

Review Article



Management of Arrhythmias Associated with Cardiac Sarcoidosis

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Received: Nov 30, 2018

Accepted: Dec 24, 2018

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Writing - original draft: Yada H. Writing - review & editing: Soejima K.

ABSTRACT

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. The annual incidence of systemic sarcoidosis is estimated at 10–20 per 100,000 individuals. Owing to the recent advances in imaging modalities, cardiac sarcoidosis (CS) is diagnosed more frequently. The triad of CS includes conduction abnormality, ventricular tachycardia, and heart failure. Atrial and ventricular arrhythmias are caused by either inflammation or scar formation. Inflammation should be treated with immunosuppression and antiarrhythmic agents and scar formation should be treated with antiarrhythmics and/or ablation, in addition to implantable cardioverter defibrillator (ICD) implantation, if necessary. Ablation can provide a good outcome, but it might require bipolar ablation if the critical portion is located mid-myocardium. Late recurrence might be caused by reactivation of sarcoidosis, which would need to be evaluated by positron emission tomography-computed tomography imaging. Risk of sudden cardiac death (SCD) in patients with advanced atrioventricular block is not low, and ICD implantation could be considered instead of a pacemaker. For risk stratification for SCD, late gadolinium enhancement by cardiac magnetic resonance imaging or program stimulation is often used.

Keywords: Arrhythmias, cardiac; Sarcoidosis; Catheter ablation; Immunosuppression; Defibrillators, implantable

CLINICAL MANIFESTATION

Sarcoidosis is a systemic, non-caseating granulomatous disease of unknown etiology, and it affects multiple organs, such as the respiratory system, skin, nerves, heart, and liver. The etiology remains unknown, but it has been suggested to be the product of endogenous genetic susceptibility and an unknown antigenic stimulus. The prognosis of sarcoidosis is mainly affected by the cardiac involvement. Clinical cardiac involvement occurs in 5% of cases, but subclinical involvement varies widely from 3.7% to 54.9%.¹

⁴) Clinically manifesting cases are just the tip of the iceberg in cardiac sarcoidosis (CS). Typical symptoms of CS include palpitations, near syncope, syncope, dyspnea, orthopnea, or sudden cardiac death (SCD).³) These symptoms occur because of atrioventricular block (AVB), supraventricular arrhythmias, ventricular arrhythmias, or heart failure.⁵) Symptomatic patients with CS are more likely to be diagnosed with and have worse adverse cardiac events.

A nationwide study in Finland over 25 years showed CS patients with heart failure symptoms have the worst long-term outcome with a transplantation-free cardiac survival of only 53%.⁵⁾ The majority of asymptomatic patients with CS have a benign clinical course. Patel et al.⁶⁾ showed that 14 of 21 (66.7%) patients who were diagnosed with CS based on positive results on late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging had no cardiac symptoms. The presence of LGE was the independent predictor of potentially lethal events and other adverse events.⁷⁾ Ventricular arrhythmias and sudden death can occur in asymptomatic patients. As such, risk stratification for SCD in CS, especially in asymptomatic patients, is important.

VENTRICULAR ARRHYTHMIAS

Mechanisms of ventricular arrhythmias associated with CS include reentrant and focal (triggered activity or abnormal automaticity). The reentrant form is more associated with a late scar phase, and triggered activity or abnormal automaticity is more associated with an inflammatory phase. Naruse et al.⁸⁾ reported on a series of 37 patients with CS. Of those, 14 patients developed recurrence of ventricular tachycardia (VT) following therapy with corticosteroid and antiarrhythmic agents. A total of 57 VTs were induced in these patients; 14 VTs were non-sustained, 6 were polymorphic, 6 were related to the Purkinje system, and 31 were related to scar areas. Purkinje-related VTs were observed in 5 patients, all of whom had conduction abnormalities such as PR prolongation and right bundle branch block. Four of the 5 patients had an infra-Hisian conduction defect, one had an H-V block, and 3 had a prolonged H-V ≥ 55 ms.

Risk stratification

In the diagnosis of cardiac involvement of sarcoidosis, CMR,⁹⁾¹⁰⁾ ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET),¹¹⁾¹²⁾ and the combination of CMR and FDG-PET¹³⁾ are all very sensitive modalities. A nationwide study in Finland reported more than a 20-fold increase in the annual detection rate and predominance of isolated CS that might be explained by the advancement of imaging modalities.⁵⁾ Furthermore, these advanced modalities help to predict death and other cardiac events. CMR is one of the established imaging modalities for risk stratification of ventricular arrhythmia and death in ischemic and non-ischemic cardiomyopathy. Cardiac FDG-PET may also be useful for risk stratification, but there has not been enough data for it to be recommended. Programmed electrical stimulation (PES) is mainly used to evaluate the indication of ICD for patients with left ventricular ejection fraction (LVEF) >35% who had myocardial scars proven by LGE on CMR.

