Electrophysiological correlates of cardiac sarcoidosis: an appraisal of current evidence

Kardiyak sarkoidozun elektrofizyolojik bağlantıları: Güncel kanıtların değerlendirilmesi

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Summary– Cardiac sarcoidosis is an underdiagnosed condition that may be present in as many as 25% of patients with systemic sarcoidosis. It is associated with significant morbidity and mortality in affected individuals. The presentation of cardiac involvement in sarcoidosis includes sudden death in the absence of preceding symptoms, conduction disturbances, ventricular arrhythmias, and heart failure. A scarcity of randomized data and a lack of prospective trials underlies the contention between experts on the most appropriate strategies for diagnosis and therapy. This review focuses on the electrophysiological sequelae of the disease, with an emphasis on current diagnostic guidelines, multimodality imaging for early detection, and the role of various therapeutic interventions. Multicentre collaboration is necessary to address the numerous unanswered questions pertaining to management of this disease.


Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The history of this enigmatic disease dates back to the year 1875 when English dermatologist Sir Jonathan Hutchinson described an unrecognized condition characterized by “red, raised lesions on the arms, face and hands”. His description was the first reported case of cutaneous sarcoidosis.[1] In 1929, Bernstein et al. reported post-mortem findings of epicardial lesions similar to those on the skin. [2] This case represents the first documentation of cardiac involvement with sarcoidosis.

While our understanding of sarcoidosis has come a long way since these original descriptions, multiple facets of this disease remain poorly understood. Cardiac involvement is one such aspect, and has received significant attention owing to the poor prognosis it portends.[3] Limited by a lack of clinical registries and randomized data, the guidelines for diagnosis and management of cardiac sarcoidosis (CS) are largely consensus-based.

The principal clinical manifestations of CS are arrhythmias,[4–6] conduction ab-

Abbreviations:

AADs Antiarrhythmic drugs
ARVD Arrhythmogenic right ventricular dysplasia
AV Atrioventricular
CMR Cardiac magnetic resonance
CS Cardiac sarcoidosis
ECG Electrocardiogram
FDG-PET Fluorodeoxyglucose positron emission tomography
fQRS Fractionation of the QRS
HRS Heart Rhythm Society
ICD Implantable cardioverter-defibrillator
LBBB Left bundle branch block
LGE Late-gadolinium enhancement
LV Left ventricular
LVEF Left ventricular ejection fraction
PVCs Premature ventricular contractions
RBBB Right bundle branch block
SAECG Signal-averaged ECG
SVT Supraventricular tachycardia
VT Ventricular tachycardia
normalities,[7,8] and heart failure,[9] with less frequently reported findings including cardiac valve involvement,[10] granulomatous disease of coronary arteries leading to myocardial ischemia,[11] and pericardial disease.[12] Early diagnosis and management of CS is critical as sudden death may be the initial presentation. In this review, we focus on the diagnosis and management of patients with CS, with a particular emphasis on the electrophysiological aspects of the disease.

Epidemiology

According to a study of the members of Health Alliance Plan, a health maintenance organization in Detroit, Michigan, the annual incidence of sarcoidosis is 10.9 per 100,000 in whites and 35.5 per 100,000 in African Americans.[13] The highest annual age-specific incidence, 107/100,000, was found in African American females aged 20–39. Approximately 3–5% of patients with sarcoidosis have clinical evidence of cardiac involvement.[14] Autopsy studies demonstrate myocardial involvement in up to 25% of patients with sarcoidosis, suggesting probable under-diagnosis of CS based on clinical grounds.[15]

Diagnosis of cardiac sarcoidosis

Sarcoidosis is characterized by the presence of non-caseating granulomas comprising foci of epithelioid histiocytes and multi-nucleated giant cells. Endomyocardial biopsy demonstrating these findings is virtually pathognomonic. However, endomyocardial biopsy is fraught with a high rate of false-negatives with an overall yield of 25%[16] due to the patchy distribution of granulomas in CS, and the natural progression of untreated granulomas to fibrosis and scarring.

