison to standard clinical evaluation with the use of consensus criteria (6,7), but furthermore may hold promise in predicting future adverse events, including cardiac death, in this patient group.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ECG = electrocardiogram

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

nsVT = nonsustained ventricular tachycardia

RV = right ventricle/ventricular

SCD = sudden cardiac death

VT = ventricular tachycardia

Consequently, the primary objective of this study was to establish the prognostic value of a comprehensive CMR examination in risk stratification of patients with suspected cardiac sarcoidosis. Specifically, we sought to demonstrate that the presence of LGE visualized by CMR predicts future lethal and other adverse events. In addition, we aimed at identifying additional predictors for adverse events in this patient group during long-term follow-up.

METHODS

Patient population. One-hundred fifty-five consecutive patients presenting at one of the participating institutions between January 2002 and December 2011 for workup of suspected cardiac sarcoidosis (all comers) were prospectively enrolled in the long-term follow-up if they fulfilled the following criteria: 1) systemic sarcoidosis diagnosed by biopsy and/or clinical criteria; *and* 2) no history of coronary artery disease or myocardial infarction; *and* 3) successfully underwent CMR imaging (Table 1). Patients with valvular or congenital heart disease demonstrated by CMR were not included. All patients gave informed consent.

CMR protocol. Electrocardiogram (ECG)-gated CMR imaging was performed in breath-hold using a 1.5-T Magnetom Symphony, Magnetom Sonata, Magnetom Espree, Magnetom Avanto, or Magnetom Aera magnetic resonance imaging scanner (Siemens Healthcare, Erlangen, Germany) in line with Society for Cardiovascular Magnetic Resonance/European Cardiovascular Magnetic Resonance recommendations (8). Both cine and LGE short-axis CMR 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 CMR was performed using a steady-state free-precession sequence. LGE images were acquired on average 5 to 10 min after contrast administration using segmented inversion recovery fast gradient echo (9), constantly adjusting inversion time (10). The contrast dose (gadodiamide or gadopentetate dimeglumine) was 0.15 mmol/kg.

CMR analysis. Cine and contrast images were evaluated by 2 experienced observers as described elsewhere (11,12). In brief, endocardial and epicardial borders were outlined on the short-axis cine images. Volumes and left ventricular (LV) ejection fraction (EF) were derived by summation of epicardial and endocardial contours. The LV mass was calculated by subtracting endocardial from epicardial volume at end-diastole and multiplying by 1.05 g/cm^3 (13). Extent of LGE was assessed using the Siemens Argus analysis software package, and the results were expressed as percentage of myocardial mass. There was good interobserver agreement when analyzing LVEF (kappa = 0.92; $p < 0.001$) and LGE extent (kappa = 0.88; $p < 0.001$).

Clinical follow-up. Clinical follow-up was performed using a standardized questionnaire at least 3 months after initial presentation. In case of a suspected event, all necessary medical records were obtained and reviewed by the authors acting as an endpoint committee.

Variables, endpoints, and definitions. All variables were collected directly from patients and/or medical records, except the CMR parameters, which were evaluated as described in the previous text. Vari-

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Table 1. Baseline Patient Characteristics

All patients with follow-up	153 (98.7)
Time to follow-up, days	944 [454–1,553]
Female	62 (40.5)
Age, yrs	49.7 ± 13
Diagnosis of sarcoidosis	
Radiological	144 (94.1)
Clinical	69 (45.0)
Confirmed by biopsy	127 (83.0)
Primary cardiac symptoms leading to CMR	
Syncope	10 (6.5)
Palpitations	46 (30.1)
Angina	27 (17.6)
Clinical heart failure	6 (3.9)
ECG abnormality	43 (28.1)
Heart block	21 (7.3)
Wall motion abnormality	4 (2.6)
Reduced LVEF	12 (7.8)
Dyspnea	46 (30.1)
CMR imaging parameters	
LVEF, %	63 [59–68]
LVEDV, ml	126 [105–155]
LVESV, ml	44 [33–61]
LV mass, g	122 [98–147]
LVEDD, mm	48 [44–52]
IVS, mm	11 [10–12]
LA dimension, cm	20 [18–24]
RA dimension, cm	19 [16–23]
PA, mm	25 [23–28]
LGE present*	39 (25.5)
LGE, % of LV mass	4.4 [2.9–8.8]
Events during follow-up	
Death	4 (2.6)
Aborted SCD	4 (2.6)
ICD shocks	7 (4.6)
VT	6 (3.9)
nsVT	14 (9.1)

Values are n (%), median [IQR], or mean ± SD. *Values are for all patients with sarcoidosis (N = 155).
CMR = cardiac magnetic resonance; ECG = electrocardiogram; EDV = end-diastolic volume; ESV = end-systolic volume; heart block = sinoatrial or atrioventricular or bundle branch block; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; IVS = interventricular septum; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; nsVT = nonsustained ventricular tachycardia; PA = pulmonary artery; RA = right atrium; SCD = sudden cardiac death; VT = ventricular tachycardia.

ables include general characteristics and follow-up results. Most variables are self-explanatory; all others are defined in the following text.