Cardiac magnetic resonance

The characteristic of LGE distribution in CS is a non-coronary artery disease pattern most frequently located in the right ventricle (RV) of the interventricular septum, followed by a patchy intramural or transmural distribution in the entire left ventricle (LV).⁷⁾ Several CMR studies⁶⁾⁷⁾¹⁴⁾ have evaluated the presence of LGE and its association with adverse events, but because of the small size of the studies, various composite end points, and inconsistent results, the magnitude of the association between LGE and adverse events has been unclear. A systemic review and meta-analysis of the prognostic value of LGE on CMR by Hulten et al.¹⁵⁾ identified 7 studies with 694 subjects. The mean age of patients was 53 years (42% male) with preserved LVEF (mean LVEF: 59 \pm 4%). One hundred and ninety-nine of 694 (29%) patients were LGE positive. Cardiovascular mortality occurred in 10 LGE-positive versus 2 LEG-

negative patients (1.9% vs. 0.3%). Ventricular arrhythmias occurred in 41 LGE-positive versus 0 LGE negative patients (5.9% vs. 0%). It was suggested that a positive LGE in patients with CS had an association with cardiovascular death or ventricular arrhythmia.

A systemic review and meta-analysis of the prognostic value of LGE has been reported.¹⁶⁾ Ten studies with a total of 760 patients and a mean follow-up of 3.0 ± 1.1 years were included. Mean age was 53 years (41% male), and the average LVEF was $57.8 \pm 9.1\%$. The LGE-positive patients had higher odds of arrhythmogenic events (ventricular arrhythmias, SCD, appropriate ICD discharge/aborted SCD) and all-cause mortality compared with those without LGE (odds ratio [OR], 10.74; $p < 0.00001$). For the annualized event rates of the composite endpoint, patients with LGE had significantly higher rates of events than patients without LGE (11.9% vs. 1.1%, $p < 0.001$).

Greulich et al.⁷⁾ reported a meta-analysis of 155 patients with systemic sarcoidosis who underwent CMR for work-up of suspected CS involvement. The 39 patients (25.5%) with LGE showed a Cox hazard ratio (HR) of 31.6 for death, aborted SCD, or appropriate ICD discharge. In this report, LGE on CMR was superior to functional and clinical parameters such as LVEF or LV end-diastolic volume, or presentation such as heart failure. The presence of myocardial scarring identified by LGE was the best independent predictor of potentially lethal events.

Risk stratification using CMR was evaluated in 205 patients with LVEF $> 50\%$ and with extracardiac sarcoidosis.¹⁷⁾ LVEF, right ventricular ejection fraction (RVEF), and LGE burden were measured. Forty-one of 205 (20%) patients had LGE on CMR and 12 of 205 died or had VT during follow-up, 10 of which (83%) were in the LGE positive group. The rate of death/VT per year was > 20 times higher than in the LGE negative group (4.9% vs. 0.2%, $p < 0.01$). Death/VT were associated with greater burden of LGE ($14 \pm 11\%$ vs. $5 \pm 5\%$, $p < 0.01$) and right ventricular dysfunction (RVEF: $45 \pm 12\%$ vs. $53 \pm 28\%$, $p = 0.04$). LGE was the best predictor of death/VT.

There was consensus that risk stratification by CMR for sudden death may be considered in patients with CS.

Cardiac positron emission tomography

FDG-PET to assess for inflammation with/rubidium-82 to assess for myocardial perfusion has been used in the evaluation of CS. In a retrospective study of 38 patients with suspected CS referred for FDG-PET CT with myocardial perfusion imaging, 9 patients experienced adverse clinical events.¹⁸⁾ Quantitative measurement of FDG volume-intensity was the only independent predictor of events by multivariate analysis. Abnormal FDG uptake was improved with immunosuppressive treatment in 5 of 6 patients.

In a larger study of 118 patients with CS, FDG-PET with myocardial perfusion imaging studies were performed,¹⁹⁾ with 31 (26%) adverse events (27 VT and 8 deaths) observed. This study also reported that cardiac PET findings were predictive of adverse events, and the presence of both perfusion defects and abnormal FDG uptake (29% of patients) was associated with adverse events (HR, 3.9; $p < 0.01$). The presence of a focal perfusion defect and FDG uptake on cardiac PET identified patients at higher risk for death or VT.

A retrospective analysis was performed on 203 patients who underwent perfusion and FDG-PET imaging with a mean follow-up of 1.8 years.²⁰⁾ Sixty-three of 203 (31%) patients developed adverse events (death, heart transplantation, or ventricular arrhythmia requiring

defibrillation). After robust adjustment, only the quantitative measures of extent and severity of perfusion-metabolism mismatch and the coefficient of variation of FDG uptake provided an incremental prognostic advantage.

Although FDG-PET can identify inflammation, it lacks the capability to detect irreversible scar tissue, which is a known substrate for reentrant VT. Another study evaluated the use of hybrid FDG-PET and CMR for diagnostic and prognostic assessment.²¹ Fifty-one patients underwent simultaneous PET/CMR following a high-fat/low-carbohydrate diet and 12-hour fast. The sensitivity and specificity of PET/CMR was estimated using Japanese Ministry of Health and Welfare guidelines.²² Hybrid PET/CMR was superior to PET or CMR alone for detecting CS with a sensitivity of 0.94, specificity of 0.44, and positive and negative predictive values of 0.76 and 0.80, respectively. There were 18 (35%) adverse events with a median 2.2-year follow-up. Abnormalities in both PET and CMR was the strongest predictor of major adverse cardiac events. Hybrid PET/CMR simultaneously evaluated cardiac inflammation and scar formation.

