ORIGINAL RESEARCH

Magnetic Resonance Imaging as a Predictor of Survival Free of Life-Threatening Arrhythmias and Transplantation in Cardiac Sarcoidosis

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***Background*—**Cardiac magnetic resonance imaging has a key role in today's diagnosis of cardiac sarcoidosis. We set out to investigate whether cardiac magnetic resonance imaging also helps predict outcome in cardiac sarcoidosis.

***Methods and Results*—**Our work involved 59 patients with cardiac sarcoidosis (38 female, mean age 46±10 years) seen at our hospital since February 2004 and followed up after contrast-enhanced cardiac magnetic resonance imaging. The extent of myocardial late gadolinium enhancement (measured as percentage of left ventricular mass), the volumes and ejection fractions of the left and right ventricles, and the thickness of the basal interventricular septum were determined and analyzed for prognostic significance. By April 2015, 23 patients had reached the study's end point, consisting of a composite of cardiac death (n=3), cardiac transplantation (n=1), and occurrence of life-threatening ventricular tachyarrhythmias (n=19; ventricular fibrillation in 5 and sustained ventricular tachycardia in 14 patients). In univariate analysis, myocardial extent of late gadolinium enhancement predicted event-free survival, as did scar-like thinning (<4 mm) of the basal interventricular septum and the ejection fraction of the right ventricle (P<0.05 for all). In multivariate Cox regression analysis, extent of late gadolinium enhancement was the only independent predictor of outcome events on cardiac magnetic resonance imaging, with a hazard ratio of 2.22 per tertile (95% CI 1.07–4.59). An extent of late gadolinium enhancement >22% (third tertile) had positive and negative predictive values for serious cardiac events of 75% and 76%, respectively.

***Conclusions*—**Findings on cardiac magnetic resonance imaging and the extent of myocardial late gadolinium enhancement in particular help predict serious cardiac events in cardiac sarcoidosis. **(*J Am Heart Assoc*. 2016;5:e003040 doi: 10.1161/JAHA.115.003040)**

Key Words: implanted cardioverter defibrillator • magnetic resonance imaging • sarcoidosis • ventricular tachycardia

Cardiac sarcoidosis (CS) presents clinically either as one component of a manifest multiorgan disease or, increasingly, as an isolated heart condition.[1] Although its prognosis appears improved,[1] CS still poses a threat to both quality and duration of life. In the current therapeutic era, including active cardiac transplant surgery, death from terminal heart failure is rarely seen in CS. Fatal arrhythmias, instead, explain 90% of cardiac mortality, and aborted arrhythmic deaths are as common as all cardiac fatalities together.[1] Implantable cardioverter-defibrillator (ICD) therapy is able to prevent sudden death in CS,[2] but its complications cannot be ignored, and today's experts advocate implantations only in patients at high risk of fatal arrhythmias.[3] Individual risk assessment is problematic, however, because there are no large outcome studies in CS. The general signs of poor cardiac prognosis, such as spontaneous ventricular tachyarrhythmias and impaired left ventricular (LV) function, are also applicable to CS,[3] but additional risk markers more specific to CS are clearly needed. Myocardial late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI) has been reported to predict serious cardiac events in patients with extracardiac sarcoidosis,[4–7] although not consistently.[8–10] Whether CMRI has prognostic value in established CS is much less studied.[11,12] LGE can expose areas of myocardial injury and fibrotic scarring that may serve as substrate to ventricular tachyarrhythmias in CS.[13] We analyzed a 10-year series of consecutive CS patients to assess whether and how CMRI is predictive of cardiac events including life-threatening

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Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/5/5/e003040/DC1/embed/inline-supplementary-material-1.pdf

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arrhythmias. Our data support extent of myocardial LGE as a strong risk marker in CS and suggest that impaired right ventricular (RV) function and scar-like thinning of the basal interventricular septum also are predictive of cardiac events.