There were 2 primary combined endpoints, named endpoint 1 and endpoint 2. Endpoint 1 was defined as either death, or aborted sudden cardiac death (SCD), or appropriate ICD discharge. Thus, endpoint 1 could only be reached by experiencing a hard, "potentially lethal" event such as death or aborted death. Endpoint 2 was defined as either endpoint 1, or ventricular tachycardia (VT) or nonsustained ventricular tachycardia (nsVT). Consequently, endpoint 2 could be reached by experiencing either a potentially lethal or a soft event such as VT or nsVT. The explicit meaning of the events is described in the following paragraphs:

Death: death from any cause.

Aborted SCD: resuscitation after cardiac arrest defined as performance of the physical act of cardioversion and/or cardiopulmonary resuscitation in a patient who remains alive 28 days later.

Appropriate ICD shocks: defibrillator discharges considered appropriate included automatic defibrillation shocks triggered by VT or ventricular fibrillation and documented by stored intracardiac electrocardiographic data.

VT: 3 or more ventricular beats with a frequency of more than 120 beats/min, lasting longer than 30 s.

nsVT: 3 or more ventricular beats with a frequency of more than 120 beats/min, lasting up to 30 s.

Statistical analysis. Absolute numbers and percentages were computed to describe the patient population. Medians (with quartiles) or means (with standard deviation) were computed as appropriate. Patients with and without LGE (Table 2), with endpoint and without any endpoint events (Tables 3 and 4) were compared by chi-square test or Fisher exact test as appropriate (categorical values) and Wilcoxon signed rank test (continuous values). Additionally, univariate odds ratios with 95% confidence intervals were calculated for dichotomous parameters. Kaplan-Meier curves were calculated for visualizing the cumulative survival free of events of patients with and without LGE. Log-rank tests were performed to compare survival curves. Multivariable Cox proportional hazard models were used for analyzing independent associations with defined endpoints. Values of $p < 0.05$ were considered significant. All p values are results of 2-tailed tests. All statistical analyses were performed using the SAS statistical package, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics. One-hundred fifty-three of all 155 patients were available for clinical follow-

Table 2. Characteristics of Patients With and Without LGE

	LGE Present (n = 39)	No LGE (n = 114)	p Value	OR (95% CI)
Age, yrs	51.0 ± 14.7	49.2 ± 12.4	0.65	
Female	10 (25.6)	52 (45.6)	<0.05	0.42 (0.19–0.95)
Diagnosis of sarcoidosis				
Radiological	36 (92.3)	108 (94.7)	0.72	1.33 (0.27–6.57)
Clinical	13(33.3)	56 (49.1)	0.10	0.53 (0.25–1.13)
Confirmed by biopsy	34 (87.2)	93 (81.5)	0.42	1.54 (0.54–4.39)
Cardiac symptoms leading to CMR				
Syncope	5 (12.8)	5 (4.3)	0.06	3.33 (0.91–12.22)
Palpitations	10 (25.6)	36 (31.5)	0.56	0.78 (0.34–1.78)
Angina	7 (17.9)	20 (17.5)	0.89	1.07 (0.41–2.78)
Clinical heart failure	4 (10.2)	2 (1.7)	<0.05	6.65 (1.17–37.88)
ECG abnormality	13 (33.3)	30 (26.3)	0.33	1.47 (0.67–3.24)
Heart block	7 (17.9)	14 (12.3)	0.52	0.79 (0.34–1.71)
Wall motion abnormality	2 (5.1)	2 (1.7)	0.24	3.14 (0.43–23.09)
Reduced LVEF	7 (17.9)	5 (4.3)	<0.01	4.97 (1.47–16.74)
Dyspnea	16 (41.0)	30 (26.3)	0.06	2.06 (0.96–4.44)
CMR imaging parameters				
LVEF, %	55.0 [46.0–66.0]	65.0 [60.5–70.0]	<0.0001	
LVEDV, ml	140.0 [96.0–196.0]	125.0 [107.0–146.0]	0.22	
LVESV, ml	58.0 [35.0–90.0]	43.0 [33.0–54.5]	<0.01	
LV mass, g	140.5 [112.0–164.0]	117.0 [96.0–140.0]	<0.01	
LVEDD, mm	50.0 [45.0–55.0]	48.0 [44.0–51.0]	0.06	
IVS, mm	11.0 [10.0–13.0]	11.0 [10.0–12.0]	0.05	
LA dimension, cm^2	21.5 [19.0–25.0]	20.0 [18.0–23.0]	<0.05	
RA dimension, cm^2	20.5 [18.0–26.0]	19.0 [16.0–22.0]	<0.05	
PA, mm	26.0 [25.0–29.0]	25.0 [23.0–27.0]	<0.01	
LGE present, %	39 (100.0)	0 (0.0)		
LGE, % of LV mass	4.4 [2.9–8.8]	0.0		
Events during follow-up				
Death	3 (7.7)	1 (0.8)	<0.05	9.42 (0.95–93.37)
Aborted SCD	4 (10.3)	0 (0.0)	<0.001	
ICD shocks	7 (17.9)	0 (0.0)	<0.0001	
VT	6 (15.3)	0 (0.0)	<0.0001	
nsVT	14 (35.8)	0 (0.0)	<0.0001	

Values are mean ± SD, n (%), or median [IQR].
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

up, yielding a follow-up rate of 98.7%. The remaining 2 patients were lost due to no contact. The following paragraphs describe the characteristics of the 153 patients who underwent clinical follow-up.

