ΣΑΡΚΟΕΙΔΟΣΗ

ΣΠΥΡΟΜΗΤΡΟΣ ΓΕΩΡΓΙΟΣ
ΚΑΡΔΙΟΛΟΓΟΣ, F.E.S.C, ΔΙΕΥΘΥΝΤΗΣ ΕΣΥ
ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ Γ.Ν.ΚΑΤΕΡΙΝΗ
The clinical presentation of cardiac sarcoidosis (CS) ranges from an incidentally discovered condition to heart failure and sudden death.

The diagnosis of CS is difficult to establish, and as a result, CS is often underrecognized in clinical practice.

CS most often occurs as a manifestation of systemic sarcoidosis, although isolated CS can occur in patients who do not have evidence of sarcoidosis in other organs.

Roberts WC, Chung MS, Ko JM, et al. Morphologic features of cardiac sarcoidosis in native hearts of patients having cardiac transplantation. Am J Cardiol 2014

The true prevalence of CS **remains unknown** and is potentially underestimated since many individuals with CS may have nonspecific symptoms or subclinical disease.

CS can affect patients of all racial backgrounds and ages, with an average age at presentation of approximately 50 years old.

**Cardiac involvement** is diagnosed clinically in as few as 5% of patients with sarcoidosis, although autopsy studies have shown that cardiac involvement is present in up to 25% of autopsy specimens.
# Table 1  Prevalence of asymptomatic CS in patients with extracardiac sarcoidosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% of patients with asymptomatic CS</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>155</td>
<td>25.5</td>
<td>LGE-CMR</td>
</tr>
<tr>
<td>2011</td>
<td>152</td>
<td>19</td>
<td>LGE-CMR</td>
</tr>
<tr>
<td>2009</td>
<td>81</td>
<td>25.9</td>
<td>LGE-CMR</td>
</tr>
<tr>
<td>2008</td>
<td>62</td>
<td>38.7</td>
<td>PET/LGE-CMR</td>
</tr>
<tr>
<td>2005</td>
<td>82</td>
<td>3.7</td>
<td>Mostly CMR, but only a few with LGE-CMR</td>
</tr>
<tr>
<td>2003</td>
<td>50</td>
<td>14.0</td>
<td>Various</td>
</tr>
<tr>
<td>2002</td>
<td>31</td>
<td>54.9</td>
<td>CMR</td>
</tr>
</tbody>
</table>

CS = cardiac sarcoidosis; LGE-CMR = late gadolinium-enhanced cardiovascular magnetic resonance; PET = positron emission tomography.
The prevalence of CS among patients with systemic sarcoidosis has been reported to be 20 to 27 percent in the United States and as high as 58 percent in Japan.

Isolated CS may occur in up to 25 percent of CS cases,

The absence of extracardiac sarcoidosis does not rule out CS.

Sarcoidosis is a heterogeneous disorder of unknown etiology whose signature lesions are noncaseating granulomata.

Sarcoidosis may involve any part of the heart.

While the ventricular myocardium is most commonly affected, involvement by the atria, papillary muscles, valves, coronary arteries, and pericardium has been described.

Similar to other involved organs, cardiac disease generally progresses from areas of focal inflammation to scar.
Limited data on how this disease progresses, it may be preferable to refer to different patterns of CS rather than stages.
CLINICAL MANIFESTATIONS

- The most frequent of CS are atrioventricular (AV) block, arrhythmias, heart failure (HF), and sudden cardiac death.
- Symptoms and signs of CS include palpitations, presyncope, syncope, fatigue, dyspnea, orthopnea, and sudden cardiac death.
- Patients with CS had more cardiac symptoms than those without CS (46% vs. 5%).

Arrhythmias

- **Conduction system disease** — **AV block** is the **most common** clinical presentation in patients with clinically evident CS.

- **Complete AV block** occurs **at a younger age** in patients with CS than in individuals with complete AV block due to other etiologies.

- **Prolongation of the PR interval** (first-degree AV block) due to disease of the AV node or bundle of His and intraventricular conduction defects is **common** and **may progress**.