Methods

Study Population and Data Collection

From February 2004 through July 2014, a total of 119 patients with CS were seen at Helsinki University Central Hospital. Our institution directly serves a population of 1.9 million in the diagnosis and treatment of severe myocardial diseases but also receives referrals from other university hospitals because ours is the only transplant center in Finland. Our strategy and practice of diagnostic procedures for suspected CS have been described in detail previously.[14–16] The diagnosis of CS requires documentation of sarcoidosis histology in a biopsy sample of myocardium or, if that is missing, extracardiac histology of sarcoidosis combined with clinical manifestations and abnormalities in either CMRI or 18F-fluorodeoxyglucose positron emission tomography or echocardiography indicative of myocardial involvement. These criteria are in conformity with the criteria advocated recently in an expert consensus report.[3] Of the 119 patients, 60 had undergone gadolinium-enhanced CMRI and were eligible for the present investigation. One-third of those patients were referred from the other university hospitals, and the rest were from our own catchment area. One patient was found to have extensive coronary artery disease and was excluded from the analyses. The hospital charts for the remaining 59 patients (Figure 1) were reviewed retrospectively for patient demographics, comorbidities, presenting clinical manifestations, results of laboratory tests and imaging studies, treatment with drugs and devices, and occurrence of cardiac death, cardiac transplantation, and life-threatening ventricular arrhythmias through the end of April 2015. Identification and confirmation of arrhythmias were based on retrospective analyses of ICD reports, 12-lead electrocardiograms, 24- to 48-hour Holter recordings, and attending physicians' documentation. The institutional ethics committee at Helsinki University Central Hospital approved the study protocol. All participants gave informed consent. Part of the study population (28 of 59 patients) was included in our recent nationwide study of CS[1] that included neither detailed analyses of CMRI nor assessment of its predictive value.

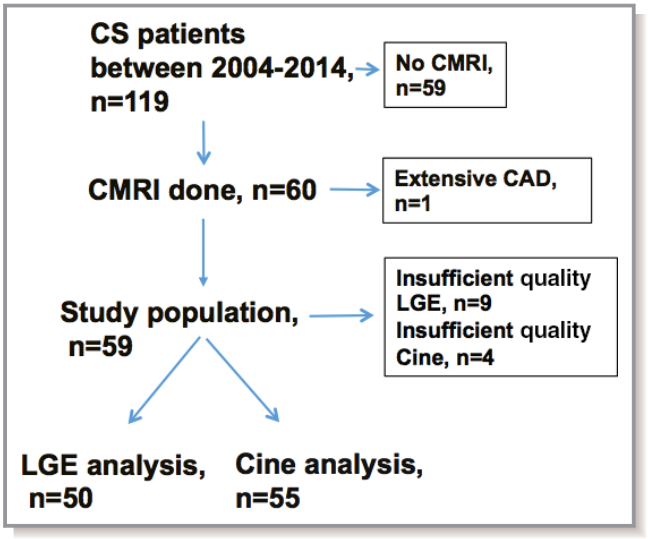

Figure 1. Diagram depicting the selection of CS patients for CMRI analyses from the 119 CS patients seen from February 2004 through July 2014. CAD indicates coronary artery disease; CMRI, cardiac magnetic resonance imaging; CS, cardiac sarcoidosis; LGE, late gadolinium enhancement.

CMRI Protocol

Because of the retrospective nature of our study, several different scanners were used during the 10-year period from which the CMRI studies were collected and reanalyzed. The scanners manufactured by Siemens (Siemens Healthcare) included the 1.5-T Avantofit (45 studies), the 1.5-T Aera (2 studies), the 1.5-T Sonata (2 studies), the 1.5-T Symphony (1 study), and the 3-T Verio (8 studies). One study was done using the 1.5-T General Electric SignaHDxt scanner (GE Healthcare). A 32-channel receiver cardiac coil was used in all CMRI examinations. Breath-hold cine studies were performed using retrospectively electrocardiographically gated segmented true fast imaging with balanced steady-state free precession. To assess LV and RV volumes and ejection fraction (EF), cine imaging was done both in vertical and horizontal long-axis planes and a stack of short-axis planes covering both ventricles. The typical cine imaging parameters were repetition time/echo time 3.0/1.6 ms, flip angle 52°, 256×256 matrix, and 240×340 field of view. Slice thickness was 6 mm, and the interslice gap was 20%. The temporal resolution was 42 to 49 ms. The typical imaging parameters of T2-weighted fat saturation images were repetition time/echo time 1503/45 ms, flip angle 57°, 256×256 matrix, and 240×240 field of view. Ten minutes after intravenous injection of a contrast agent (0.15 mmol/kg gadoterate meglumine [Dotarem; Guerbet]), LGE images were acquired in the same views as the cine images using an inversion-recovery spoiled gradient echo sequence. The imaging parameters were repetition time/echo time 2.58/2.3 ms, flip angle 50°, 256×256 matrix, and 240×340 field of view. Slice thickness was 8 mm, and the interslice gap was 0%. Inversion time was optimized for each measurement to null the signal intensity of normal myocardium (240–360 ms).