At inclusion, patients were 50 ± 13 years of age. All were initially diagnosed with systemic sarcoidosis by clinical and/or radiological criteria. The diagnosis of systemic sarcoidosis was confirmed by noncardiac biopsy in 83%. Palpitations and dyspnea were the primary reason to suspect cardiac sarcoidosis (n = 46, respectively), followed by ECG abnormalities (n = 43) and various combinations of angina, heart failure, and other symptoms (Table 1).

Systemic sarcoidosis was treated according to current guidelines during the entire follow-up. In addition, all patients with heart failure received state-of-the-art heart failure medication. If indicated clinically, ICD implantation was offered, which was accepted by 13 patients.

CMR findings. The mean LVEF was 63%, and the mean LV end-diastolic volume (LVEDV) was 126 ml (Table 1). LGE was present in 39 of 153 patients, most commonly occurring in a non-coronary artery disease pattern at the right ventricle (RV) side of the interventricular septum, followed by a patchy intramural or transmural distribution in the entire LV. In addition, LGE was also observed in the RV

Table 3. Univariate Analysis Endpoint 1—Death or Aborted SCD or Adequate ICD Discharge

	Endpoint 1 (n = 12)	No Endpoint (n = 141)	p Value	OR (95% CI)
Age, yrs	54.8 ± 16.5	49.1 ± 12.7	0.23	
Female	4 (33.3)	56 (39.7)	0.66	0.76 (0.22–2.64)
Diagnosis of sarcoidosis				
Radiological	10 (83.3)	133 (94.3)	0.10	0.26 (0.05–1.44)
Clinical	1 (8.3)	67 (47.5)	<0.01	0.10 (0.01–0.80)
Confirmed by biopsy	10 (83.3)	116 (82.2)	0.97	1.03 (0.21–5.03)
Cardiac symptoms leading to CMR				
Syncope	3 (25.0)	7 (4.9)	<0.01	6.33 (1.40–28.72)
Palpitations	1 (8.3)	45 (31.9)	0.08	0.19 (0.02–1.53)
Angina	3 (25.0)	24 (17.0)	0.49	1.61 (0.41–6.40)
Clinical heart failure	1 (8.3)	5 (3.5)	0.42	2.45 (0.26–22.90)
ECG abnormality	4 (33.3)	39 (27.6)	0.69	1.29 (0.37–4.55)
Heart block	4 (33.3)	17 (12.0)	0.36	2.71 (0.26–21.90)
Wall motion abnormality	1 (8.3)	3 (2.1)	0.20	4.15 (0.40–43.32)
Reduced LVEF	2 (16.7)	10 (7.1)	0.24	2.60 (0.50–13.52)
Dyspnea	8 (66.7)	38 (26.9)	<0.01	5.37 (1.53–18.86)
CMR imaging parameters				
LVEF, %	52.0 [48.0–58.0]	64.0 [60.0–69.0]	<0.01	
LVEDV, ml	112.5 [98.0–150.0]	126.0 [107.0–155.0]	0.39	
LVESV, ml	58.5 [40.5–70.5]	44.0 [33.0–59.0]	0.22	
LV mass, g	128.5 [110.0–167.5]	122.0 [97.0–147.0]	0.35	
LVEDD, mm	48.0 [42.0–50.5]	48.0 [44.0–52.0]	0.65	
IVS, mm	13.5 [10.5–15.5]	11.0 [10.0–12.0]	<0.05	
LA dimension, cm^2	20.5 [19.5–23.5]	20.0 [18.0–24.0]	0.91	
RA dimension, cm^2	25.0 [21.0–28.5]	19.0 [16.0–22.0]	<0.01	
PA, mm	28.0 [25.5–30.0]	25.0 [23.0–28.0]	<0.05	
LGE present	91.7 [11.0–12.0]	19.9 [28.0–141.0]	<0.0001	44.39 (5.50–358.4)
LGE, % of LV mass	7.4 [2.9–14.7]	4.4 [2.9–7.4]	0.43	
Events during follow-up*				
Death	4 (33.3)	—		
Aborted SCD	4 (33.3)	—		
ICD shocks	7 (58.3)	—		
Medication ever during follow-up				
Steroids	8 (66.6)	102 (72.3)	0.08	
Methotrexate	0 (0.0)	7 (4.9)	0.52	
Azathioprine	0 (0.0)	11 (7.8)	0.41	
Infliximab	0 (0.0)	1 (0.7)	0.81	
Others	0 (0.0)	18 (12.7)	0.28	

Values are mean ± SD, n (%), or median [IQR]. *3 patients had aborted SCD as well as an adequate ICD discharge occurring after ICD implantation due to aborted SCD.
Abbreviations as in Tables 1 and 2.

free wall or the RV outflow tract. Most patients with LGE underwent x-ray coronary angiography, and none had evidence of obstructive coronary disease.