The Japanese Ministry of Health and Welfare published the first diagnostic algorithm for CS in 1993.[17] The initial publication focused on tissue biopsy with positive cardiac histology or a histological diagnosis of extracardiac sarcoidosis with clinical parameters on invasive and non-invasive testing that supported a diagnosis of CS. These criteria were revised in 2006, with the inclusion of a clinical/imaging pathway that did not require a positive biopsy.[18] Neither set of criteria has been prospectively evaluated.

The Heart Rhythm Society (HRS) convened experts in the field to formulate a Consensus Statement on the Diagnosis and Management of Arrhythmias Associated with Cardiac Sarcoidosis in May 2014.[19] This statement provides histological and clinical/imaging pathways for diagnosis (Table 1). Similar to the 1993 criteria, it requires a tissue biopsy with a histological diagnosis from myocardial tissue or a histological diagnosis of extracardiac sarcoidosis and clinical parameters. The HRS consensus statement incorporates contemporary modalities of imaging such as fluorodeoxyglucose positron emission tomography (FDG-PET and cardiac magnetic resonance (CMR). Despite the utilization of these advanced imaging modalities, the proposed criteria still risk underdiagnosing isolated CS, owing to the reliance on endomyocardial biopsy. There is data to support an improved diagnostic yield of endomyocardial biopsy by incorporating electroanatomic mapping or image guidance.

Screening patients with extracardiac sarcoidosis for cardiac involvement

Cardiac signs or symptoms in a patient with extracardiac sarcoidosis should prompt a physician to perform an aggressive workup for CS. The HRS consensus statement recommends screening patients with biopsy-proven extracardiac sarcoidosis for cardiac involvement with a detailed history to identify possible cardiac symptoms, a 12-lead electrocardiogram (ECG), and transthoracic echocardiogram.[19] If an abnormality is detected on initial evaluation, further investigation with CMR or FDG-PET is recommended, ideally at a centre with experience in managing CS.

Sarcoidosis is a chronic, progressive disease, prompting frequent surveillance for cardiac involvement in patients with extracardiac sarcoidosis. While there are no formal recommendations regarding frequency of screening, yearly evaluation is believed to be reasonable. Patients should also be made aware of the symptoms that may indicate cardiac involvement.

Multimodality imaging

Echocardiography

Echocardiographic abnormalities are present in 24–77% of CS patients.[20–22] CS may present with preserved left ventricular (LV) function, mildly reduced LV function, a dilated cardiomyopathy with global hypokinesis, or regional wall motion abnormalities in a non-coronary distribution.[9] While wall thickening
and diastolic dysfunction are common, more specific findings include wall thinning of the basal anterior septum or the presence of an intra-cardiac mass (representing a large granuloma).\textsuperscript{[20]}

Diastolic dysfunction precedes systolic dysfunction in patients with CS. The most common pattern being a prolonged isovolumic relaxation time and reversed E:A Doppler ratio, suggesting an abnormality of LV active relaxation, rather than diminished compliance alone.\textsuperscript{[23]}

**Radionuclide scintigraphy**

CS may present with areas of decreased uptake of thallium-201 (\textsuperscript{201}Th) or technetium-99m (\textsuperscript{99m}Tc) in the ventricular myocardium, with improvement in uptake on stress or administration of vasodilator. This finding, called reverse perfusion, is seen in other cardiomyopathies as well, and is caused by microvascular vasoconstriction and local metabolic derangements.

While data comparing different radionuclide tracers is sparse, one study reported a superior sensitivity of \textsuperscript{99m}Tc compared to \textsuperscript{201}Th (65\% vs. 46\%), in diagnosing CS.\textsuperscript{[24]} \textsuperscript{67}Ga scintigraphy is held to be less useful, with a lower sensitivity than other modalities for detecting CS, estimated at 18–50\%.\textsuperscript{[25]}

**Cardiac magnetic resonance (CMR)**

CMR is playing an increasingly crucial role in the diagnosis and management of CS due to the high spatial resolution and ability to differentiate active inflammation from fibrosis. Acute myocardial inflammation is indicated by wall thickening, increased signal intensity on T2-weighted images representing myocardial edema, and early gadolinium-enhancement.