Given the paucity of data, the Heart Rhythm Society (HRS) expert consensus recommendation did not include FDG-PET in the sudden death risk stratification.⁴ The main roles of cardiac FDG-PET are to evaluate inflammation of the myocardium, decide whether to utilize immunosuppressive therapy, or to evaluate efficacy of the treatment.

Programmed electrical stimulation

PES is usually performed for patients with LVEF >35% and positive LGE-CMR. Aizer et al.²³ reported the usefulness of PES in 32 patients with CS. In their series, patients with spontaneous (n=6), inducible sustained ventricular arrhythmia by PES (n=6), inducible non-sustained ventricular arrhythmia (n=1), sustained ventricular arrhythmia after PES (n=1), or syncope at presentation (n=1) received ICD implantation. Younger patients and men were more likely to be inducible for sustained arrhythmias by PES. During a mean follow-up of 32 months, 9 of 12 (75%) patients received appropriate ICD shock. In contrast, two of 20 (10%) patients without ICD insertion experienced sustained ventricular arrhythmia or sudden death. Mehta et al.²⁴ reported on 76 patients with evidence of CS on PET or CMR who underwent PES. Over a median follow-up of 5 years, 6 of 8 (75%) patients in the group with inducible ventricular arrhythmias developed ventricular arrhythmia or death, compared with 1 death in the negative group. Positive PES may be useful to identify patients at risk for ventricular arrhythmia. The authors of this study emphasized that patients in the cohort with a negative PES appear to have a benign course within the first several years following diagnosis.

Immunosuppressive therapy and more

While immunosuppressive therapy may be useful in the inflammatory phase, it is unlikely to be useful in the late scar phase. Of the immunosuppressants, corticosteroids are most commonly used in CS. However, a majority of the studies on corticosteroids evaluated its effect on atrioventricular (AV) conduction recovery²⁵ with a small series on ventricular arrhythmia with conflicting data. Futamatsu et al.²⁶ reported on 7 CS patients with VT (6 sustained and 1 non-sustained) who received corticosteroid therapy. Six of the 7 (86%) patients had no recurrence of VT over a 48.8±38.7-month follow-up, but 5 of the 7 (71%) patients were concomitantly started on amiodarone therapy. As a result, the pure effect of corticosteroid for ventricular arrhythmias was unclear. Yodogawa et al.²⁷ reported the effect of corticosteroid therapy (initial dose 30 mg/day) on 31 patients with premature ventricular contraction (PVC; ≥300 /day) or non-sustained VT (NSVT) using 24-hour Holter ambulatory monitoring before

and after therapy. Overall, corticosteroid therapy did not alter PVC or NSVT. However, a significant reduction of PVCs (from $1,820 \pm 2,969$ to $742 \pm 1,425$, $p=0.048$) and NSVT (from 41% to 6%, $p=0.039$) was found in less advanced LV dysfunction patients ($EF \geq 35\%$, $n=17$). This study concluded that corticosteroid therapy may be effective for ventricular arrhythmias in the early stage, but less effective in the late stage. Another recent report evaluated the time course and factors associated with VT in 68 CS patients treated with a corticosteroid.²⁸⁾ Twenty patients (29%) experienced VTs; 14 of 20 (70%) patients had VTs in the first 12 months after corticosteroid therapy. The gallium (Ga) scintigraphy had a significant correlation with VTs (HR, 11.33; $p<0.001$). VTs frequently recurred in the first 12 months after initiation of corticosteroid therapy. Electrical storm had 2 peaks after corticosteroid therapy: in the first 12 months and in the very late phase (after 60 months). A multivariable analysis showed that positive Ga scintigraphy (HR, 11.33; $p<0.001$) and low LVEF (HR, 0.94; $p=0.001$) were predictors for VT recurrence. This result suggested that VTs after corticosteroid treatment might be related to reactive cardiac sarcoid inflammation proven by Ga scintigraphy.

Methotrexate and azathioprine are used for CS as an alternative for patients who were refractory to corticosteroid or were unable to tolerate its side effects. Nagai et al.²⁹⁾ evaluated the efficacy of combination therapy of a low dose steroid and weekly methotrexate ($n=10$) when compared with steroid-treated patients ($n=7$) in CS. The study was a small open-label study that included 17 patients. LVEF, cardiothoracic ratio and N terminal pro B-type natriuretic peptide levels were significantly more stabilized in the combination group than in the corticosteroid-only group. However, no data exist regarding this combination therapy in ventricular arrhythmia.

If steroids or antimetabolites do not work, targeted tumor necrosis factor alpha can be used. Infliximab and adalimumab have shown some efficacy in treating pulmonary sarcoidosis. Theodore et al.³⁰⁾ reported a case with electrical storm who failed antiarrhythmics and endocardial and epicardial ablation, but was controlled with adalimumab.