Analyses of CMRI Studies

All CMRI studies were analyzed on a separate workstation using a dedicated software package (QMass MR 7.60.30.0; Medis). Studies with insufficient quality for either volumetric measurements (4 studies) or LGE extent analysis (9 studies) were excluded (Figure 1). Comprehensive LGE analysis was prevented by the failure of LV short axis slices to span the ventricle entirely from base to apex in 7 studies and by poor image quality in 2 studies. LV and RV volumes and LV mass were derived by manually drawing LV endo- and epicardial contours and RV endocardial contours on all short-axis slices from base to apex at end-diastole and end-systole. Papillary muscles and endocardial trabeculations were regarded as part of the ventricular cavity. LV wall thickness was derived automatically by the software from the end-diastolic contours and recorded according to the American Heart Association 17-segment model. The presence of marked basal septal thinning suggestive of scarring, defined as wall thickness <4 mm in American Heart Association segments 2 and 3, was separately noted.

In LGE images, the presence or absence of LGE was initially assessed visually. Epicardial and endocardial end-diastolic LV contours were traced, as in the cine images. Regions of interest representing (1) healthy myocardium free of LGE and (2) myocardium with intense LGE were drawn on a slice optimally distinguishing healthy from diseased heart muscle. The extent of LGE as a percentage of LV mass was calculated automatically by the software. The full width at half maximum method[17] was used for defining the threshold for LGE: Tissue with a signal intensity >50% of the maximum signal of the enhanced myocardium was quantified as scar tissue. In T2-weighted images, regions of interest were drawn on remote skeletal muscle and on the LV segments in which myocardial edema was suspected. Edema was defined as myocardial signal intensity >1.9-fold the intensity in the skeletal muscle and classified as present or absent. All images were analyzed by a CMRI-trained physician. To assess repeatability of the LGE data, 10 randomly selected studies were later reanalyzed blindly by the same physician and by an independent expert. The repeatability coefficients for the extent of LGE, determined by the Bland-Altman method,[18] were ±6.1% and ±11.9% for intra- and interobserver measurements, respectively.

Statistical Analysis

Baseline characteristics are presented as mean±SD or as median (minimum–maximum) for continuous variables and as frequencies for categorical data. The Pearson *r* was calculated when testing for linear correlation between 2 continuous variables, and the Student *t* test was used to compare continuous variables between 2 groups. The end point event in outcome analyses was a composite of cardiac death, cardiac transplantation, and life-threatening arrhythmia, whichever came first. Life-threatening arrhythmia was defined as ventricular fibrillation (VF) or ventricular tachycardia (VT) requiring external synchronized cardioversion or defibrillation or ICD therapy (shock or antitachycardia pacing). In survival analyses, follow-up times were calculated from the date of the CMRI study. Survival curves were plotted by the Kaplan–Meier method, and the log-rank test was used to test group differences in survival. Cox proportional hazards modeling was used to calculate univariate and multivariate hazard ratios and the associated 95% CIs and *P* values. The validity of the proportional hazards assumption was tested by plotting Schoenfeld (partial) residuals against ranked survival time. The assumption was considered valid if no statistically significant time-dependent correlation was observed. *P* values <0.05 were considered statistically significant in all analyses, which were performed using SPSS version 21 software for Macintosh (IBM Corp).

Results

Characteristics of the Study Population

The study population comprised 38 women and 21 men, with a mean age of 46±10 years. In 31 patients (53%), the diagnosis of CS was confirmed by myocardial biopsy, whereas 27 patients (45%) were diagnosed based on sarcoidosis histology in mediastinal lymph nodes (n=18), skin (n=4), liver (n=3), cervical lymph nodes (n=1), or central nervous system (n=1) combined with cardiac imaging indicative of myocardial involvement. In addition, 1 patient was diagnosed at autopsy. Table 1 summarizes the key characteristics of the study population at the time of CS presentation. As Tables S1 through S3 show, there were no statistically significant differences in any covariate comparisons between included and excluded patients. This suggests that the baseline characteristics of our CS patients were representative of the total CS population seen at our institution during the period covered by our work. In addition to CS, 13 patients had history of hypertension and 6 had diabetes, but none had significant renal dysfunction or chronic lung disease aside from pulmonary sarcoidosis. A total of 15 patients had extracardiac sarcoidosis involving lungs (n=10), liver (n=3), skin (n=2), central nervous system (n=1), and bone marrow (n=1). The remaining 44 patients (75%) had isolated CS. Significant coronary artery disease was excluded by invasive coronary angiography (n=26), coronary computed tomography angiography (n=3), treadmill exercise stress test (n=7), and myocardial perfusion imaging (n=1) or by clinical judgment alone based on the absence of risk factors, symptoms, and signs of ischemic heart disease (n=22).