Late-gadolinium enhancement (LGE) signifying scar/fibrosis, is found predominantly in the mid-myocardium and epicardium in CS, as opposed to the endocardium in patients with ischemic heart disease. The lesions have a predilection towards the basal and lateral segments of the left ventricle, the basal interventricular septum, and the papillary muscles.\textsuperscript{[26,27]}

Figure 1 demonstrates extensive mid-myocardial and epicardial delayed gadolinium enhancement in the anterior wall, lateral wall, inferior wall, basal septum, and inferoseptum.

Given the high spatial resolution of CMR, it may be used to target lesions for endomyocardial biopsy. In a case series comparing CMR to FDG-PET, the two modalities had a similar sensitivity, with CMR demonstrating a higher specificity for detection of CS.\textsuperscript{[28]}

CMR was incorporated in the 2014 HRS consensus statement as part of the clinical/imaging pathway for diagnosis.\textsuperscript{[19]}

Traditionally, a limitation of CMR has been the inability to utilize it in patients with a cardiac implantable electronic device (CIED). This hurdle is steadily being overcome with new protocols in tertiary centers designed to perform magnetic resonance imaging safely in patients with devices.

**Fluorodeoxyglucose positron emission tomography (FDG-PET)**

\textsuperscript{18}F-Fluorodeoxyglucose is a glucose analogue that is taken up by tissues with a high metabolic rate, such as

![Figure 1. CMR in a patient with CS demonstrating extensive mid-myocardial and epicardial delayed gadolinium enhancement in the anterior wall, lateral wall, inferior wall, basal septum, and inferoseptum.](image-url)
inflammatory and malignant lesions. It is used either alone, or integrated with computed tomography (CT), to detect organ involvement in patients with sarcoidosis. It has also gained favor as a modality for functional imaging of patients with CS. Combined with a PET perfusion tracer, it serves to exclude significant coronary artery disease. The pattern of FDG uptake in CS is usually focal and patchy (heterogeneous), with or without resting perfusion defects and wall motion abnormalities.\(^{[29]}\)

FDG-PET has been found to have a high sensitivity (82–100%),\(^{[3,28]}\) and a variable specificity (39–91%).\(^{[3,30]}\) Studies have also demonstrated superiority of FDG-PET in diagnosing early stages of CS over \(^{210}\)Th, \(^{99m}\)Tc, and \(^{67}\)Ga scintigraphy.\(^{[3,30]}\) FDG-PET is also being used to assess response to therapy in CS. Figure 2 demonstrates \(^{18}\)F-FDG uptake in a patient with CS.

FDG-PET holds distinct promise in the diagnosis and management of CS, though interpretation of images can be challenging. The HRS consensus statement recommends interpretation in the appropriate clinical context by a specialist with expertise in the field.\(^{[19]}\)

**Electrocardiographic findings**

There are electrocardiographic features that are more prevalent in patients with CS. In a study of 112 patients with biopsy-proven extracardiac sarcoidosis and symptoms suggestive of cardiac involvement, fractionation of the QRS complex (fQRS) was seen in 75% of patients eventually diagnosed with CS, compared to 33.9% in patients with no cardiac involvement (p<0.01).\(^{[31]}\) A left bundle branch block (LBBB) or right bundle branch block pattern (RBBB) pattern was found to be more prevalent in the CS patients (RBBB: 23.1% vs. 6.7%, p=0.016; LBBB: 3.8% vs. 1.7%, p=0.6), and 90.4% had at least 1 of the 2 findings (fQRS or bundle branch block), compared to 36.7% in patients with non-cardiac sarcoidosis (p<0.01). In addition, detection of atrial or ventricular tachyarrhythmias, heart block, or pseudo-infarct patterns may also denote cardiac involvement.\(^{[32]}\) While nonspecific for CS, these findings should raise one’s suspicion for cardiac involvement. Figure 3 demonstrates an ECG in a CS patient with incomplete RBBB, left-anterior fascicular block, and left-atrial abnormality.