Antiarrhythmic therapy

The data on the antiarrhythmic medication in CS is scarce. Class I agents are not recommended in patients with scarring based on adverse outcomes reported in other structural heart diseases.³¹⁾ Usually, class III agents are used. However, the incidence of amiodarone pulmonary toxicity is 5% to 15% in patients on higher (daily dose of 400 mg or more) doses of amiodarone, and 1.6% in patients on lower doses. Therefore, amiodarone might be deferred in patients with advanced pulmonary sarcoidosis.

Kron et al.³²⁾ reported that 197 of 235 patients (83.8%) had lung involvement of sarcoidosis. Sotalol was frequently used in 58 patients (24.7%), compared with 45 patients (19.2%) treated with amiodarone. In Naruse's report on 37 patients, 27 patients were on amiodarone, 4 were on procainamide, and 1 was on bepridil although, 32 patients had pulmonary sarcoidosis.⁸⁾

Device therapy

Implantable cardioverter defibrillator

The general implantable cardioverter defibrillator (ICD) guideline documents apply to patients with CS. ICD implantation is recommended in patients with CS and spontaneous sustained ventricular arrhythmia, including those with prior cardiac arrest and/or LVEF $\leq 35\%$ despite optimal medical therapy and a period of immunosuppression if indicated (class I). Left ventricular function should be reassessed following heart failure medication

optimization and immunosuppression if indicated. The only additional CS-specific class IIa recommendation is that an ICD can be useful in patients with an indication for permanent pacemaker implantation.⁴⁾ Implantation of a dual chamber pacemaker defibrillator in CS patients has several advantages including potential AVB development and atrial fibrillation (AF) detection. However, some CS patients with normal LVEF and no symptoms of heart failure have high event rates when LGE is confirmed on magnetic resonance imaging (MRI).

Several papers reported that a lower LVEF in CS was associated with appropriate ICD therapy, and even patients with relatively preserved LVEF (36–49%) carried a substantial risk with appropriate ICD therapy.³²⁻³⁴⁾ Schuller et al.³⁴⁾ reported that covariates associated with appropriate ICD therapies were LVEF <55% (OR, 6.52), RV dysfunction (OR, 6.73), and symptomatic heart failure (OR, 4.33). Of 112 patients, 16 patients (14.3%) developed ICD storm (3 or more shocks in 24 hours); identified predictors of ICD storm were LV dysfunction (OR, 6.71) and RV dysfunction (OR, 3.86). The HRS expert consensus statement summarized the class IIb ICD recommendation for those patients with mild-to-moderately reduced LVEF (36–49%) and/or reduced RVEF (<40%) despite optimal medical therapy and a period of immunosuppression.⁴⁾ Class IIa ICD indications in CS are as follows: 1) An indication for patients with permanent pacemaker implantation, 2) unexplained syncope or near-syncope, felt to be of arrhythmic etiology, 3) inducible ventricular arrhythmia (>30 seconds of monomorphic or polymorphic VT) or clinically relevant VF. For some asymptomatic CS patients with normal LVEF and RVEF, CMR and PES are useful for further risk stratification of SCD. Patients with both LGE-MRI and PES positivity are classified as having class IIa indications for ICD (summarized in **Figure 1**).

