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Rates and predictors for sustained ventricular tachycardia in patients with cardiac sarcoidosis and AV block as first cardiac presentation: Implications for device implantation

Borislav Dinov, MD,[1] Carsten Henfling,[2,3] Hans Ebbinghaus, MD,[2] Konrad Latuscynski, MD,[2] Ingo Paetsch, MD,[2] Cosima Jahnke, MD,[2] Samuel Sossalla, MD,[1] Ulrich Laufs, MD,[3] Laura Ueberham, MD[3]

ABSTRACT

BACKGROUND Atrioventricular block (AVB) is a frequent initial presentation of cardiac sarcoidosis (CS), but dangerous ventricular arrhythmias (VA) can occur. Despite the scarcity of data, guidelines recommend implantable cardioverter-defibrillator (ICD) rather than a pacemaker implantation whenever a device is needed.

OBJECTIVE In this study, we aimed to establish predictors for sustained VA in patients with CS presenting with pacing indication because of an AVB.

METHODS We prospectively enrolled 112 patients with CS. Excluding those with VA, 82 patients remained and were divided into 2 groups: 34 individuals with AVB as initial presentation and 48 with other symptoms as first presentation (OSF). Both groups were compared for clinical characteristics, rates of VA, left ventricular assist device (LVAD) implantation, heart transplantation, and mortality.

RESULTS During follow-up, VA was detected in 50% in the AVB and 10.4% in the OSF group ($P = .001$). Death, LVAD implantation, and heart transplantation occurred in 11.8% in AVB group vs 10.4% in the OSF group ($P = .847$). Late gadolinium enhancement (LGE) was equally observed in both groups: 70% vs 70.5% ($P = .966$), whereas more patients in the AVB group exhibited abnormal positron emission tomography (PET) uptake: 86.2% vs 54.3% ($P = .007$). In multivariate analysis, AVB (hazard ratio [HR], 25.15), right ventricular (RV) LGE in cardiovascular magnetic resonance (CMR) (HR, 7.39) were predictors for VA occurrence, whereas the use of immunosuppressive therapy was associated with less VA (HR, 0.26).

CONCLUSIONS Patients with CS presenting with AVB have a high risk of sustained VA. Although immunosuppressive drugs may reduce the occurrence of VA, ICD implantation is reasonable, especially in case of RV LGE.

KEY WORDS Cardiac sarcoidosis; AV block; Ventricular tachycardia; Pacemaker; ICD; Late gadolinium enhancement; Immunosuppressive therapy

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Introduction

Cardiac sarcoidosis (CS) is considered an infrequent manifestation of systemic sarcoidosis, although the reported prevalence in some populations and geographical regions is unusually high.[1–5] Frequent cardiac presentations are heart failure, syncope, ventricular tachycardia (VT), atrioventricular block (AVB), and rarely sudden cardiac death (SCD).[4–6] Because none of these is specific for CS, the diagnosis can be easily overlooked, which can lead to delayed therapy and poor survival. Older data from autopsy studies of patients with sarcoidosis indicated that the cause of death may be related to heart lesions in 46.9% of cases.[7]

AVB can be the first manifestation of CS long before the occurrence of VT, and in patients with preserved left

From the [1]1st Department of Cardiology and Angiology, Medical University of Giessen and Marburg (UKGM), Giessen, Germany, [2]Department of Electrophysiology, Helios Heart Center of Leipzig (HZL), Leipzig, Germany, and [3]Department of Cardiology, University Hospital of Leipzig, Leipzig, Germany.

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ventricular ejection fraction (LVEF) may result in withdrawal of life-saving implantable cardioverter-defibrillator (ICD) therapy. Therefore, the Heart Rhythm Society and European Society of Cardiology/European Heart Rhythm Association guidelines recommend ICD implantation in CS patients with indications for pacemaker (PM) (level of evidence IIA).[8,9] However, studies show high rates of inappropriate ICD shocks in CS that are related to progression of scarring, poor ventricular sensing, and high prevalence of atrial fibrillation.[10,11] Moreover, the effects of immunosuppressives on the cardiovascular outcomes is not well studied and controversial.[12–14] Therefore, in the broad spectrum between asymptomatic cardiac lesions and malignant ventricular arrhythmias (VA), we need to identify those patients who are most likely to require prophylactic ICD implantation.