Dividing our patient population into groups with and without LGE reveals that patients with LGE had larger ventricles, poorer LVEF, and were more likely to have clinical symptoms of heart failure (Table 2). Typical CMR results are displayed in Figure 1.

Follow-up results. During follow-up, 4 of 153 patients died, 4 patients experienced SCD but were successfully resuscitated, and 7 patients survived SCD due to appropriate ICD discharge. Because 3 patients experienced aborted SCD, as well as an appropriate ICD discharge occurring after ICD implantation due to aborted SCD, 12 patients reached endpoint 1 as described in the previous text (Table 3). Almost all of these potentially lethal events (n = 11) occurred for cardiac reasons.

Table 4. Univariate Analysis Endpoint 2—Death or Aborted SCD or Adequate ICD Discharge or VT or nsVT

	Endpoint 2 (n = 20)	No Endpoint (n = 133)	p Value	OR (95% CI)
Age, yrs	54.6 ± 15.5	48.8 ± 12.5	0.11	
Female	7 (35.0)	53 (39.8)	0.68	0.81 (0.30–2.17)
Diagnosis of sarcoidosis				
Radiological	18 (90.0)	125 (93.9)	0.41	0.50 (0.10–2.62)
Clinical	4 (20.0)	64 (48.1)	<0.05	0.27 (0.09–0.85)
Confirmed by biopsy	18 (90.0)	108 (81.2)	0.37	2.00 (0.43–9.20)
Cardiac symptoms leading to CMR				
Syncope	4 (20.0)	6 (4.5)	<0.01	5.25 (1.34–20.62)
Palpitations	4 (20.0)	42 (31.5)	0.28	0.54 (0.17–1.70)
Angina	3 (15.0)	24 (18.0)	0.73	0.79 (0.22–2.93)
Clinical heart failure	3 (15.0)	3 (2.2)	<0.01	7.59 (1.42–40.65)
ECG abnormality	6 (30.0)	37 (27.8)	0.86	1.10 (0.39–3.08)
Heart block	6 (30.0)	15 (11.2)	0.26	0.74 (0.11–1.80)
Wall motion abnormality	1 (5.0)	3 (2.2)	0.48	2.26 (0.22–22.89)
Reduced LVEF	7 (35.0)	5 (3.7)	<0.0001	13.68 (3.80–49.28)
Dyspnea	10 (50.0)	36 (27.0)	<0.05	2.67 (1.02–6.94)
CMR imaging parameters				
LVEF, %	48.0 [41.5–54.5]	65.0 [61.0–69.0]	<0.0001	
LVEDV, ml	150.0 [101.5–204.5]	124.0 [105.0–148.0]	0.13	
LVESV, ml	70.5 [56.0–106.5]	43.0 [33.0–55.0]	<0.001	
LV mass, g	139.0 [108.0–165.0]	121.0 [96.5–145.0]	0.09	
LVEDD, mm	50.5 [47.5–59.0]	48.0 [44.0–51.0]	<0.05	
IVS, mm	11.0 [9.5–14.0]	11.0 [10.0–12.0]	0.37	
LA dimension, cm^2	23.0 [20.0–28.0]	20.0 [18.0–23.0]	0.06	
RA dimension, cm^2	25.0 [19.0–27.0]	18.5 [16.0–22.0]	<0.001	
PA, mm	28.0 [26.0–30.0]	25.0 [23.0–27.0]	<0.001	
LGE present	95.0 [19.0–20.0]	15.0 [20.0–133.0]	<0.0001	107.4 (13.60–847.6)
LGE, % of LV mass	5.9 (2.9–14.7)	4.4 (2.9–5.9)	0.36	
Events during follow-up*				
Death	4 (20.0)	—		
Aborted SCD	4 (20.0)	—		
ICD shocks	7 (35.0)	—		
VT	6 (30.0)	—		
nsVT	14 (70.0)	—		
Medication ever during follow-up				
Steroids	16 (80.0)	94 (70.7)	<0.05	
Methotrexate	1 (5.0)	6 (4.5)	0.76	
Azathioprine	1 (5.0)	10 (7.5)	0.85	
Infliximab	0 (0.0)	1 (0.8)	0.73	
Others	0 (0.0)	18 (13.5)	0.12	

Values are mean ± SD, n (%), or median [IQR]. *8 patients had 2 or more events during follow-up.
Abbreviations as in Tables 1 and 2.

In addition, 20 VTs or nsVTs were documented on Holter ECG during follow-up (Table 4). The average Holter monitoring time during follow-up was 2.6 days per patient. Note that only 1 patient without LGE died (Table 2). This patient died from rapid pulmonary infection, which she developed during immunosuppressive treatment for systemic sarcoidosis. Furthermore, no patient with normal CMR upon initial presentation (defined as LVEF ≥60% and LVEDV <180 ml and no LGE) died or experienced any other event during follow-up (n = 92).