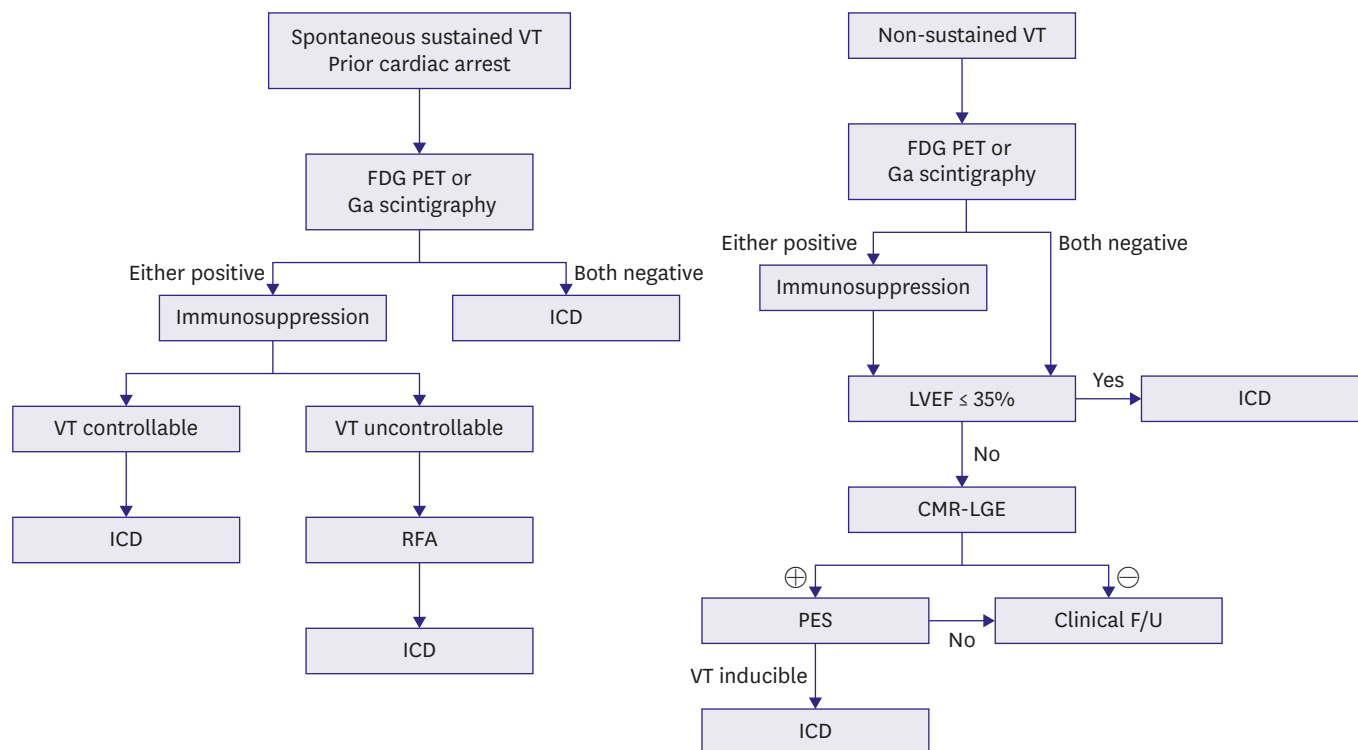


Figure 1. Management of ventricular arrhythmias in patients with CS. CS = cardiac sarcoidosis; CMR = cardiac magnetic resonance; FDG-PET = ¹⁸F-fluorodeoxyglucose-positron emission tomography; F/U = follow-up; Ga = gallium; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; PES = programmed electrical stimulation; RFA = radiofrequency ablation; VT = ventricular tachycardia.

Adverse events associated with device therapy

The frequency of adverse events associated with CS has been reported at approximately 15%.^{32,33)} The most common adverse event was lead trouble, including dislodgement or fracture, which might be because of the relatively young age and high number of advisory ICD leads included in the study. The second most common adverse event was device infection. Six of 235 patients (2.6%) had infection complications and 4 patients were on steroids. There is not enough data to guide relative timing of immunosuppression and device implantation. However, ICD implantation should ideally be performed when immunosuppressive therapy is at the lowest possible maintenance dose or is temporarily withheld, if clinically feasible.

Inappropriate ICD shocks have been reported at a rate of 4.1–5.7% per year,³²⁻³⁴⁾ most commonly for supraventricular tachycardia, including AF, atrial flutter (AFL), and atrial tachycardia (AT). Patients with CS are relatively young and sinus tachycardia also causes inappropriate shocks. On the basis of these data, ventricular arrhythmia detection and therapy settings should be tailored to each patient with CS. Many patients with CS have NSVT and longer tachycardia detection may be useful to avoid unnecessary ICD shock delivery.

Wearable cardioverter defibrillator

The wearable cardioverter defibrillator (WCD) has been shown to be beneficial, especially in patients with acute myocardial infarction, newly diagnosed heart failure, or a transient condition that will require later assessment.³⁵⁾ Reek et al.³⁵⁾ reported the utility of WCD in 46 patients with CS. The median age was 48 years and LVEF was 30%. Of these, 10 patients (22%) developed ventricular arrhythmias over a range of 1 to 79 days. The first shock successfully terminated ventricular arrhythmia in 100% of cases. Seven patients received an ICD, 1 died after the discontinuation of WCD, and 2 were lost to follow-up. Among the patients without shock, 16 patients received an ICD, while 7 patients had improved LVEF.

Ablation

VT is considered to be caused by reentry associated with scarring, triggered activity, or abnormal automaticity due to active inflammation. Therefore, the management of VT with active inflammation is somewhat difficult. It is often resistant to drug or immunosuppression therapy.

A systemic review of catheter ablation for VT in patients with CS³⁶⁾ included 83 patients from 5 papers. The mean age was 50±8 years, 53 males/30 females with a maximum of 56 patients receiving immunosuppressive therapy. The mean LVEF was 39.1±3.1% and 94% had ICD. The median number of VTs was 3 (2.6–4.9)/patient, and the mean cycle length was 360 ms (326–400 ms). All patients received endocardial ablation and 18% required epicardial ablation. Relapse occurred in 45 of 83 (54.2%) patients; 26 patients underwent a second and 4 patients required a third ablation. For the less stringent endpoint (i.e., freedom from arrhythmia or reduction of ventricular arrhythmia burden), 61 of 83 (88.4%) patients showed improvement after the ablation. Overall, the effectiveness of catheter ablation to diminish or abolish VTs in patients with CS has been shown on the basis of the pooled data, with a relapse incidence of 0.33 (95% confidence interval [CI], 0.108–0.551; $p < 0.004$).