Table 1. Selected Characteristics of the 59 Patients With Cardiac Sarcoidosis at Presentation

Characteristics	Results
Main presenting clinical manifestation	
Atrioventricular conduction block	25 (42)
Ventricular tachycardia or fibrillation	18 (31)
Heart failure	13 (22)
Other	3 (5)
New York Heart Association functional class	
1	27 (46)
2	25 (42)
3–4	7 (11)
LVEF at echocardiograpy, %	48±13
NT-proBNP, pg/mL*	450 (56–6428)
Abnormal cardiac ^{18}F-FDG PET†	28/31 (90)

The data are number (%) of patients, mean±SD or median (minimum–maximum). ^{18}F-FDG PET indicates ^{18}F-fluorodeoxyglucose positron emission tomography; LVEF, left ventricular ejection fraction; NT-proBNP indicates N-terminal brain natriuretic propeptide.
*Measurements were made using a commercial assay (Elecsys 2010 or Modular e170; Roche Diagnostics GmbH) and were available for 56 patients.
†Abnormally increased focal myocardial fluorodeoxyglucose uptake with or without a perfusion defect (the study was done in 31 of 59 patients).

All 58 patients diagnosed during life prior to transplantation were administered prednisone as disease-modifying immunosuppressive therapy. In addition, 31 patients received azathioprine, 9 received mycophenolate mofetil, 2 received methotrexate, 2 received infliximab, and 1 patient was given cyclosporine. ICD was implanted in 35 patients (59%), of whom 20 received the device for primary prevention and 15 patients received the device after a life-threatening ventricular arrhythmia. In addition, 13 patients (22%) received a permanent pacemaker. Of the 48 intracardiac devices, 43 were implanted after CMRI, with a median time interval of 0.5 month (range 0–72 months). Two ICDs and 3 pacemakers were implanted 2 to 22 months prior to CMRI (median interval 3 months). β-Adrenergic blockers, angiotensin-converting enzyme inhibitors, and amiodarone were given to 58, 40, and 12 patients, respectively. One patient underwent catheter ablation for frequent VT episodes.

Table 2. Results of Cardiac Magnetic Resonance Imaging in the Study Population*

Myocardial LGE present	48/50 (96)
The extent of myocardial LGE, %	17 (2–52)
Myocardial edema present	15/40 (38)
Basal interventricular septal thickness <4 mm	6/55 (11)
Left ventricular ejection fraction, %	43±13
Right ventricular ejection fraction, %	50±13
Left ventricular end-diastolic volume, mL	201±68
Right ventricular end-diastolic volume, mL	161±48
Left ventricular mass, g	109±33

The data are given as number of patients (%) or mean±SD or median (minimum–maximum). LGE indicates late gadolinium enhancement.
*LGE analyses, myocardial edema analysis, and volumetric measurements were possible in 50, 40, and 55 patients, respectively, of the 59 patients studied.

Findings at CMRI

Table 2 summarizes the results of CMRI. Myocardial LGE was found in all except 2 of the 50 analyzable studies (prevalence 96%), with a median extent of 17% of the LV mass. Myocardial edema and scar-like interventricular septal thinning (<4 mm) were less common observations (prevalence 38% and 11%, respectively). Examples of myocardial LGE and septal thinning

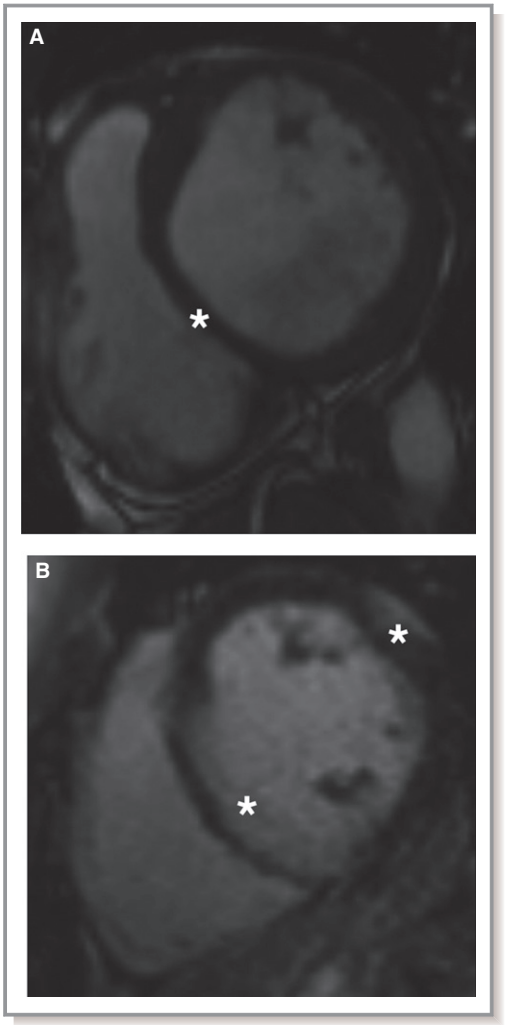

Figure 2. Examples of basal short-axis cardiac magnetic resonance imaging showing pathological thinning of the basal septum (A, asterisk) and late gadolinium enhancement in the interventricular septum and in the lateral left ventricular wall (B, white asterisks).