Abbreviations

ACE: angiotensin-converting enzyme

AVB: atrioventricular block

COPD: chronic obstructive pulmonary disease

CMR: cardiovascular magnetic resonance

CS: cardiac sarcoidosis

EMB: endomyocardial biopsy

FDG: fluorodeoxyglucose

FU: follow-up

HR: hazard ratio

ICD: implantable cardioverter-defibrillator

IS: immunosuppressive

LBB: left bundle branch

LGE: late gadolinium enhancement

LV: left ventricular

LVAD: left ventricular assist device

LVEF: left ventricular ejection fraction

OSF: other symptoms as first presentation

PET: positron emission tomography

PM: pacemaker

RV: right ventricular

SCD: sudden cardiac death

sIL2R: soluble interleukin-2 receptor

SUV: standardized uptake value

TCL: tachycardia cycle length

VA: ventricular arrhythmia

VF: ventricular fibrillation

VT: ventricular tachycardia

Methods

Purpose of the study

The purpose of this study was to establish the rate of new-onset sustained VT/ventricular fibrillation (VF) in a contemporary group of patients with CS, excluding those with the highest risk for SCD. More specifically, we compared the survival and the rates of VT in CS patients presenting with an AVB and indication for PM with a group of lower-risk individuals without AVB or VT. Furthermore, we aimed to identify predictors for the occurrence of sustained VA that may help to refine the indication for ICD or PM implantation.

Patient cohort

Between 2015 and 2023, we included in a registry 196 patients with suspected CS who were evaluated after a comprehensive protocol including cardiovascular magnetic resonance (CMR), fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), left ventricular (LV) and right ventricular (RV) endomyocardial biopsy (EMB) or transbronchial lymph nodes biopsy, and serum markers for sarcoidosis. Genetic testing was performed in some patients; however, no systematical genetic counseling had been performed. Of the 196 cases, 112 patients fulfilled the Japanese Circulation Society 2016 criteria for sarcoidosis with cardiac involvement.[15] Finally, 82 patients were included in the analysis after exclusion of those who presented initially with VA. Of them, 19 were diagnosed based on positive EMBs; 43 were clinically diagnosed based on positive histology in the lungs; 1 had parotid gland epithelioid granulomas; the rest were diagnosed based on clinical (chest radiograph or history of sarcoidosis) and laboratory findings strongly suggesting sarcoidosis and symptoms of cardiac involvement after exclusion of other possible causes. Isolated CS was histologically confirmed in 12 patients (Table 1).

Patients who presented with high-degree AVB as well as those who had already received a PM implantation because of AVB (AVB first) were compared with the rest (OSF, other

Table 1 Baseline clinical characteristics

Baseline characteristics	AVB (n = 34)	OSF (n = 48)	*P*
Age, y, mean ± SD	49.4 ± 11.5	52.6 ± 11.6	.222
Sex (F), n (%)	17 (50)	18 (37.5)	.365
Arterial hypertension, n (%)	17 (50)	29 (60.4)	.375
Diabetes mellitus, n (%)	2 (5.9)	10 (20.8)	.110
Extracardiac sarcoidosis (histo+), n (%)	14 (41.2)	30 (62.5)	.073
Pulmonary sarcoidosis (histo +), n (%)	14 (41.2)	29 (60.4)	
Parotitis (histo +), n	0	1 (2.1)	
Isolated cardiac sarcoidosis (EMB+), n (%)	8 (23.5)	4 (8.3)	.066
Previous COPD/asthma diagnosis, n (%)	4 (11.8)	11 (22.9)	.253
Smoking, n (%)	3 (8.8)	8 (16.7)	.348
Dyspnea, n (%)	22 (64.7)	38 (79.2)	.206
Syncope, n (%)	18 (52.9)	5 (10.4)	.001
Atrial arrhythmias, n (%)	13 (38.2)	28 (58.3)	.116
Previous pacemaker/ICD devices, n (%)	11 (32.4)	1 (2.1)	.001
Devices, end of FU, n (%)	32	17	.0001
No device	2	31	
2-pacemaker	10	3	
2-ICD	9	2	
1-ICD	0	5	
S-ICD	0	1	
CRT-P	1	0	
CRT-D	12	6	
LVEF, mean ± SD	46.4 ± 13.3	43.9 ± 16	.471
Beta-blockers, end of FU, n (%)	22 (64.7)	33 (68.8)	.812
Antiarrhythmic drugs (class I and III), n (%)	7 (20.6)	4 (8.3)	.201
Amiodarone, n	4	3	
Sotalol, n	1	0	
Flecainide, n	1	1	
Sotalol + Mexiletine, n	1	0	

AVB = atrioventricular block; COPD = chronic obstructive pulmonary disorder; CRT–D = cardiac resynchronization therapy with a defibrillator; CRT–P = cardiac resynchronization therapy pacemaker; EMB = endomyocardial; FU = follow-up; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; OSF = other symptoms as first presentation.