Predictors of events. For evaluation of predictors for adverse events, we looked at: 1) all patients who reached endpoint 1 (potentially lethal events only, including death, successful resuscitation, and ap-

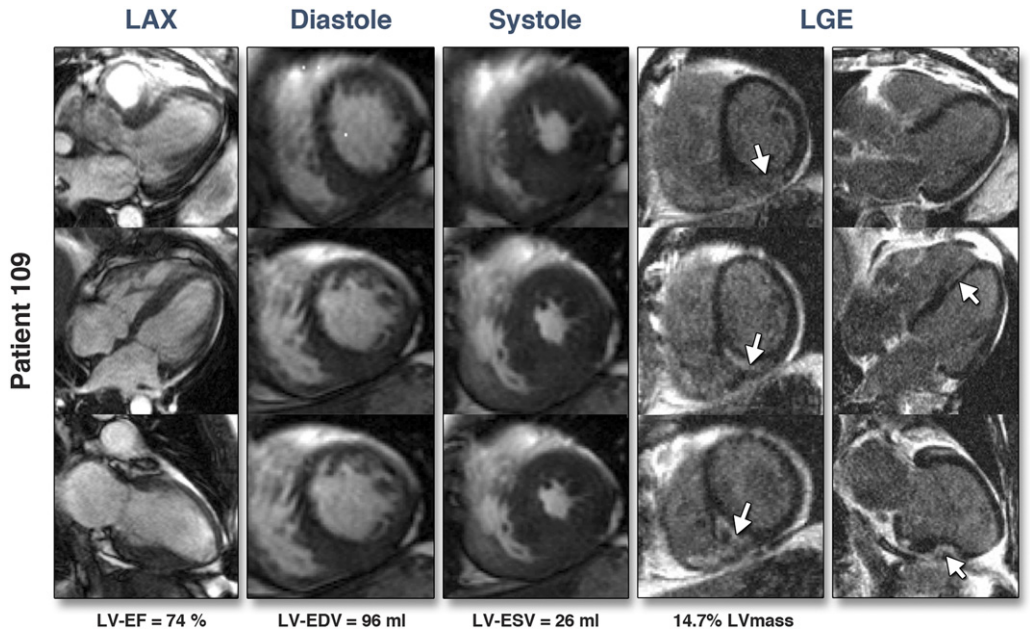

Figure 1. Typical CMR Results in the Setting of Cardiac Sarcoidosis

Cardiac magnetic resonance (CMR) of a 48-year-old woman presenting with shortness of breath and new onset of third-degree atrioventricular block. Cine images reveal a normal left ventricle (LV) with preserved left ventricular ejection fraction (LVEF). Late gadolinium enhancement (LGE) is present in multiple locations **(white arrows)** adding up to 14.7% of LV mass. Endomyocardial biopsy confirmed cardiac sarcoidosis in the LV and right ventricle. This patient received an implantable cardioverter-defibrillator due to reoccurring sustained ventricular tachycardia, which discharged appropriately several times during follow-up despite amiodarone and high-dose beta-blockers. LAX = long axis; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

propriate ICD discharge) (Table 3); and 2) all patients who experienced any event (potentially lethal or other event, including VT and nsVT) (Table 4).

There is no significant correlation between events and clinical presentation except syncope, which may be a surrogate parameter for undetected arrhythmias, and symptoms of heart failure, which is a surrogate parameter of impaired LVEF.

In addition, functional parameters such as LVEF, LVEDV, as well as the presence of LGE reached statistical significance. In fact, the presence of LGE yields an odds ratio for a potentially lethal event of 44.4 (endpoint 1), and of 107.4 for any event (endpoint 2, including VT and nsVT). Typical examples are displayed in Figure 2.

Kaplan-Meier survival curves for endpoint 1 and endpoint 2 comparing patients with LGE to patients without LGE are displayed in Figures 3A and 3B. Note that only 1 patient without LGE died during follow-up (pulmonary infection as described in the previous text).

Multivariable Cox regression analysis including the presence of LGE, the initial LVEF, the initial LVEDV, and the initial presentation as heart failure also revealed LGE as the best independent predictor of potentially lethal events ($p = 0.0014$, hazard ratio [HR]: 31.6 for endpoint 1). In this model, neither initial LVEDV ($p = 0.06$, HR: 1.001 per ml increase in LVEDV), nor initial LVEF ($p = 0.34$, HR: 0.99 per % increase in LVEF), nor clinical presentation as heart failure ($p = 0.97$, HR: 1.04) reached significance. Looking at patients experiencing any event (endpoint 2), LGE was the best independent predictor ($p < 0.001$, HR: 33.9). However, in this model, initial LVEF ($p = 0.04$, HR: 0.94 per % increase in LVEF) and LVEDV ($p = 0.046$, HR: 1.004 per ml increase in LVEDV), but not presentation as heart failure ($p = 0.69$, HR: 1.2), also reached significance.