are shown in Figure 2. LVEF was impaired (<50%) in 36 of 55 patients (65%) and correlated inversely with both plasma N-terminal brain natriuretic propeptide on admission (r=−0.48; P<0.01) and the extent of LGE (r=−0.44; P<0.01). An impaired RVEF (<50%) was observed in 26 patients (47%). There was no difference between the means of RVEF in patients with and without pulmonary sarcoidosis (P=0.958).

Cardiac Events and Predictors of Event-Free Survival

The total follow-up time from CMRI to the end of the study varied from 1 to 132 months (median 26 months). Altogether 23 of 59 patients experienced an event contributing to the composite end point analysis after a median of 15 months of follow-up (range 1–130 months). The events comprised 3 cardiac deaths (all sudden cardiac arrests), 1 transplantation due to terminal heart failure, and 19 life-threatening arrhythmias including 5 aborted deaths due to VF and 14 VTs prompting ICD therapy (n=8) or needing external synchronized shock or defibrillation (n=6). After the end point VT, 1 additional patient died suddenly, 1 underwent transplantation, and 3 suffered an aborted sudden death owing to VF. Table 3 shows the results of Cox regression analyses on the CMRI variables as predictors of event-free survival. The univariate predictors were RVEF, the extent of LGE, and the presence of scar-like basal interventricular septal thinning (Figure 3) with no violation of the proportional hazards assumption. In multivariate analysis involving these 3 measurements, the extent of LGE by tertiles appeared as an independent prognostic factor (Table 3). The positive and negative predictive values for an end point event were 50% and 81%, respectively, for LGE extent >13% (second and third tertiles) and 75% and 76%, respectively, for LGE extent >22% (third tertile).

In addition to their relation to the CMRI measurements, the end point events were associated, without violation of the proportional hazards assumption, with VT/VF as the presenting manifestation of CS (hazard ratio 7.72, 95% CI 3.23–18.45, P<0.001) and with elevated plasma N-terminal brain natriuretic propeptide at presentation (hazard ratio 1.07 per +200 pg/mL difference, 95% CI 1.01–1.10, P=0.016) but not with either age or sex or New York Heart Association functional class. A multivariate Cox regression assessing the predictive value of myocardial LGE extent, plasma N-terminal brain natriuretic propeptide, and presentation with VT/VF was done in the 48 patients with complete data available. The results, given in Table 4, show that each variable was an independent predictor of event-free survival. Analyzed separately in the 41 patients without VT/VF at presentation, LGE predicted end point events with an hazard ratio of 4.35 (95% CI 1.33–14.22) per tertile of LGE extent (P=0.015). A combination of presentation with VT/VF or LGE extent >22% of LV mass had positive and negative predictive values for end point events of 74% and 92%, respectively.

Discussion

Our observations show that a comprehensive analysis of contrast-enhanced CMRI can provide a variety of clues to help clinicians evaluate the risk of life-threatening cardiac events in CS. Although extent of myocardial LGE, RVEF, and thickness of the basal interventricular septum were all predictive of event-free survival, extent of LGE was the predictor conveying

Table 3. Results of Cox Regression Analyses Involving the Different Cardiac Magnetic Resonance Imaging Measurements as Predictors of Event-Free Survival in Cardiac Sarcoidosis

	Univariate Analysis HR (95% CI)	*P* Value	Multivariate Analysis* HR (95% CI)	*P* Value
LVEF, per 5%	0.90 (0.77–1.06)	0.202		
LVEDV, per 10 mL	1.01 (0.96–1.06)	0.743		
RVEF, per 5%	0.81 (0.69–0.93)	0.004	0.99 (0.96–1.01)	0.277
RVEDV, per 10 mL	1.08 (1.00–1.17)	0.063		
LV mass, g	1.05 (0.94–1.17)	0.417		
LGE extent				
Per 1%	1.05 (1.02–1.09)	0.003		
Per tertiles	3.06 (1.56–6.04)	0.001	2.22 (1.07–4.59)	0.032
Myocardial edema present	1.55 (0.53–4.50)	0.425		
Thinning of basal septum	3.64 (1.31–10.12)	0.013	1.98 (0.65–6.03)	0.229

HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction.
*The multivariate model included RVEF, thinning of basal septum, and tertiles of extent of LGE.