symptoms first) in regard to baseline characteristics, EMB, imaging findings, and immunosuppressive (IS) therapy. The presence of late gadolinium enhancement (LGE) in myocardium was evaluated with contrast-enhanced T1 CMR, using 2 SD from the pixel signal intensity of the remote myocardium and the extent of the LV LGE was calculated as a percentage of the LV mass. The volume of the LV scar (%) was measured automatically from the 3D LGE sequences, using a short-axis stack covering the LV, using dedicated software (Philips IntelliSpace Portal 7; Philips Healthcare, Best, The Netherlands). The images were magnified, and the endocardial and epicardial contours were traced manually for each slice. Scar was defined using the full width at half maximum technique. The presence of LV myocardial edema was assessed using T2 mapping. ^{18}FDG-PET was performed after a 24-h low-carbohydrate, high-fat diet and at least 12 hours of fasting, accepting standardized uptake value (SUV_{max}) > 2.4 as a diagnostic threshold.

Patients with symptoms suggesting active and ongoing inflammation were treated with IS drugs, mostly glucocorticoids, according to the same protocol. Individuals with weight >80 kg received 40 mg prednisolone/day, whereas patients <80 kg received 30 mg prednisolone/day. This dose was maintained for a month and was reduced by 5 mg every 2 weeks until a maintenance dose of 7.5 mg/day, which was continued for at least 2 years. In cases with a lack of sufficient therapeutic effects or adverse reactions under glucocorticoids, another IS drug, usually methotrexate or azathioprine, was started.[16]

All patients were followed up for at least 1 year for occurrence of sustained VA. ICD implantation was performed in cases with recurrent VA, worsening LV function, or induction of VA with programmed RV stimulation. Adverse events such as death, heart transplantation, or implantation of LV assist devices (LVAD) were documented. The study complies with the Declaration of Helsinki and was approved by the local ethics committee (016/20–ek).

Statistical analysis

Continuous variables with normal distribution were presented as mean value ± SD, or median with interquartile range if not normally distributed. Categorical variables were reported as percentages. We tested for normal distribution using the Kolmogorov–Smirnow's test. Categorical variables were compared with Fisher's exact test. Continuous variables were compared using either a Student *t* test or Mann–Whitney *U* test. Event–free survival was estimated with Kaplan–Meier method. We used Cox proportional hazards model to find the predictors for the VT/VF occurrence. As a dependent variable, we used the time to occurrence of first VT/VF. The model included relevant variables as well as variables that showed significant difference in the univariate analysis with a 2-sided $P < .1$. Statistical significance was considered as 2-sided $P < .05$. Analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY).

Results

Baseline clinical characteristics

Of the 112 patients included, 34 (30.3%) presented initially with high-degree AVB (AV block II Mobitz, 2:1 or more, AVB III or previously implanted PM); 30 (26.8%) with VA, 23 (20.5%) with newly diagnosed heart failure with reduced ejection fraction (EF), and 25 (22.4%) with other symptoms (supraventricular arrhythmias, premature ventricular beats, fatigue, bundle branch blocks, asymptomatic LGE in CMR). After exclusion of the VT/VF patients, 82 remained and were divided into 2 groups, AVB-first and OSF. Both groups were comparable with respect to baseline characteristics (Table 1). The mean LVEF in both groups was nearly normal. Significantly more patients in the AVB group experienced syncope (52.9% vs 10.4%; $P < .0001$) or already had an implanted pacemaker.

Differences in the laboratory and imaging characteristics

EMB was performed in 54 patients, 26 (76%) in the AVB group and 28 (58.3%) in the OSF group ($P = .103$). Significantly more EMB with noncaseating granulomas was observed in the AVB group: 35.3% vs 14.6 % ($P = .036$). The plasma levels of ACE, soluble interleukin-2 receptor, and neopterin at the time of diagnosis were not different.

Table 2 Imaging and laboratory characteristics

Laboratory characteristics	AVB (n = 34)	OSF (n = 48)	*P*
EMB performed, n (%)	26 (76 %)	28 (58.3 %)	.103
EMB positive for CS, n (%)	12 (35.3 %)	7 (14.6 %)	.036
ACE at diagnosis, mean ± SD	40.8 ± 18	41 ± 22.2	.924
sIL2R at diagnosis, mean ± SD	465 ± 250	496 ± 391	.711
Neopterin at diagnosis, mean ± SD	13.9 ± 9.7	12.2 ± 6.8	.408
Imaging			
CMR with LGE, n = 74 (%)	21/30 (70%)	31/44 (70.5%)	.966
LGE Vol%, mean ± SD	14.7 ± 13.7	15.4 ± 13.5	.856
CMR myocardial edema, n (%)	10/30 (30%)	13/44 (29.5%)	.805
RV involvement	6/30 (20%)	8/44 (18.2%)	.809
^{18}FDG PET abnormal, n = 64 (%)	25/29 (86.2%)	19/35 (54.3%)	.007
$SUV_{max,}$ mean ± SD	8.0 ± 5.0	4.3 ± 4.9	.005

ACE = angiotensin-converting enzyme; CMR = cardiovascular magnetic resonance; EMB = endomyocardial; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement; PET = positron emission tomography; RV = right ventricular; sIL2R = soluble interleukin-2 receptor; SUV = standardized uptake value.