Signal-averaged ECG (SAECG) has also been studied for findings predictive of CS. In a cohort of 88 patients, of whom 27 had evidence of cardiac involvement, SAECG was abnormal in 51.9%, as opposed to 18.0% in patients with non-cardiac sarcoidosis.\(^{[33]}\) Based on these data, SAECG predicts CS with a sensitivity of 52% and specificity of 82%. Of the SAECG parameters, low amplitude signal duration <40mV (LAS40) was associated with the diagnosis of CS (p<0.01).\(^{[33]}\)

**Electrophysiological manifestations**

Conduction block is the most common electrophysiological finding in CS. It is caused either by direct granulomatous infiltration of the interventricular septum, or involvement of the nodal artery causing ischemia of the conduction system.\(^{[19,34]}\) Involvement of the ventricular myocardium serves as a focus for ventricular tachyarrhythmias initiated by abnormal automaticity, or more commonly macroreentry, given the abnormal substrate.

Atrial arrhythmias are believed to occur less frequently in patients with CS, and are usually seen in the setting of generalized cardiac involvement and

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**Figure 2.** FDG-PET in a patient with CS. There is evidence of increased heterogeneous uptake of \(^{18}\)F-FDG in the anterior, septal, and lateral walls (base to apex) extending into the interospetum and inferolateral wall.
atrial dilatation, rather than isolated involvement of the atria.[30]

A rare, yet aggressive manifestation of CS is acute sarcoid myocarditis. This condition is characterized by high-degree atrioventricular (AV) block, malignant ventricular arrhythmias and congestive heart failure. [35] The clinicopathological resemblance to giant cell myocarditis complicates diagnosis.

The presentation of CS has also been reported to mimic arrhythmogenic right ventricular dysplasia (ARVD).[15,30,36] In a prospective study of 23 patients referred for evaluation of suspected ARVD, endomyocardial biopsy demonstrated noncaseating granulomas consistent with sarcoidosis in 3 patients.[37] The left ventricular ejection fraction (LVEF) was reduced in all 3 patients with evidence of CS, as opposed to in only 2 of the 17 patients diagnosed with ARVD.

**Atrioventricular block**

The prevalence of AV block during the course of disease in patients with CS is 26–67%, with complete heart block in 23–30% of patients.[7,36] High-degree AV block in a young patient with no cardiac history warrants a workup for sarcoidosis after excluding reversible causes such as Lyme disease.

In a study of 49 patients with no history of sarcoidosis, aged 18–60 years, presenting with Mobitz II or complete heart block, 8 (15%) patients were diagnosed with CS. [8] Kandolin et al. evaluated 72 patients under 55 years of age, with unexplained, new-onset AV block.[38] Fourteen (19%) patients were diagnosed with CS based on endomyocardial biopsy, with 4 (6%) patients receiving a “probable” diagnosis. Patients with CS had a worse prognosis than patients with idiopathic heart block, emphasizing the importance of maintaining a high-index of suspicion for CS in patients with AV block.

Reversal of AV block with early initiation of steroid therapy has been demonstrated in a subset of patients. Yodogawa et al. studied 14 patients with high-grade AV block retrospectively.[39] All patients were treated with prednisone at an initial dose of 30 mg/day, with subsequent taper to a maintenance dose of 5–10 mg/day. During the following 7 years, high-grade AV block resolved to normal or first-degree AV block in 7 (47%) patients, with no evidence of recurrence during the follow-up period. Of the responders, 4 (29%) demonstrated a recovery within the first week of steroid therapy. Early initiation of therapy and a higher LVEF were associated with a favorable response to steroids.
The HRS Consensus Statement recommends permanent pacing in all patients with evidence of advanced heart block given the unpredictable course of CS, and possibility for recurrence.[19]