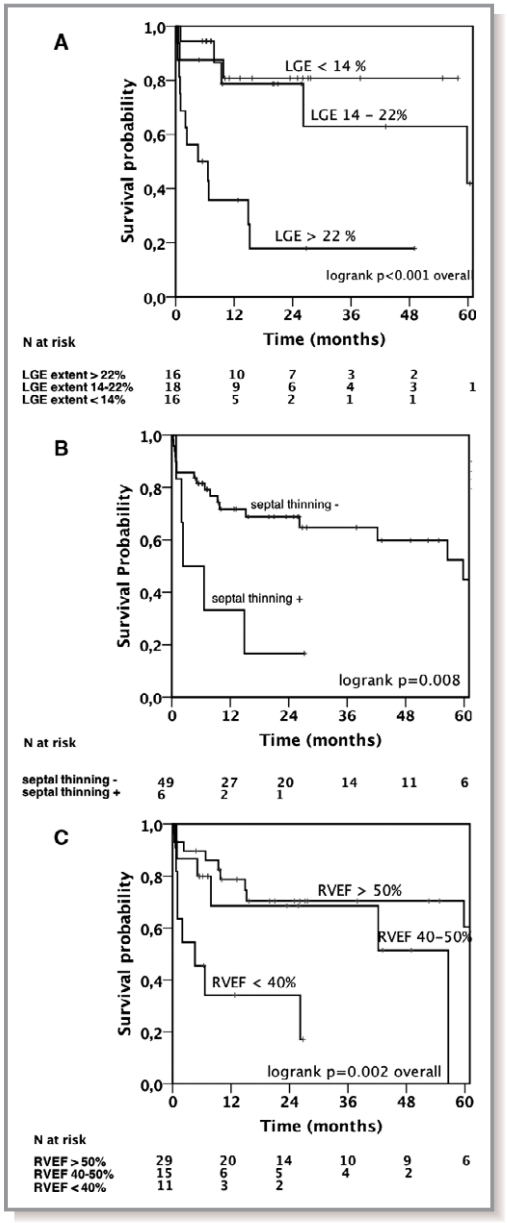

Figure 3. Kaplan–Meier curves for cardiac survival free of transplantation and life-threatening arrhythmias by tertiles of LGE extent (A), by absence (−) or presence (+) of septal thinning (B), and by RVEF (C). LGE indicates late gadolinium enhancement; RVEF, right ventricular ejection fraction.

most of the prognostic information from CMRI. Importantly, extent of LGE retained its prognostic value even after adjustment for the effects of clinical and laboratory predictors of outcome.

Life-Threatening Cardiac Events and Survival With CS

In our recent 25-year nationwide study of CS, the 10-year cardiac survival estimate was 93%, and the estimate of

Table 4. HRs From Multivariate Cox Regression Analysis Involving Extent of LGE in Cardiac Magnetic Resonance Imaging, Presentation With VT/VF, and Plasma NT-proBNP on Admission as Predictors of Event-Free Survival in 48 Patients With Cardiac Sarcoidosis

Predictors	HR (95% CI)	*P* Value
LGE extent, per tertiles	2.27 (1.08–4.77)	0.031
VT/VF as the main presenting clinical manifestation	9.63 (3.01–30.81)	<0.001
NT-proBNP, per +200 pg/mL difference	1.09 (1.02–1.16)	0.008

HR, hazard ratio; LGE, late gadolinium enhancement; NT-proBNP, N-terminal brain natriuretic propeptide; VF, ventricular fibrillation; VT, ventricular tachycardia.

transplant-free cardiac survival was 91% in patients diagnosed clinically and given contemporary treatment with drugs and devices.[1] Although these estimates are better than the earlier figures, even for 5-year survival (40–75%),[19–21] CS remains a potentially fatal disease. With current heart failure therapy, including use of mechanical support devices and heart transplantation, the overwhelming majority of deaths from CS are caused by sudden cardiac arrests. In our nationwide study, 11 of 110 patients underwent heart transplantation and only 1 patient died of terminal heart failure, whereas 21 patients had either a sudden (n=10) or an aborted sudden (n=11) arrhythmic death.[1] Although an acute complete heart block may sometimes initiate the cascade of fatal events, spontaneous ventricular tachyarrhythmias and VF ultimately arrest the heart in CS. Prevention and management of VT and VF take priority in today's clinical care and research of CS,[3] especially because rapid progress in the treatment of the underlying myocardial inflammation is unlikely in the near future. It is worth noting that 22 of 23 end point events analyzed in this study were attributable to fatal or life-threatening arrhythmias; heart failure was not an event unless it was severe enough to lead to transplantation.