Seventy-four of 82 patients (90%) without contraindications (CMR-incompatible devices, electrodes not connected, or temporary pacing electrodes) underwent CMR either before or after PM implantation. Myocardial edema and LGE were frequently observed without significant differences between the groups (Table 2). The volume of LGE (LGE Vol%) was calculated in 48 patients, and the mean LGE was comparable between the AVB and OSF groups: 14.7 ± 13.7 vs 15.4 ± 13.5 Vol% ($P = .856$), respectively. RV involvement was present in 20% of the AVB group vs 18% in the OSF ($P = .809$).

^{18}FDG-PET during the first hospital admission was performed in 64 patients and was abnormal in 25 (86.2%) in the AVB group vs 19 (54.3%) in the OSF group ($P = .007$). Furthermore, SUV_{max} of the myocardial ^{18}FDG uptake was more intense in the AVB: 8.0 ± 5.0 vs 4.3 ± 4.9 ($P = .005$). Fifty-eight patients received both CMR and ^{18}FDG-PET during the same period; 39 showed overlap between LGE and FDG uptake; 10 patients had LGE in CMR but normal myocardial uptake, indicating fibrotic, noninflammatory stage; 9 showed no signs of cardiac involvement in CMR but abnormal myocardial ^{18}FDG uptake.

Rates of unfavorable outcomes: Death, LVAD, heart transplantation, and new VT/VF

The median follow-up for VT was 24 (interquartile range, 12–48) months. Rates of death, LVAD, or heart transplantation were similar between the groups: 4 of 34 patients (11.8%) in the AVB group vs 5 of 48 (10.4%) ($P = .847$). During follow–up, sustained VT/VF occurred in 50% in the AVB group vs 10.4% in the OSF group ($P = .001$; Figure 1). For the entire cohort, the mean ventricular tachycardia cycle $length_{min}$ was 330 ± 83 ms. and the mean ventricular tachycardia cycle $length_{max}$ was 355 ± 91 ms, without significant differences between the AVB and OSF groups. Most VTs, except in 1 case, were monomorphic; 5 patients in the AVB group experienced ICD shocks (Table 3 and Figure 2). Furthermore, no significant differences were found in the major adverse cardiac events and rate of VT between both sexes: major adverse cardiac events in males, 4 of 37 (8.5%) vs that in females, 5 of 35 (14.4%; $P = .486$); rates of VT in males vs that in females: 14 of 47 (29.8%) vs 8 of 35 (22.9%; $P = .616$). However, RV was significantly more frequently affected in men than in women: 12 of 47 (25.5%) vs 1 of 35 (2.9%; $P = .002$).

Table 3 Therapy and adverse events

Outcomes	AVB (n = 34)	OSF (n = 48)	P
VT occurrence	17 (50 %)	5 (10.4)	.001
Mono vs polymorphic/VF, n	16/1	5/0	
ICD shocks	5	0	
Death	3 (8.8%)	2 (4.2%)	.385
Death, heart transplantation or LV assist device	4 (11.8 %)	5 (10.4%)	.847
Immunosuppressive drugs	28 (82.4%)	28 (58.3%)	.030

AVB = atrioventricular block; ICD = implantable cardioverter-defibrillator; LV = left ventricular; OSF = other symptoms as first presentation; VF = ventricular fibrillation; VT = ventricular tachycardia.

Predictors for VT/VF occurrence in patients with AV block

In univariate analysis, AVB (HR, 8.55; 95% confidence interval [CI], 2.86–25.52) and RV LGE in CMR (HR, 2.92; 95% CI, 1.33–6.99) were associated with occurrence of VT/VF. In the multivariate model, the presence of AVB (HR, 25.15; 95% CI, 7.07–120) and RV LGE (HR, 7.39; 95% CI, 2.64–20.68) were associated with VT/VF (Table 4). IS therapy was associated with a lower probability of VT/VF (HR 0.26; 95% CI, 0.06–0.82).