DISCUSSION

This study is unique in that we could demonstrate that the presence of LGE is the best independent predictor of death and other adverse events in patients presenting for workup of suspected cardiac sarcoidosis in an international multicenter setting. Our data not only confirm earlier single-center findings in smaller groups (6,7), suggesting a po-

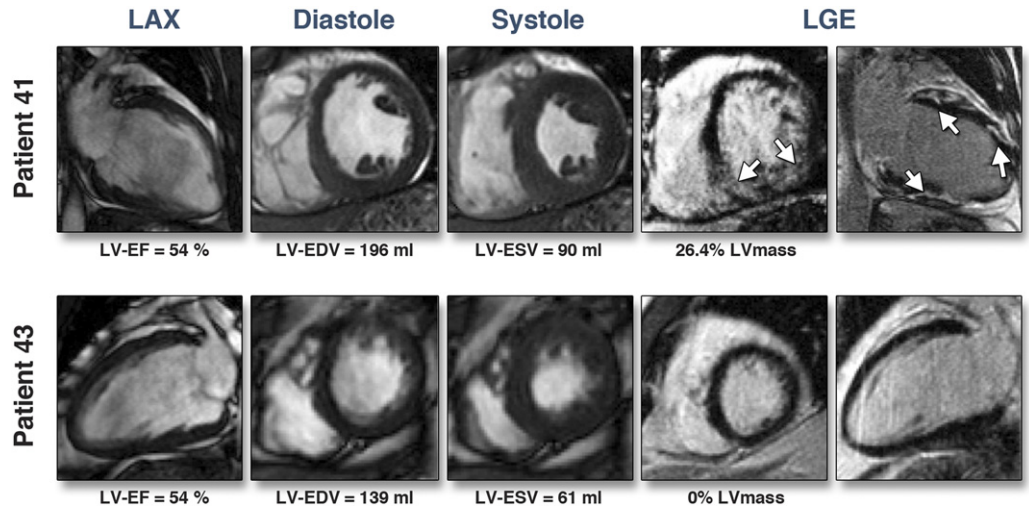

Figure 2. Typical Example of Patients With LGE With an Event Versus Patients Without LGE Without Any Events

The **upper panel** demonstrates CMR findings of a 46-year-old man with biopsy-proven systemic sarcoidosis. This patient has an almost normal LVEF with diffuse LGE located mainly in the interventricular septum and the inferior and lateral wall (26.4% of LV mass, **white arrows**). During follow-up, he received an implantable cardioverter-defibrillator (ICD) after sudden cardiac death (SCD) and successful resuscitation, and was shocked appropriately several times. The **bottom row** demonstrates CMR images of a 41-year-old man with biopsy-proven systemic sarcoidosis. This patient also had an almost-normal LVEF but no LGE and did not experience an event during follow-up. Abbreviations as in Figure 1.

tential use of LGE in the setting of cardiac sarcoidosis, but clearly indicate a clinical role for LGE for noninvasive risk stratification of sarcoid patients, yielding a Cox HR of 31.6 for endpoint 1 and of 33.9 for endpoint 2. This is superior to functional or clinical parameters such as LVEF, LVEDV, or presentation as heart failure, yielding HRs between 0.99 and 1.004, and between 0.94 and 1.2 for endpoints 1 and 2, respectively. Importantly, except for the 1 patient dying from pulmonary infection reported in the previous text, no patient without LGE died or experienced any event during follow-up, even if the LV was enlarged and the LVEF severely impaired (LVEDV >180 ml and LVEF <35% and no LGE; n = 3) (Fig. 4).

Patient characteristics. Cardiac sarcoidosis was suspected due to palpitations and dyspnea (n = 46, respectively) in most patients, followed by ECG abnormalities (n = 43), and various combinations of angina, heart failure, and other symptoms (Table 1), which is in line with previous reports (6,7). Also, the average patient age in our population is similar to previous reports of cardiac sarcoidosis (6,7,14) or myocarditis (15), but lower than in other nonischemic cardiomyopathies (16). However, in comparison to previous studies, our patients were less symptomatic on average, which is nicely reflected by the fact that in the current population, the median LVEF at presentation was 63%.

CMR findings. Despite a median LVEF of 63%, some patients presented with dilated ventricles and/or impaired function. LGE was present in 39 of 153 patients, and was usually located at the RV side of the interventricular septum, followed by a patchy intramural or transmural distribution in the entire LV, in line with other reports (7).

Furthermore, our data demonstrate that patients with scar indicated by LGE have larger ventricles and poorer LVEF compared with those without scar (Table 2). This finding matches the results from other inflammatory (15) or nonischemic cardiomyopathy (16) populations, but is different from the results reported by Patel et al. (7) in cardiac sarcoid patients. However, this discrepancy is most likely explained by the systematic exclusion of patients with depressed LV function in the study of Patel et al (7).