Jefic et al.³⁷⁾ described the role of catheter ablation in 9 patients with CS. Most of the VTs were due to the reentrant mechanism and were mapped using entrainment mapping and pace mapping. The most common location of the reentrant circuit was the para-tricuspid area, and the ablation was based on the predominant location of scarring detected by LGE-CMR to eliminate VTs in these patients.³⁸⁾

Kumar et al.³⁹⁾ reported the result of VT ablation in 21 patients with CS. Multiple reentrant VTs (median of 3 VTs with a median cycle length of 355 ms) were inducible. Eight patients underwent epicardial mapping in addition to the endocardial mapping. Mapped chambers were RV only (6 patients, 29%), LV only (3 patients, 14%), and both (12 patients, 57%). The pattern of the scarring was different for RV and LV. RV scarring was confluent with no predilection for any particular region. LV scarring was patchy with predilection for the septum, anterior wall, and perivalvular regions. Epicardial RV scarring was present in 7 of 8 (88%) patients and exceeded the region of the corresponding endocardial scar. The LV epicardial scar did not correspond to the endocardial scar, was patchy, and was located in the basal septum, lateral mitral annulus, the crux of the heart, and LV summit. Catheter ablation was effective in terminating ≥ 1 VT in the majority of patients (19 of 21 patients, 91%). Complete success was achieved in 43% of patients. Non-clinical VT remained inducible in 24% of patients. Some clinical VTs remained inducible in 24%, and spontaneous VT remained inducible in 10% of patients. Of 7 patients with VT storm, ablation resolved 5, or 71%, of VT storm. Nine patients underwent a second ablation and 7 of 9 (78%) patients had at least one VT abolished. Reasons for failed ablation for some inducible VTs were as follows: septal intramural circuits (9 procedures), extensive RV scarring with multiple reentry circuits (6 procedures), or sites of origin in close proximity to the left anterior descending coronary (3 procedures), the ramus intermedius (1 procedure), or the para-Hisian region (1 procedure).

VT recurrence was common, but ablation was particularly effective in treating VT storm and may provide palliation of recurrent uncontrollable ventricular arrhythmias.

Predictors of long-term outcomes of catheter ablation for VT in patients with CS have been evaluated.⁴⁰⁾ Twenty-three patients were evaluated by both of LGE-MRI and PET; 21 (91%) were LGE positive, and 15 (65%) were PET positive. Immunosuppressive treatment with steroids was started before the ablation for patients with active inflammation. Overall, VT-free survival was 55% at 2-year follow-up. Although VT recurrence occurred in 16 patients (52%), VT burden was significantly reduced: 8 patients (50%) had only isolated VT episodes. Positive PET predicted a 4-fold VT recurrence, and a 2-fold recurrence if there was no improvement of PET despite immunosuppressive therapy. Therefore, inflammation status was considered the definite predictor for recurrent ventricular arrhythmia.

Recent report on electroanatomical mapping and imaging modalities, including CMR and PET/CT, showed that abnormal electrograms were more likely located in segments with more scar transmural by LGE and a lower degree of inflammation.⁴¹⁾ Catheter ablation was a safe and effective approach for long-term control of ventricular arrhythmias. Advanced imaging of CMR and PET was helpful for identifying a higher risk of VT recurrence after ablation.

Differentiating from arrhythmogenic right ventricular cardiomyopathy/dysplasia

There have been several reports on clinically similar manifestations of CS and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).³⁸⁾⁴³⁾ The 2010 diagnostic criteria for ARVC/D occasionally cannot discriminate ARVC/D from CS.⁴⁴⁾ The discrimination of these two etiologies is challenging but crucial, as immunosuppressive therapy could prevent the progression of heart failure, conduction abnormality, or tachyarrhythmia. Among 1,140 patients enrolled in the Johns Hopkins ARVC/D registry, 15 patients with definite 2010 diagnostic criteria for ARVC/D were subsequently diagnosed with

CS. Patients with CS were older at presentation, had longer PR or high-grade AVB, longer H-V, more inducible VT, and mediastinal lymphadenopathy.⁴⁵⁾

Dechering et al.³⁸⁾ compared VTs in 18 patients with CS (n=8) and ARVC/D (n=10). Patients with CS had significantly lower LVEF ($35.6 \pm 19.3\%$ vs. $60.6 \pm 9.4\%$; $p=0.02$) and wider QRS (0.146 vs. 0.110 seconds; $p=0.004$) than did patients with ARVC/D. Almost all patients with CS had reduced LVEF (<50%). The number of inducible VT was 3.7 VTs in patients with CS vs 1.8 in patients with ARVC/D ($p=0.0001$). In their cohort, the VT origin was apical more often in CS than in ARVC/D.

Kumar et al.³⁹⁾ reviewed 100 consecutive patients with RV cardiomyopathy and/or who received RV-related VT ablation with RV cardiomyopathy (51 ARVC/D, 22 CS, 27 RV cardiomyopathy of unknown source [RCUS]). Baseline characteristics of patients with CS showed a high prevalence of bundle branch block and advanced AVB, wide QRS, and lower LVEF. RV endocardial mapping demonstrated larger RV endocardial scars in CS. All 3 groups had perivalvular (peri-tricuspid and/or peri-pulmonic) RV endocardial scarring and RV apical involvement was equally observed. In contrast, RV septal involvement was more common in CS. Patients with CS displayed more LV involvement compared with patients with ARVC/D and RCUS. Patients were followed up for a median 25 months after their final catheter ablation procedure. The VT-free survival and survival free of death or transplant were significantly worse in the CS group than in other groups. The results of catheter ablation are summarized in **Table 1**.