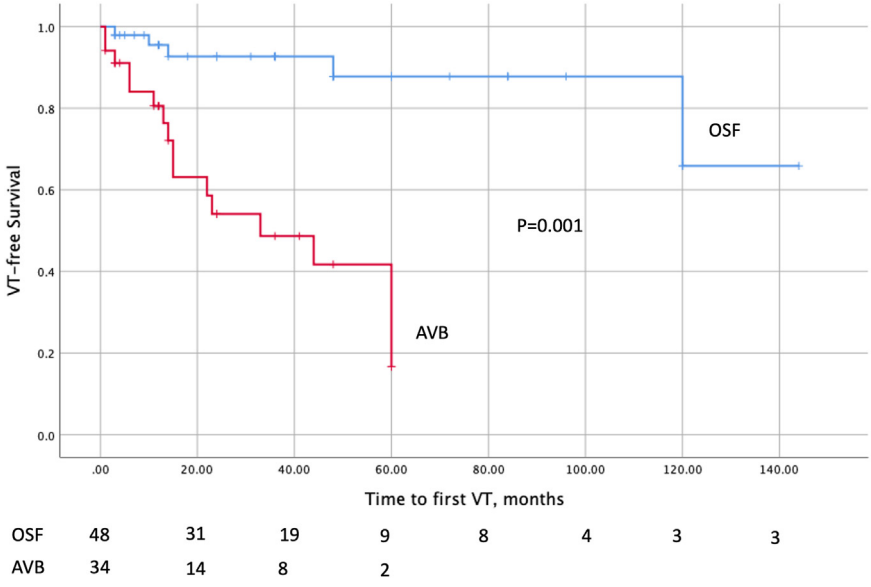

Figure 1
Kaplan–Meyer curves for VT occurrence in AVB and OSF. The *red line* shows the freedom of VT in AVB, and the *blue line* shows the VT–free survival of patients with OSF, showing significantly higher likelihood of VT in patients with AVB. AVB = atrioventricular block; OSF = other symptoms as first presentation; VT = ventricular tachycardia.