Follow-up results and predictors of events. In our population of patients with nonspecific symptoms, 12 patients died or had aborted sudden cardiac death or appropriate ICD discharge, and reached endpoint 1, as described in the previous text, during a median follow-up time of 2.6 years (Table 3), yielding a hard event rate of 3% per year. The majority of these events (n = 11) occurred for cardiac reasons. Thus, the cardiac mortality of our sarcoid patients is lower than that reported previously (1–3), most probably due to a lower disease severity upon inclusion. However, the annual mor-

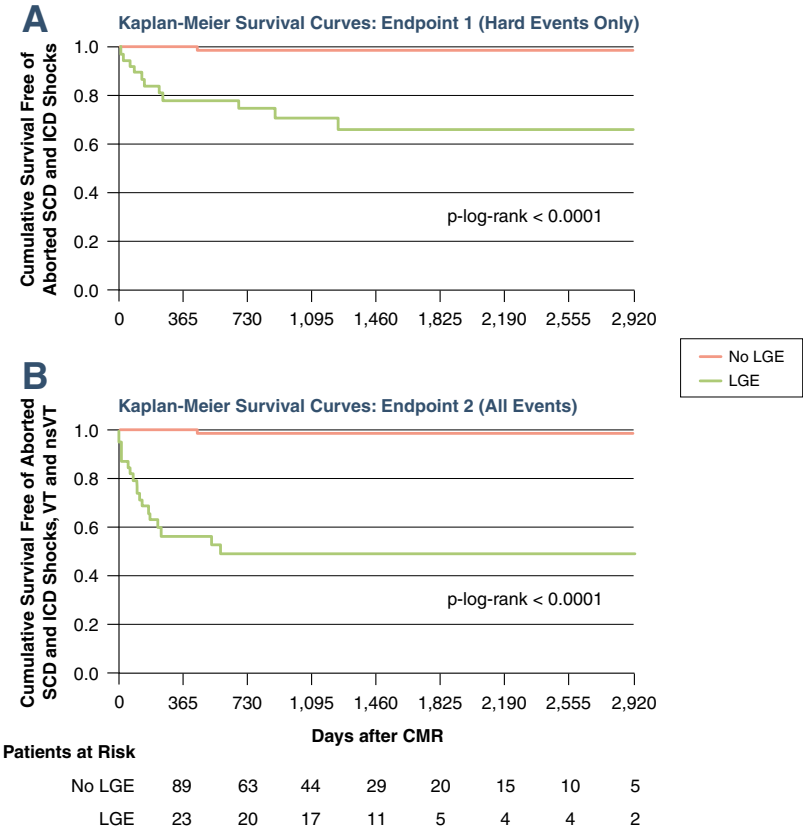

Figure 3. Kaplan-Meier Survival Curves

Kaplan-Meier survival curves with regard to endpoint 1 (**A**, including death, aborted SCD, and appropriate ICD discharge only), and endpoint 2 (**B**, including death, aborted SCD, appropriate ICD discharge, as well as ventricular tachycardia [VT] and nonsustained VT [nsVT]). The number of patients at risk is shown at the **bottom** of the figure. Note that in the group without any LGE, only a single patient experienced an event (death due to pulmonary infection, see text for details) during follow-up. Abbreviations as in Figures 1 and 2.

tality is about 60% of the nonischemic cardiomyopathy group of the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (3% vs. 5%) (17), although LV function was much better in our patients (median 63%), underscoring the importance of risk stratification and optimal clinical management in cardiac sarcoidosis.

In clinical routine, however, risk stratification based on clinical and functional parameters remains difficult despite the value of LVEF, LVEDV, and clinical symptoms (2,18,19). For example, in the current study, 4 patients without any clinical signs of heart failure experienced SCD (Table 3), and 15 additional patients without heart failure had documented VT or nsVT (Table 4). In addition, several patients suffered an adverse event despite only mildly impaired LV function (endpoint 1: n = 11, LVEF ≥45%; endpoint 2: n = 14, LVEF ≥45%) or a normal sized LV (endpoint 1: n = 10, LVEDV ≤180 ml; endpoint 2: n = 12, LVEDV ≤180 ml). Other factors, such as ECG abnormalities, suggested to be of prognostic value in cardiac sarcoid by previous studies (18,19) could not be confirmed, despite a trend toward a poorer outcome in patients with palpitations or syncope in their medical history (Table 3).

Our findings fit to the fact that LGE is also a good predictor of adverse events in other nonischemic heart diseases, such as myocarditis (15) or hypertrophic cardiomyopathy (16). These results may help to explain why only 1 patient without LGE suffered any event (1 of 114) (Table 2), who died for noncardiac reasons from pulmonary infection as described in the previous text. Note that not a single patient without LGE had VT or nsVT during follow-up. This concept is highlighted by Figures 2 and 4.