### Ventricular arrhythmias

Ventricular tachycardia (VT) is the most frequently encountered arrhythmia in CS. In a cohort of 14 patients with CS and refractory VT, 57 VTs were induced on electrophysiological testing, of which 37 were monomorphic and sustained. Six VTs were related to the Purkinje system and 31 VTs were related to areas of scar. The site of successful ablation was the left ventricular free wall in 5 (14%) patients, perimital valve in 6 (16%) patients, left ventricular septal wall in 9 (24%) patients, right ventricular free wall in 2 (5%) patients, peritricuspid valve in 5 (14%) patients, and right ventricular septal wall in 10 (27%) patients.[40]

Steroid therapy in the management of ventricular arrhythmias in CS is controversial. Steroid therapy has been associated with a reduction in the risk of VT, though exacerbation of ventricular ectopy during the initiation of therapy has also been reported.[40,41] Antiarrhythmic drugs (AADs) are often used in conjunction with steroids for the management of ventricular arrhythmias. In patients with refractory VT, despite immunosuppression and AADs, catheter-based ablation may be considered.

### Supraventricular arrhythmias

In a retrospective study of 100 patients with CS, the prevalence of supraventricular tachycardia (SVT) was 32% over a mean follow-up period of 5.8 years.[5] Atrial fibrillation was the most common SVT and left atrial enlargement was the only variable predictive of atrial arrhythmias. Amongst the non-AF arrhythmias, implicated mechanisms are triggered activity in 11%, abnormal automaticity in 47%, and reentry in 42%.[21]

There is limited data demonstrating a benefit of steroids in reducing SVT. The HRS writing committee voted on whether a trial of steroids is warranted to suppress atrial arrhythmias. 8 of 14 (57.1%) members were in favor of steroid therapy, though the vote did not reach threshold for inclusion in the final recommendations.[19]

Patients with sarcoidosis, as with other systemic inflammatory disorders, might have an increased rate of thromboembolic events. Owing to a paucity of evidence in this population, the current consensus is to anticoagulate based on a risk assessment using the CHADS2 and CHAD-S2-VASc scores as in patients without sarcoidosis.[19]

### Immunosuppressive therapy

Initiation of immunosuppressive therapy early in the course of disease, before the onset of LV dysfunction and LGE, has demonstrated the most benefit.[42,43] While randomized data regarding the optimal dose and duration is sparse, there is consensus that the initial therapy for CS should include steroids at moderate to high doses. In a retrospective study of 75 patients, there was no difference in survival between patients on 40 mg or more (range; 40–60 mg) of prednisone per day and patients on less than 30 mg/day (range; 10–30 mg).[7] Studies have utilized an initial dose of at least 30 mg/day (up to 1mg/kg/day) with subsequent taper to 10–20 mg every other day, demonstrating a decrease in negative ventricular remodeling and arrhythmic sequelae.[39,40,42,43] Yodogawa et al. investigated 31 patients with CS and premature ventricular contractions (PVCs, ≥300/day). Patients were treated with corticosteroids at an initial dosage of 30 mg/day, with subsequent taper to 10mg/day over a period of 6 months. While there was no significant difference in the number of PVCs and in the prevalence of non-sustained VT overall, in patients with less advanced LV dysfunction (EF ≥35%, n=17), there was a significant reduction in the number of PVCs (from 1820±2969 to 742±1425, p=0.048), and in the prevalence of non-sustained VT (from 41 to 6%, p=0.039).[43] Due to the multitude of side effects associated with long-term corticosteroid use, taper and discontinuation may be considered once active disease is quiescent. Ongoing surveillance is essential though, as a relapse rate of 25% with steroid cessation has been reported.[9]

Steroid-sparing agents also play a role in the management of CS. Clinical improvement has been reported with cyclophosphamide, methotrexate, cyclosporine, and mycophenolate mofetil.[44,45] Further studies are needed to delineate optimal doses and comparative outcomes of steroid-sparing agents.

### Antiarrhythmic medications

Antiarrhythmic medications are often used, alone or in combination with immunosuppressive therapy, to
control the arrhythmic manifestations of CS. As with other aspects of CS, literature pertaining to the role of AADs in this population is deficient. Class IA, IB, IC, beta-blockers, and class III agents have all been used, with varied success. Therapy is recommended based on guidelines for patients without sarcoidosis, although specific factors related to sarcoidosis must be taken into consideration while deciding on an AAD. Evidence of significant structural heart disease precludes the use of Class I AADs. Kidney and liver dysfunction due to granulomatous infiltration is not uncommon in sarcoidosis, and may also influence choice of AADs.