CONDUCTION ABNORMALITIES

Right bundle branch block can be observed in 12–32% of patients with CS,⁴⁷⁾ even with relatively preserved left ventricular function. In known extracardiac sarcoidosis patients, newly-developed right bundle branch block can be a sign of CS. AV nodal conduction could recover with corticosteroids. Patients who were treated with corticosteroids had AV conduction improvement, with no improvement in the untreated group.²⁵⁾ Although AV conduction recovers in some patients, device implantation is recommended as recovery is unpredictable. Also, because of the possible infection risk of immunosuppression, device implantation might be better performed before steroid initiation.

Per the 2014 expert consensus statement of the HRS,⁴⁾ device implantation can be useful in patients with CS with an indication for pacing, even if the AVB reverses transiently (class IIa). Immunosuppression can be useful in patients with CS presenting with Mobitz II or 3rd degree AVB. ICD implantation can be useful in patients with CS and can be an indication for permanent pacemaker implantation. Nordenswan et al.⁴⁸⁾ reported that high-grade AVB is not a benign condition, not even when presenting as the only manifestation of cardiac involvement. The 5-year risk of SCD in middle-aged patients was 34% if the AVB presented with VT or severe LV dysfunction, and was still significant (9–14%) when AVB was the only sign of CS or when presented with non-severe LV dysfunction. The 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/HRS Focused Update listed ICD implant for CS as reasonable and class IIa (level of evidence: C).⁴⁹⁾ Although these findings support the ICD implant for all CS patients presenting with high-grade AVB, it is not reimbursed in some countries. In addition, if a temporary pacemaker is inserted, it is not

Table 1. Baseline characteristics and outcomes of VT ablation studies in patients with CS

Study	Number of patients	Age	Gender (No.)	LVEF (%)	RVEF (%)	Mapping system, catheters	Power, temperature, duration	Number of inducible VTs and CL	Ablation site, No. (%)			VT recurrence
									RV endo	LV endo	Epi	
Koplan et al. ⁴²⁾	8	42±8	Male: 6 Female: 2	34±15	N/A	CARTO	Max 50 W, 60° (non-irrigation)	Mean: 4	Ablation site: N/A	Ablation site: N/A	Ablation site: N/A	6/8 (75%)
						Navistar 4/8 mm	40–50° (irrigation)	CL: N/A	RV mapping: 8 (100%)	LV mapping: 6 (75%)	Epi mapping: 2 (25%)	
						Thermocool 3.5 mm						
Jefic et al. ³⁷⁾	9	46.7±8.6	Male: 7 Female: 2	42±14	N/A	CARTO	60°, 30–60 seconds (non-irrigation)	Mean: 4.9	6 (67%)	4 (44%)	1 (11%)	4/9 (44%)
						Navistar 4 mm	10 Ω impedance drop (irrigation)	Mean CL: 348±78 ms				
						Thermocool 3.5 mm						
Dechering et al. ³⁸⁾	8	39.1±10.3	Male: 4 Female: 4	39.1±10.3	40.4±9.6	CARTO	Endo: max power 50 W, 43°	Mean: 3.7	7 (88%)	1 (13%)	1 (13%)	4/8 (50%)
						Thermocool	Epi: <50 W with flow 20 mL/min	Mean CL: 326±88 ms				
Naruse et al. ³⁹⁾	14	60±10	Male: 3 Female: 11	40±12	N/A	CARTO	40–50 W, max 58° (non-irrigation)	Mean: 2.6	17/37 VTs (46%)	20/37 VTs (54%)	0	6/14 (43%)
						Navistar	30–40 W, max 42° (irrigation)	Mean CL: 400±97 ms				
						Thermocool						
Kumar et al. ⁴⁶⁾	21	47±9	Male: 17 Female: 4	36±14	RV dysfunction: 16/21 (76%) RVEF: N/A	CARTO	25–50 W, 10–20 Ω impedance drop	Median: 3	Endo 21 (100%) (detail of RV and LV: N/A)		5 (24%)	15/21 (71%)
						Navistar 4 mm		Median CL: 355 ms (240–600 ms)	RV mapping: 18 (86%)			
						Thermocool/Thermocool SF 3.5 mm			LV mapping: 15 (71%)			
Muser et al. ⁴⁰⁾	31	55±10	Male: 22 Female: 9	42±15	46±11	CARTO	Up to 50 W, 10–15 Ω impedance drop	Median: 3	Endo 31 (100%) (detail of RV and LV: N/A)		8 (26%)	16/31 (52%)
						Thermocool 3.5 mm		Mean CL: 369±77 ms	RV mapping: 18 (58%)	LV mapping: 21 (68%)		

CL = cycle length; CS = cardiac sarcoidosis; LV = left ventricle; LVEF = left ventricular ejection fraction; N/A = non-available; RVEF = right ventricular ejection fraction; RV = right ventricle; VT = ventricular tachycardia.

possible to obtain CMR. It might be useful to conduct PES with a temporary wire in a patient with preserved LVEF to evaluate for the risk of ventricular arrhythmia (Figure 2).