- Conduction system disease may **initially be silent** and then progress to complete AV block and cause syncope or even sudden death.

Arrhythmias

- **Tachyarrhythmias** — Supraventricular and ventricular arrhythmias are both common in CS.

- **Ventricular arrhythmias** (sustained or nonsustained ventricular tachycardia and VPBs are the second most common clinical presentation of CS, approximately 30 percent of cases)

- **Supraventricular arrhythmias** seen with CS include paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation, and sinus arrest secondary to granulomatous involvement of the sinus node.

- **Sudden death due to VT** tachyarrhythmias or conduction block accounts for 25 to 65 percent of deaths caused by CS.

- Sudden death can occur in the absence of symptoms or a previous cardiac event.


Cardiomyopathy and heart failure

- HF is less common than arrhythmia at initial presentation and is the first clinical manifestation of CS in fewer than 20 percent of cases.
- CS may even be diagnosed after transplant in the explanted hearts of patients thought to have an idiopathic cardiomyopathy.
- CS can cause either a dilated cardiomyopathy (with dilated left ventricular [LV] volumes and depressed LV ejection fraction [LVEF], which can lead to HF with reduced ejection fraction [HFrEF]) or a restrictive cardiomyopathy (with normal LV volumes and preserved LVEF), which can lead to HF with preserved ejection fraction.
Cardiomyopathy and heart failure

- Some patients with CS present with signs of predominantly right-sided HF, which can be caused by sarcoid-related inflammation or scar affecting the right ventricle or less commonly secondary to CS involving the tricuspid valve.

- Right HF due to CS involving the right ventricle should be distinguished from other causes of right HF including pulmonary hypertension secondary to lung disease.

Patel MB, Mor-Avi V, Murtagh G, et al. Right Heart Involvement in Patients with Sarcoidosis. Echocardiography 2016;
Coronary artery disease — Sarcoidosis can involve the coronary arteries with a vasculitis, which has been reported as a rare cause of unstable angina or myocardial infarction.

However, patients with CS may also be more likely to have CAD.

When to consider cardiac sarcoidosis

- Patients with histologic or clinical diagnosis of extracardiac sarcoidosis, with or without cardiac symptoms, should be evaluated for subclinical, as well as clinical, cardiac involvement (arrhythmias, conduction disease, heart failure [HF], etc).

- Young adults (age <60 years) with unexplained syncope or unexplained new onset conduction system disease such as sustained second- or third-degree AV block.

- Patients with sustained ventricular tachycardia (VT) not explained by typical outflow tract VT, fascicular VT, or VT due to other structural heart disease such as coronary artery disease (CAD).

- Patients with unexplained dilated, restrictive, or arrhythmogenic cardiomyopathy.

Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. J Cardiovasc Electrophysiol 2009

Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. Heart 2011

Biopsy proven examples

Screen with CMR and/or FMR:
- Symptoms: -- significant -- pre-syncope
- Abnormal EKG
- Abnormal echocardiography

Specific presentations with CMR and/or FMR:
- Unexplained Mobitz II or 3rd degree AV block in adults aged <60 years
- Sustained Monomorphous Tachycardia

Figure 4. Suggested criteria for diagnosis of cardiac sarcoidosis. Abnormal echocardiography: wall abnormality, wall aneurysm, biventricular ejection fraction <40%. Abnormal EKG: left bundle branch block or right bundle branch block, or unexplained pathological Q waves in third-degree AV block, or sustained tachycardia (VT). Reprinted from the publisher. Copyright ©2017.

Figure 4  Suggested algorithm for the investigation of patients with unexplained Mobitz II or third-degree AV block who are younger than 60 years. AV = atrioventricular; CMR = cardiovascular magnetic resonance; CS = cardiac sarcoidosis; CT = computed tomographic; ECG = electrocardiogram; EMB = endomyocardial biopsy; FDG-PET = 18F-fluorodeoxyglucose positron emission tomography.