CMRI as a Prognostic Study for CS

Two earlier works provided valuable information on the predictive value of CMRI in CS.[11,12] Both were retrospective in design and relied on the criteria of the Japanese Ministry of Health and Welfare for diagnosis of CS.[22,23] Crawford et al[11] studied 51 patients with normal or mildly reduced LVEF (>35%) and showed that life-threatening arrhythmias during follow-up (VT/VF, 13 events) were associated with myocardial LGE, particularly when this was multifocal or involved the right ventricle. Ise et al[12] followed 43 CS patients for a composite end point of cardiac death, life-threatening ventricular arrhythmias (VT/VF), and hospitalization for heart failure. Of the 23 events observed, 16 were related to heart failure (5 deaths and 11 hospitalizations), and 7 were due to ventricular

arrhythmias (1 death and 6 VT/VF). No cardiac transplantations were reported despite the frequency of severe heart failure. The extent of myocardial LGE was superior to all other CMRI variables (including LVEF) in predicting event-free survival and retained its significance even after adjustment for the prognostic effects of New York Heart Association functional class and plasma brain natriuretic peptide. Our findings support these 2 data sets but also add to the knowledge by identifying impaired RVEF and basal septal thinning as CMRI variables portending poorer outcome. The predictive value of RV function had also been suggested in an earlier study by Schuller et al[24] revealing that RV dysfunction, shown by echo, nuclear imaging, or MRI, predicted life-threatening arrhythmias in CS patients with an ICD. In addition, the data of Crawford et al[11] and Blankstein et al[25] suggest that life-threatening arrhythmic events in CS may be related to inflammatory involvement of the RV wall. Unfortunately, we could not distinguish whether RV dysfunction in our patients resulted mainly from direct RV involvement or from LV disease-related pulmonary hypertension.

Scar-like thinning of the basal interventricular septum at echocardiography has long been known as a typical but nonspecific diagnostic sign of CS.[26] In a very recent retrospective analysis of echocardiographic studies in 74 patients with CS, Nagano et al[27] showed that basal septal thickness <4 mm (or ≤60% of middle septal thickness) predicted future symptomatic arrhythmias and admissions for heart failure. Our work showed that a comparable degree of septal thinning by CMRI also predicted serious events, mainly fatal and life-threatening ventricular arrhythmias, even if not incrementally to the prognostic value of myocardial LGE extent. The low prevalence (11%) of septal thinning, as defined in this study (<4 mm), limits its value as an outcome predictor. As shown in Figure 3B, the great majority of end point events were seen in patients without septal thinning.

Could Myocardial LGE Help Select Patients for ICD Implantation in CS?

According to the expert consensus statement of the Heart Rhythm Society,[3] ICD implantation "is recommended" (class 1 indication) in CS for patients with spontaneous sustained ventricular arrhythmias or LVEF <35%. Furthermore, ICD "can be useful" (class 2a indication) for patients with (1) an indication for permanent pacemaker, (2) unexplained syncope or near syncope felt to be arrhythmic in origin, or (3) inducible sustained VT or relevant VF. Finally, ICD "may be considered" (class 2b indication) in patients with LVEF between 36% and 49% and/or RVEF <40%. The last recommendation was based mainly on 3 cohorts of CS patients with an ICD showing that ICD therapies were common, even in patients with mildly reduced LVEF.[2,24,28] The value of myocardial LGE as an indication for an ICD in patients with normal LVEF was considered but dismissed by the experts.[3] We think that the late observations on the predictive value of myocardial LGE, summarized in Table 5, call for a reevaluation of the recommendation at this point. Importantly, LGE predicted cardiac events despite normal or mildly reduced LV function,[11] and in the study by Ise et al[12] and in our study, it even outperformed LVEF, the key prognostic factor in CS reported previously.[1,2,8,24,29] It is worth discussing whether some definition of myocardial LGE, for example, extent ≥22% of LV mass or involvement of the RV wall or involvement of ≥9 of 29 combined LV and RV segments (Table 5), should be added as a new or strengthening indication for an ICD in patients with CS and normal or mildly reduced LV function. In our study, extent of LGE had prognostic value over and above the

Table 5. Summary of Reports Describing the Value of LGE at CMRI as a Predictor of Serious Cardiac Events in CS

Study	Number of Patients	Follow-up, Months	Composite End Point Events	Number of Events	CMRI Finding	Predictive Value for End Point Events	
						Positive, %	Negative, %
Crawford et al[11]	51	48 (mean)	Death or VT/VF	15	LGE ≥6% of LV mass	58	91
					LGE in ≥9 of 29 segments*	72	97
					RV LGE present	100	95
Ise et al[12]	43	39 (mean)	Cardiac death, VT/VF or hospitalization for heart failure	23	LGE ≥21.9% of LV mass	62	86
Present work	59	26 (median)	Cardiac death, VT/VF or transplantation	23	LGE >22% of LV mass	75	76
					LGE >22% of LV mass or VT/VF at CS presentation	74	92

CMRI indicates cardiac magnetic resonance imaging; CS, cardiac sarcoidosis; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Seventeen LV and 12 RV segments.

significance of presenting life-threatening arrhythmias, suggesting it could genuinely help clinicians decide which patients need an ICD for primary prevention.