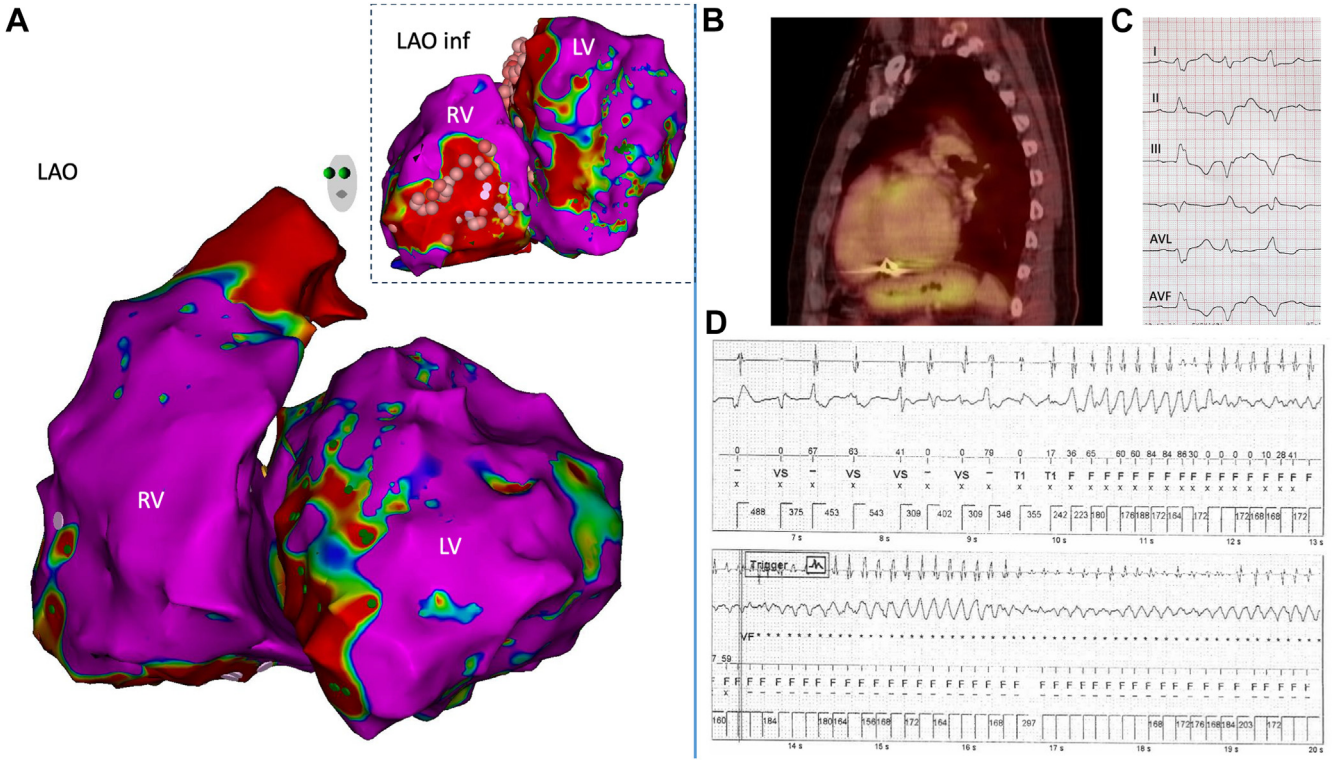

Figure 2
Voltage map and occurrence of polymorphic VT/VF in a patient with cardiac sarcoidosis. **A:** Electro-anatomical map showing low-voltage areas in the RV outflow tract and inferior wall as well as LV septum in LAO view and inferior. **B:** ^{18}FDG–PET showing corresponding areas of increased SUV_{max}. **C:** Polymorphic premature ventricular beats arising from inferior. **D:** ICD interrogation showing occurrence of a polymorphic VT with degeneration in VF. FDG = fluorodeoxyglucose; ICD = implantable cardioverter-defibrillator; LV = left ventricular; PET = positron emission tomography; RV = right ventricular; SUV = standardized uptake value; VF = ventricular fibrillation; VT = ventricular tachycardia.

Discussion

Cardiac sarcoidosis is an important cause of AVB in younger patients, which untreated may progress to VA, heart failure, and even death.[5,6,14] Despite the initially preserved LV EF, the risk of VA in patients with CS is considered high. In the 2014 Heart Rhythm Society guidelines for diagnosis and management of arrhythmias in CS, the writing group reached consensus that "ICD implantation can be useful in patients with CS and indication for permanent pacemaker," although the evidence is limited.[8] More recently, the 2022 European Society of Cardiology guidelines for prevention of SCD recommended an ICD implantation if there is significant LGE in CMR and after resolution of the acute inflammation.[9] However, in patients with CS who received ICD for primary

Table 4 Univariate and multivariate Cox regression analysis for predictors for VA

	Univariate			Multivariate		
Co–variates	HR	CI 95%	*P*	HR	CI 95%	*P*
AV block	8.55	2.86–25.52	.001	25.15	7.07–120	.001
Male sex	1.4	0.59–3.35	.447			
Age, y	0.97	0.93–1.00	.068			
LVEF	0.99	0.97–1.02	.648			
^{18}FDG PET (+)	0.396	0.11–1.40	.149			
^{18}FDG PET SUV_{max}	1.064	0.98–1.15	.125			
LGE in CMR	0.46	0.13–1.59	.219			
LGE Vol %	0.97	0.93–1.04	.296			
RV involvement	2.92	1.33–6.99	.016	7.39	2.64–20.68	.001
EMB (+)	0.47	0.19–1.14	.093			
Immunosuppressants	1.05	0.40–2.78	.925	0.26	0.06–0.82	.011

CMR = cardiovascular magnetic resonance; EMB = endomyocardial; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; PET = positron emission tomography; RV = right ventricular; SUV = standardized uptake value; VA = ventricular arrythmias.

prevention, Betensky and colleagues[10] observed a 17% rate of inappropriate ICD therapies. Moreover, in those who experienced appropriate ICD therapies, the mean LVEF was 35%, suggesting limited benefit from primary prevention ICD in the general population of CS patients.[10]

For the clinical practice, establishing criteria that may help to select those patients who are most likely to benefit from ICD implantation is important. Because of the rarity of the disease, randomized studies comparing ICD with PM are scarce, and the existing evidence is limited to small, poorly characterized cohorts. In a retrospective study, Takaya et al[17] observed high prevalence (50%) of VT in 22 individuals with CS and AVB, which was comparable to the rates in those who presented initially with VA.[17] Recently, in a retrospective study of 398 patients with definite and probable CS, Nordeswan et al[18] identified 59 cases without an ICD indication. In this small fraction of CS patients (15%), the reported 5-year incidence of VA or SCD was 53 %.[18] Unfortunately, because of the retrospective nature of the study, CMR and PET data were missing, and the results did not reflect the contemporary management of CS patients. In contrast to the latter, we studied prospectively a larger, contemporary cohort of CS patients who were diagnosed using a structured protocol including CMR, ^{18}FDG-PET, and EMB. During the follow–up period of 5 years, 50% of those who initially presented with AVB returned with VA, as compared with only 12% in the control group, despite the preserved LVEF. In this regard, our results are in line with the VA rates observed in the Finnish registry and confirm the high risk of VA in patients with AVB. More cases with positive EMB were observed in the AVB group, which is also in line with the observations of Nordeswan et al,[18] who found that the only predictor for future ICD was the histological proof in EMB.[18]