**Catheter ablation**

Medical therapy alone is ineffective in controlling arrhythmic manifestation of CS in up to 50% of patients. Catheter-based ablation should be considered in patients with arrhythmias refractory to medical therapy. Both atrial and ventricular arrhythmias have been treated with catheter ablation.

Ablation of ventricular tachycardia in CS is challenging, with mixed results due to transmural substrate and the dynamic nature of lesions. Koplan et al. reported a series of 8 patients with refractory VT who underwent electrophysiological testing, with evidence of multiple inducible monomorphic VTs (4±2 VTs per patient). Low-voltage scar was present in the right ventricle in all 8 patients, in the left ventricle in 5 (63%) patients, and in the epicardium in 2 (25%) patients. There was successful ablation of one or more VTs in 6 (75%) patients; however, inducible VTs remained in all but one patient. On follow-up (range 6 months to 7 years), 4 of these 8 patients remained free of VT with antiarrhythmic drugs and immunosuppression. Five patients went on to require cardiac transplantation, 4 of which were due to intractable VT.

In a cohort of 21 patients with CS referred for VT ablation, there was evidence of widespread, confluent scarring in the right ventricle, and patchy scarring in the left ventricle with a predilection for the basal septum, anterior wall, and perivalvular regions. Successful abolition of ≥1 inducible VT was achieved in 90% patients, and elimination of VT storm in 78% patients. Multiple inducible VTs remained inducible in all patients, though VT control could be achieved with fewer AADs compared to preablation (2.1±0.8 versus 1.1±0.8; p<0.001).

**Table 1. HRS expert consensus guidelines for diagnosis of CS**

<table>
<thead>
<tr>
<th>Pathways for diagnosis of cardiac sarcoidosis:</th>
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<tbody>
<tr>
<td>1. Histological diagnosis from myocardial tissue:</td>
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<tr>
<td>CS diagnosed in the presence of noncaseating granulomas on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains, if applicable).</td>
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<tr>
<td>2. Clinical diagnosis for Invasive and non-invasive testing:</td>
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<tr>
<td>It is probable* there is CS if:</td>
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<tr>
<td>a) There is a histological diagnosis of extracardiac sarcoidosis and</td>
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<tr>
<td>b) One of more of the following is present</td>
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<tr>
<td>- Steroid +/- immunosuppressant responsive cardiomyopathy or heart block</td>
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<tr>
<td>- Unexplained reduced LVEF (&lt;40%)</td>
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<tr>
<td>- Unexplained sustained (spontaneous or induced) VT</td>
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<tr>
<td>- Mobitz type II 2nd degree heart block or 3rd degree heart block</td>
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<tr>
<td>- Patchy update on dedicated cardiac PET (in a pattern consistent with CS)</td>
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<tr>
<td>- Late gadolinium enhancement on CMR (in a pattern consistent with CS)</td>
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<tr>
<td>- Positive gallium uptake (in a pattern consistent with CS) and</td>
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<tr>
<td>c) Other causes for the cardiac manifestation(s) have been reasonably excluded.</td>
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</tbody>
</table>

*: In general, “probable involvement” is considered adequate to establish a diagnosis of CS.
Cardiac transplantation serves as a last resort for patients with VT or congestive symptoms unresponsive to conventional therapies.