Strengths and Limitations

A major strength of our work was that the diagnosis of CS was based on myocardial histology in the majority of patients and conformed to the latest diagnostic criteria[3] in the remainder. Most of the comparable previous work[11,12,19,24,25,27] relied mainly on the Japanese diagnostic criteria,[22,23] which suffer from problems with sensitivity and specificity[3,4,8,10,29] and are no longer endorsed by experts in the field.[3] The generic limitations of retrospective studies apply to our work, as they do to all other outcome data in CS because of the lack of prospective research. It is also worth recognizing that our study population may have been skewed toward the severe end of the CS spectrum because ours is the only transplant center in Finland. Our study was relatively small in size, and we had to reject a modest part (15%) of the LGE studies from analyses because of quality problems. Still, we believe the number of end point events in LGE analyses (20 events in 50 patients) was sufficient for meaningful survival analyses.[30] Our composite end point event of life-threatening arrhythmias consisted of VF (fatal if not treated) and sustained VT requiring ICD therapy or external cardioversion or defibrillation. It is quite likely that not all of the VTs prompting appropriate ICD therapy would have resulted in cardiac arrest at the time of the event. Finally, it is also a limitation that LGE of the RV free wall was not studied.

Conclusions

Our study suggests that carefully analyzed CMRI helps predict serious cardiac events in patients with CS. The extent of myocardial LGE in particular appears to contain useful prognostic information. We recommend its routine measurement and inclusion in the assessment of the risk of life-threatening cardiac events in CS.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of CS patients with and without CMRI data

	Present study (n=59)	No CMRI done (n=59)	p
Main presenting clinical manifestation, n			
Atrioventricular conduction block	25	33	0.141
Ventricular tachycardia or fibrillation	18	11	0.134
Heart failure	13	11	0.647
Other	3	4	0.697
New York Heart Association functional class			
I	27	21	0.261
II	25	27	0.711
III – IV	7	10	0.432
Left ventricular ejection fraction at echocardiograpy, %	48 ±13	45 ±16	0.297
NT-proBNP, pg/mL	450 (56 - 6428)	363 (85 - 23022)	0.102
Abnormal cardiac ^{18}F-FDG PET	28/31	28/35	0.243

Data are number of patients, mean±standard deviation or median and range in parentheses

NT-proBNP indicates N-terminal brain natriuretic propeptide; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

Table S2. Comparison of patients with and without quality cine CMRI images

	Good quality cine (n=55)	Excluded due to cine quality (n=4)	p
Main presenting clinical manifestation, n			
Atrioventricular conduction block	23	2	0.749
Ventricular tachycardia or fibrillation	18	0	0.170
Heart failure	11	2	0.162
Other	3	0	0.632
New York Heart Association functional class			
I	26	1	0.388
II	23	2	0.749
III – IV	6	1	0.400
Left ventricular ejection fraction at echocardiograpy, %	47 ±13	55 ±11	0.263
NT-proBNP, pg/mL	476 (56 - 6428)	324 (67 - 1460)	0.574
Abnormal cardiac ^{18}F-FDG PET	25/28	3/3	0.551

Data are number of patients, mean±standard deviation or median and range in parentheses

NT-proBNP indicates N-terminal brain natriuretic propeptide; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

Table S3. Comparison of patients with and without quality LGE CMRI images

	Good quality LGE (n=50)	Excluded due to LGE quality (n=9)	p
Main presenting clinical manifestation, n			
Atrioventricular conduction block	20	5	0.385
Ventricular tachycardia or fibrillation	16	2	0.558
Heart failure	11	2	0.988
Other	3	0	0.451
New York Heart Association functional class			
I	21	6	0.277
II	23	2	0.278
III – IV	6	1	0.939
Left ventricular ejection fraction at echocardiograpy, %	47 ±13	50 ±12	0.651
NT-proBNP, pg/mL *	439 (56 - 6428)	580 (85-1291)	0.315
Abnormal cardiac ^{18}F-FDG PET †	22/23	6/8	0.156

Data are number of patients, mean±standard deviation or median and range in parentheses

NT-proBNP indicates N-terminal brain natriuretic propeptide; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.