An advantage of our study was that data on the LV scar and inflammation were available in most of the patients because we used CMR and ^{18}FDG–PET routinely as a part of the diagnostic workup protocol. LGE in CMR is recognized as a major risk factor for VA and death in patients with nonischemic CM, and a similar association was also reported for patients with CS.[19–21] Previously, Assomull et al[22] demonstrated that LGE extent >5 % of the LV mass was associated with an excessive risk for SCD and adverse events in patients with nonischemic cardiomyopathy.[22] In individuals with CS, LGE > 22% of the LV was associated with the worst survival, whereas LGE < 14 % was associated with more favorable outcomes.[23] In our study, the amount of LGE was equally large in both groups; however, the fact that VAs occurred more frequently in the AVB patients suggests that LGE is not the only predisposing factor for VT in those. A hypothetical explanation could be the inflammatory infiltration of the His–Purkinje system causing both conduction abnormalities and increased automaticity. Also, the combination of conduction slowing, retrograde His–Purkinje fibers activation, and myocardial scars may predispose to occurrence of reentry VA in AVB patients. Nevertheless, some technical limitations of LGE quantification such as incomplete LV coverage, devices artifacts, and LGE definition method make the establishing of a valid LGE cutoff for SCD risk a difficult task.

In AVB patients, ^{18}FDG-PET was frequently positive and SUV_{max} was twice higher than the OSF, suggesting more severe inflammation and more aggressive course in the former. Regarding the role of ^{18}FDG-PET, several studies reported that higher SUV_{max} in CS was associated with more VTs and unfavorable events.[24–26] In our study, abnormal ^{18}FDG uptake was a risk factor in univariate analysis, although in a multivariate model its significance was mitigated by other confounders. However, ^{18}FDG-PET scan can be particularly useful for evaluation of the effects of IS therapy and may prompt adjustments of the therapy in phases of acute relapses. An LGE to FDG uptake mismatch occurs in some AVB patients that may be explained by more severe and recent onset of inflammation in the AVB group as compared with the later fibrotic stage.

In case reports and small studies, IS treatment improved the patient's condition so AVB and PM implantation could be avoided.[13,14] However, no convincing data suggest the risk of SCD diminishes under IS therapy even after the AVB resolution. Therefore, the most challenging task in the management of CS patients with AVB is to identify those in whom ICD implantation might still be necessary. In multivariate analysis, we identified several patients' characteristics that were linked to VA occurrence. The presence of AVB itself was a strong independent predictor for VT/VF and was associated with a 21-fold risk of VT/VF. Although LGE was linked to higher risk for malignant VA in patients with nonischemic dilated cardiomyopathy and in CS in particular, in our cohort, the presence of LGE and its extent were not associated with occurrence of new VTs. A possible explanation is that both groups already had high amounts of LGE (approximately 15%) at the time of diagnosis; furthermore, the highest-risk patients with VA as presenting symptom were excluded from the analysis.[23]

Although not the main purpose of this research, we observed that use of IS therapy was associated with fewer VTs. Evidence for the therapeutic effects of glucocorticoids in CS is controversial, and some authors even suggest deleterious pro-arrhythmic effects of glucocorticoids.[16] In a smaller study of 20 patients with CS, the burden of ventricular premature beats increased under glucocorticoids therapy.[27] In contrast, we found that glucocorticoids alone or in combination with a second immunosuppressive drug may reduce the risk for VA.

In contrast to ischemic cardiomyopathy, neither the LVEF nor the presence and extent of LGE could reliably distinguish CS patients who will develop VT in a lifetime. Special considerations pertain to patients with an AVB and RV involvement in CMR, because of the very high risk of VT occurrence. The latter has been confirmed in previous studies reporting associations between RV LGE, abnormal RV uptake in PET on 1 side, and SCD and VA on the other side.[28] An example of a patient with an AVB, RV LGE, and positive PET scan who developed sustained VT is shown in Figure 3.