Even with these encouraging data, however, it is important to keep in mind that there is not a 1-to-1 relationship between the presence of LGE and

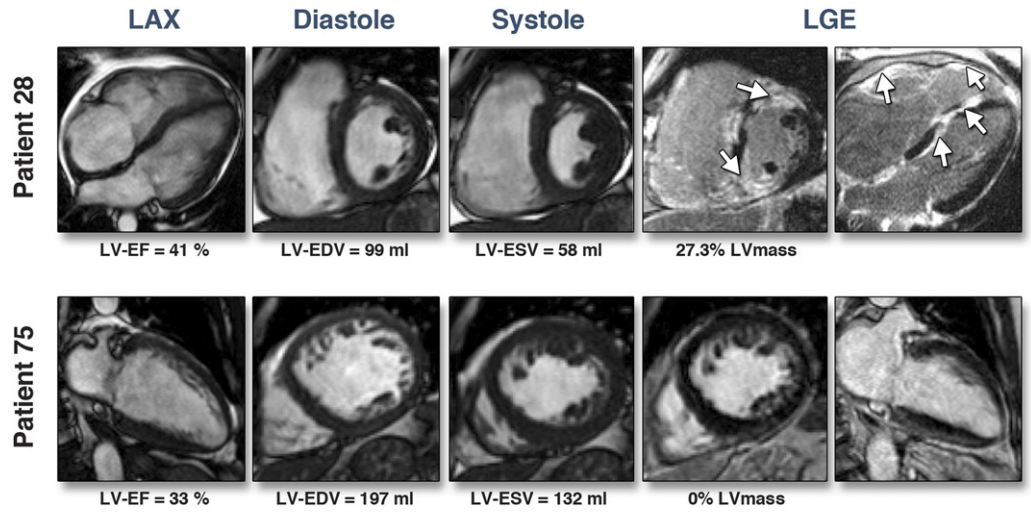

Figure 4. Typical Patient Examples Illustrating LGE as a Better Predictor of Events Than Other Parameters (Such as LVEF)

The **upper panel** displays typical CMR results of a 31-year-old woman with biopsy-proven sarcoidosis. Initially, her LVEF was 41% with multiple patchy foci of LGE in the left and right ventricles **(white arrows)**. She had SCD during follow-up and was successfully resuscitated. Unfortunately, her systolic function worsened over time, and she had to undergo heart transplant later. The **bottom panel** shows CMR images of another female patient with even more severely impaired LVEF (33%) but no LGE. Despite the worse LVEF compared with patient 28 **(upper panel)**, she experienced no events during follow-up. Abbreviations as in Figures 1 and 2.

cardiac death. Thus, to further improve possible CMR risk stratification, we also thought about a possible incremental value of additional CMR-related parameters, such as the pattern of LGE (12), or scar volume and surface area (16). However, we were not able to discriminate their individual predictive potential due to the limited number of cases and events available in the present study.

Clinical implications. Although our data demonstrate an association between LGE and death as well as other adverse events in sarcoid patients with nonspecific symptoms, additional multicenter data from randomized studies and the EuroCMR Registry (20,21) are required to definitively establish LGE as causally related to death risk. Additional data are also needed to determine the value of an additional electrophysiology study in CMR-positive patients as suggested by the pilot data of Mehta et al. (14). However, with regard to our data and the results from other groups, some speculations can be made that may influence current clinical management: 1) sarcoid patients with normal CMR (LVEF ≥60% and LVEDV ≤180 ml and no LGE) seem to have a good prognosis, independent of clinical symptoms, which may give suffering patients and worrying physicians some peace of mind; 2) sarcoid patients without LGE did not experience SCD or VT in our study, even if the LV was dilated and the LVEF severely impaired. Consequently, if LGE and not LV function or size is closer to the substrate for SCD, it may be prudent to treat all sarcoid patients demonstrating LGE with beta-blockers, independent of LV function and size, to prevent potentially lethal arrhythmias. This speculation satisfactorily fits to the results of Grün et al. (15) reporting the same relation between LGE and arrhythmic events in myocarditis, as well as the results of Kindermann et al. (22) describing the lack of beta-blocker therapy as a predictor for poor clinical outcome in inflammatory heart disease; and 3) we also found impaired LVEF and enlarged LVEDV as predictors for adverse events. Thus, one should carefully optimize heart failure therapy in all sarcoid patients presenting with even the mildest signs of heart failure.

Study limitations. The relatively low number of events is an important limitation of this study. This prevented us from evaluating the predictive potential of other parameters such as the pattern of LGE, scar transmurality, scar surface area, and so on. In addition, it may be possible that CMR reports influenced treatment decisions with regard to ICD implantation, which may result in more endpoints such as ICD shocks to be detected in patients with abnormal CMR results.

CONCLUSIONS

Among our population of sarcoid patients with nonspecific symptoms, the presence of myocardial

scar indicated by LGE is the best independent predictor of potentially lethal, as well as other adverse events, yielding a Cox HR of 31.6 and of 33.9, respectively. These data support the necessity for future large longitudinal follow-up studies to definitely establish LGE as an independent predictor of cardiac death in sarcoidosis, as well as to evaluate the incremental prognostic value of additional parameters.

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Key Words: cardiac magnetic resonance ■ death ■ LGE ■ prognosis ■ risk stratification ■ sarcoidosis.