*Voltage guided or advanced imaging guided endomyocardial biopsy (see text in Section 4 for details)
### Table 1. Guidelines for Diagnosis Cardiac Sarcoidosis

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological diagnosis group:</strong> endomyocardial biopsy specimens demonstrate epithelioid granuloma without caseding granuloma.</td>
<td><strong>Histological diagnosis group:</strong> endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis.</td>
</tr>
<tr>
<td><strong>Clinical diagnosis group:</strong> in patients with a histological diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is suspected when item a and ≥1 items b through e are present, and other causes such as hypertension and coronary artery disease have been excluded.</td>
<td><strong>Clinical diagnosis group:</strong> although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid cell granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies either of the following conditions:</td>
</tr>
<tr>
<td>a. ECG: RBBB, left-axis deviation, AV block, ventricular tachycardia, PVCs (over grade 2 in Lown classification of premature ventricular tachycardia), or abnormal Q or ST-T change</td>
<td>• ≥2 of the 4 major criteria are satisfied</td>
</tr>
<tr>
<td>b. Echocardiography: abnormal wall motion, regional wall thinning, or dilatation of the left ventricle</td>
<td>• 1 in 4 of the major criteria and ≥2 of the 5 minor criteria are satisfied</td>
</tr>
<tr>
<td>c. Myocardial scintigraphy: perfusion defect by $^{201}$TI or abnormal accumulation by $^{67}$Ga-citrate or $^{99m}$Tc-PYP</td>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>d. Catheter: abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle</td>
<td>• Advanced AV block</td>
</tr>
<tr>
<td>e. Endomyocardial biopsy: interstitial fibrosis or cellular infiltration over moderate grade even if the findings are nonspecific</td>
<td>• Basal thinning of the interventricular septum</td>
</tr>
<tr>
<td>CMR indicates cardiac magnetic resonance; RBBB, complete right bundle branch block; $^{67}$Ga, gallium-67; PVC, premature ventricular contraction; PYP, pyrophosphate; $^{99m}$Tc, technetium-99 m; and $^{201}$TI, thallium-201.</td>
<td>• Positive $^{99m}$Tc Gallium uptake in the heart</td>
</tr>
<tr>
<td></td>
<td>• Depressed ejection fraction of the left ventricle (&lt;50%)</td>
</tr>
<tr>
<td></td>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• Abnormal ECG findings: ventricular arrhythmias (ventricular tachycardia, multifocal or frequent PVCs) CRBBB, abnormal axis deviation or abnormal Q wave</td>
</tr>
<tr>
<td></td>
<td>• Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening)</td>
</tr>
<tr>
<td></td>
<td>• Nuclear medicine: perfusion defect detected by $^{201}$TI or $^{99m}$Tc myocardial scintigraphy</td>
</tr>
<tr>
<td></td>
<td>• Gadolinium-enhanced CMR imaging: delayed enhancement of myocardium</td>
</tr>
<tr>
<td></td>
<td>• Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade</td>
</tr>
</tbody>
</table>
The WASOG organ assessment instrument used this premise to define three categories of the likelihood of organ involvement: highly probable, >90% likelihood of organ involvement; probable, 50%–90% likelihood of organ involvement; possible, <50% likelihood of organ involvement.
## Diagnostic categories of cardiac sarcoidosis based on clinical and imaging findings

<table>
<thead>
<tr>
<th>Findings suggesting cardiac sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical findings</strong></td>
</tr>
<tr>
<td>- LVEF &lt;40%</td>
</tr>
<tr>
<td>- Sustained ventricular tachycardia (spontaneous or induced)</td>
</tr>
<tr>
<td>- Mobitz type II second degree or third degree atrioventricular block (whether or not shown to be immunosuppressant responsive)</td>
</tr>
<tr>
<td><strong>Imaging findings</strong></td>
</tr>
<tr>
<td>- Cardiac FDG-PET with patchy focal uptake in a pattern consistent with CS</td>
</tr>
<tr>
<td>- CMR imaging with LGE in a pattern consistent with CS</td>
</tr>
</tbody>
</table>