Finally, although primary prevention ICD implantation is reasonable for CS patients presenting with an AV block, the

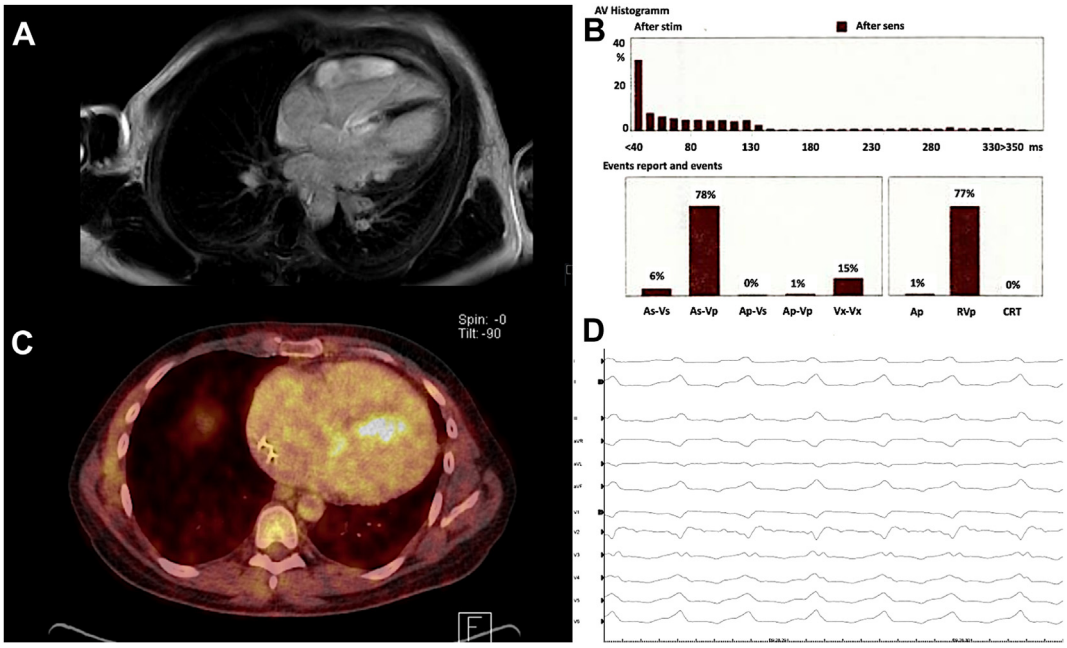

Figure 3
Example of a patient with EMB-proven isolated cardiac sarcoidosis presenting with AVB as first symptom. **A:** CMR image showing wall-thickening and LGE at basal intraventricular septum and RV free wall as in acute stages of CS. **B:** Interrogation of a pacemaker 1 month after implantation showing continuous RV stimulation. **C:** FDG-PET after 6 months of glucocorticoid therapy showing persistent inflammation at the basal intraventricular septum. **D:** Occurrence of a monomorphic VT, LBB with an early precordial transition, positive concordance, TCL 380 ms, after 9 months. AVB = atrioventricular block; CMR = cardiovascular magnetic resonance; CS = cardiac sarcoidosis; EMB = endomyocardial; FDG = fluorodeoxyglucose; LBB = left bundle branch; LGE = late gadolinium enhancement; PET = positron emission tomography; RV = right ventricular; TCL = tachycardia cycle length; VT = ventricular tachycardia.

high anxiety burden associated with this chronic illness necessitates an appropriate discussion about the high likelihood of experiencing appropriate and inappropriate shocks, as well as obtaining informed consent and providing continuous psychological support.

Limitations

The baseline characteristics and the outcomes might be biased because of the special profile of our institution. Possibly more patients with heart failure would present in general hospitals. Although not significant, more patients with AVB received EMB that further resulted in more histologically positive EMB, which explains why more patients in the AVB group were treated with IS. Changes in the IS medication during the course of the disease could influence the outcomes but were not addressed in this paper. Also, in the AVB group, VTs can be more frequently detected by interrogation of the PMs. An important limitation of this cohort is its racial structure, because it consists of patients of the white race and of North European decent only; however, sarcoidosis shows significant racial and geographical differences in incidence, phenotypic presentation, and mortality. Therefore, these results cannot be transferred unconditionally to Asians or black Americans. Finally, from a statistical point, the size of the population is small, which may influence the results and explains the wide range of the CIs.

Conclusions

Individuals with CS and AVB as initial symptoms have a very high risk for developing sustained VT/VF in their lifetime. At the time of presentation, most patients have large amounts of LGE in CMR despite the nearly normal LVEF and ongoing inflammation in FDG -PET. Special considerations pertain to patients with AV block and RV LGE in CMR that is associated with a high risk for VA. Our observations support the current recommendations that ICD implantation may be reasonable in patients with CS and high-degree AVB, regardless of the LVEF. However, it seems that the risk for VA remains high regardless of the amount of LGE or inflammation status. Treatment with IS drugs may reduce the rates of future VTs and can be considered in CS patients to reduce the burden of ICD therapies.

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Address reprint requests and correspondence: Borislav Dinov, MD, 1st Department of Cardiology and Angiology, Medical University of Giessen and Marburg, Klinikstrasse 33; 35392 Giessen, Germany. E-mail address: dinov@gmx.de

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