**Implantable cardioverter-defibrillator (ICD)**

ICD implantation is indicated in CS patients for secondary prevention in the setting of spontaneous ventricular arrhythmias, including prior cardiac arrest. The recommendation for primary prevention is more complex. Several studies have evaluated risk stratification for sudden cardiac death in CS. In a retrospective study by Schuller et al., 483 patients received an ICD for primary prevention. Over a mean follow-up period of 30.6 months, 23 patients received an appropriate ICD shock. Of note, none of the patients with a normal LVEF or RVEF received an appropriate shock.\[^{47}\]

In a study of 76 patients with systemic sarcoidosis and evidence of cardiac involvement, 8 patients had inducible ventricular arrhythmias on programmed electrical stimulation (PES).\[^{48}\] In the ensuing 5 years, 6 of these 8 patients had ventricular tachyarrhythmia or sudden death, compared to only 1 in the group that was non-inducible (p<0.0001). Although limited by small numbers, this study demonstrates an impressive negative predictive value in patients without inducible arrhythmia, a factor that may be utilized in risk stratification. Table 2 outlines the HRS Consensus Statement recommendations for ICD implantation in patients with CS.\[^{19}\] The ACC/AHA/HRS guidelines for device based therapies state that ICD implantation is reasonable in patients with CS (IIA recommendation), though there is no specification regarding LVEF, presenting history, or arrhythmias.\[^{49,50}\]

**Conclusion**

Cardiac involvement is one of the leading causes of mortality in patients with sarcoidosis. The onset may be insidious, with malignant ventricular arrhythmias and sudden death being the first and only symptoms. It is important for the clinician managing patients with sarcoidosis to be vigilant for findings suggestive of cardiac involvement, such as ventricular arrhythmias, AV block or heart failure. Early diagnosis and institution of therapy has shown the most benefit. While further work in this field will help delineate the optimum management strategy, immunosuppression with steroids remains the mainstay of therapy. Patients with cardiac involvement are best served in a multidisciplinary setting, with involvement of experienced

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**Table 2. HRS Consensus Statement guidelines for ICD implantation in patients with CS**

<table>
<thead>
<tr>
<th>Class</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Class I</td>
<td>ICD implantation is recommended in patients with CS and one of the following:</td>
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<tr>
<td></td>
<td>1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest</td>
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<td></td>
<td>2. LVEF ≤35%, despite optimal medical therapy and a period of immunosuppression</td>
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<tr>
<td>Class IIa</td>
<td>ICD implantation can be useful in patients with CS, independent of ventricular function,</td>
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<tr>
<td></td>
<td>1. An indication for permanent pacemaker implantation;</td>
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<td></td>
<td>2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology;</td>
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<td></td>
<td>3. Inducible sustained ventricular arrhythmias (&gt;30 seconds of monomorphic VT or polymorphic VT) or clinically relevant ventricular fibrillation (VF)*.</td>
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<tr>
<td>Class IIb</td>
<td>ICD implantation may be considered in patients with LVEF in the range of 36–49%, and/or an RV ejection fraction &lt;40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).</td>
</tr>
<tr>
<td>Class III</td>
<td>ICD implantation is not recommended in patients with no history of syncope, normal LVEF/RV ejection fraction, no LGE on CMR, a negative EP study, and no indication for permanent pacing. However, these patients should be closely followed for deterioration in ventricular function. ICD implantation is not recommended in patients with one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Incessant ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>2. Severe New York Heart Association class IV heart failure.</td>
</tr>
</tbody>
</table>

* VF with triple premature beats of <220 ms is considered a nonspecific response.
physicians at a centre with high-volume and sufficient expertise in the management of CS.

The current recommendations for management of CS are consensus-based. Limited by small patient volumes at individual centres, the future revolves around collaboration between institutions. The Cardiac Sarcoidosis Consortium (cardiacsarcoidosisconsortium.org) is one such undertaking, with over 50 contributing sites worldwide. Enrolled patients are followed prospectively in an attempt to better understand issues pertaining to the natural history of the disease, the role of diagnostic imaging modalities, and effects of therapy. As further data becomes available, prospective validation of the various diagnostic and therapeutic modalities will help in delineating the optimum management strategy for patients with CS.

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References


**Keywords:** Cardiac sarcoidosis; implantable cardioverter-defibrillator; sudden death; ventricular tachycardia.

**Anahtar sözcükler:** Kardiyak sarkoidoz; yerleştirilebilir kardiyoverter defibrilatör; ani ölüm; ventrikül taşikardisi.