ATRIAL ARRHYTHMIAS

Incidence and mechanism

The data regarding the incidence of atrial arrhythmia in CS is scant. However, atrial arrhythmia is likely due to left ventricular dysfunction causing granulomatous inflammation, scarring of the atrium, and left atrial enlargement. Cain et al.⁵⁰⁾ evaluated 192 consecutive patients with biopsy-proven extracardiac sarcoidosis with CMR and found that atrial arrhythmias were more frequently observed (36%) than ventricular arrhythmias. Viles-Gonzalez et al.⁵¹⁾ reported that the prevalence of atrial arrhythmias was 32% (AF 18%, AT 7%, and AFL 5%). The scarring and inflammation of atrial tissue and left atrial enlargement caused by left ventricular dysfunction might have contributed to the atrial arrhythmias. The

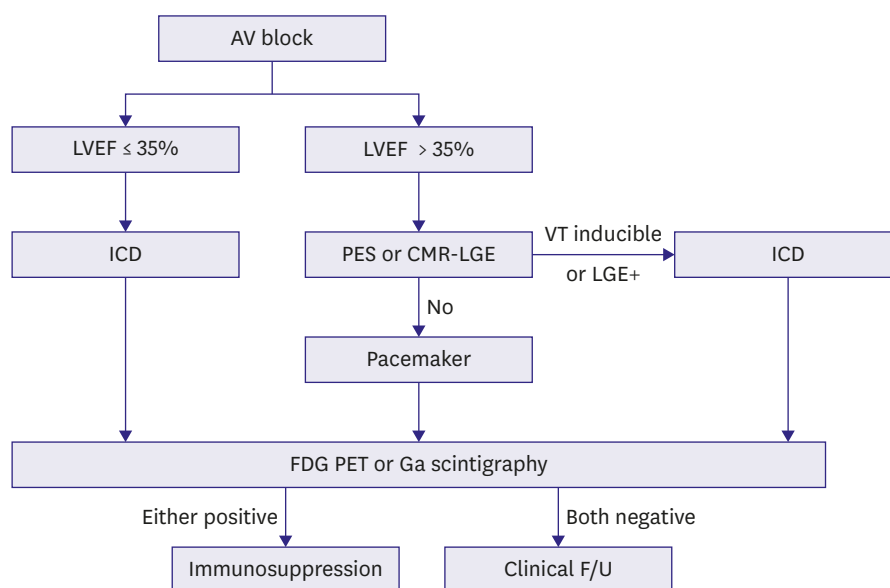


Figure 2. Management of AVB in patients with CS. AVB = atrioventricular block; CMR = cardiac magnetic resonance; CS = cardiac sarcoidosis; F/U = follow-up; FDG-PET = ¹⁸F-fluorodeoxyglucose-positron emission tomography; Ga = gallium; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; PES = programmed electrical stimulation; VT = ventricular tachycardia.

incidence of atrial arrhythmias was more frequent in patients with left atrial enlargement (267.8 vs. 38.3/1,000 person-years, RR, 6.99; 95% CI, 3.31–14.77).⁵¹⁾ Left atrial enlargement was the only variable associated with atrial arrhythmia by a multivariate analysis.

Immunosuppression

There is paucity of data on the efficacy of immunosuppression to control atrial arrhythmias.⁵²⁾⁵³⁾ Although catheter ablation and class III antiarrhythmics were ineffective to control AF, initiation of steroid therapy significantly decreased AF burden.⁵²⁾

Antiarrhythmic drugs and anticoagulation

Considering that some patients have ventricular scarring, class I agents should be deferred, and class III agents are preferred, as discussed in the ventricular arrhythmia section. Patients with CS may be at increased risk of venous thrombosis,⁵⁴⁾⁵⁵⁾ but whether CS patients with AF are at an increased risk of thrombosis is unknown. A patient's need for anticoagulation is based on the CHADS₂-VASC score, as estimated for non-valvular AF.

Catheter ablation

Limited data exists regarding the use of catheter ablation for AF associated with CS. In a case series of 9 patients with CS who underwent catheter ablation,⁵⁶⁾ 2 had paroxysmal AF, 3 had persistent AF, 1 had cavotricuspid isthmus-dependent AFL, 2 had atypical flutter, and 1 had both cavotricuspid isthmus-dependent flutter and paroxysmal AF. Both patients with paroxysmal AF underwent circumferential pulmonary vein isolation with no recurrence during 1.8±1.9 years. For persistent AF, bipolar voltage mapping showed a small low voltage area in the septum in one patient and diffuse, extensive left atrial scarring in another. Both of these patients underwent pulmonary vein isolation and complex fractionated atrial electrogram ablation. The other patient with persistent AF underwent minimal atrial scarring and pulmonary vein isolation.

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