### Diagnostic category of cardiac sarcoidosis

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite (100% probability of CS)</strong></td>
</tr>
<tr>
<td>- Detection of noncaseating granuloma on histologic examination of myocardial tissue (endomyocardial biopsy or other myocardial specimen) with no alternative cause identified</td>
</tr>
<tr>
<td><strong>Probable (≥50% probability of CS)</strong></td>
</tr>
<tr>
<td>- With histologic diagnosis of extracardiac sarcoidosis; requires both of the following criteria:</td>
</tr>
<tr>
<td>- One or more of the following types of cardiac findings:</td>
</tr>
<tr>
<td>- Clinical finding suggesting CS (refer to above)</td>
</tr>
<tr>
<td>- Imaging finding by CMR or FDG-PET typical for CS (refer to above)</td>
</tr>
<tr>
<td>- Other potential causes for the clinical and imaging findings have been excluded</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction; FDG-PET: $^{18}$F-fluorodeoxyglucose-positron emission tomography; CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement; CS: cardiac sarcoidosis.

Original table modified for this publication. From: Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014; 11:1305. Table used with the permission of Elsevier Inc. All rights reserved.
Echocardiographic findings

- Focal areas of edema resulting in increased **wall thickness** and mimicking hypertrophic cardiomyopathy (asymmetric septal hypertrophy or in more advanced patterns of involvement, **focal areas of akinesis or dyskinesis, wall thinning, or aneurysm**).

- Among patients with CS, **LVEF can be either preserved or reduced**

- **Reduced global longitudinal strain** is a feature that may be present in CS with **preserved ejection fraction**, and reduction in longitudinal strain magnitude may vary inversely with LGE burden.

Transthoracic echocardiography imaging of patient with cardiac sarcoidosis
Parasternal long axis view demonstrates thinning of the basal and midventricular anteroseptum, which is a characteristic finding in advanced cardiac sarcoidosis.
Patients with CS may have a normal echocardiogram, and accordingly echocardiography has a low sensitivity to diagnose early or localized mild disease.

Supporting these concepts, Mehta et al.24 found echocardiographic abnormalities in only 25% of the patients who exhibited CMR or (FDG)

In patients with extracardiac sarcoidosis who have symptoms or signs of possible cardiac involvement, echocardiography should not be used as a screening test, as a negative echocardiogram cannot be used to rule out cardiac involvement.
Cardiovascular magnetic resonance

- **Multifocal areas of LGE** (as opposed to a single area)

- **Subepicardial and midmyocardial LGE** (ie, noninfarct pattern), although some patients may have subendocardial involvement in a pattern similar to myocardial infarction

- **Direct LGE extension** from the LV, across the interventricular segment, into the right ventricle

- The presence of increased **T2 weighted signal**, a marker of increased water content, **identify areas of increased inflammation**

Noncontrast cardiac magnetic resonance imaging of patient with cardiac sarcoidosis
Noncontrast image shows left ventricular chamber dilation with marked thinning of the interventricular septum (arrows).
• The main strength of CMR lies in its **high negative predictive value** for excluding CS when no LGE is detected.

• **The sensitivity of this test likely exceeds 90 percent** and has been reported to be as high as 100 percent when compared with the JMHW criteria.

Figure 2.
Annualized event rates according to late gadolinium enhancement (LGE) positive vs negative. CV indicates cardiovascular.

Columns represent n(%) or mean±SD or median (IQR), where appropriate. AA indicates African American; LGE, late gadolinium enhancement; LVEDd, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; and VT, ventricular tachycardia.
FDG-PET

- FDG-PET can detect active myocardial inflammation,
- In the appropriate clinical context, can be used to determine the likelihood of CS
- More sensitive than galium-67, thallium-201 technicium-99m SPECT
- A comprehensive PET imaging exam for CS involves three components

Rest myocardial perfusion imaging – with either a SPECT or PET camera. Perfusion defects may represent either fibrosis or inflammation.

Cardiac FDG-PET images – dedicated PET camera. Areas of focal FDG uptake by the myocardium represent myocardial inflammation, not specific for sarcoidosis, other inflammatory myocardial diseases and hibernating myocardium.

• **Extracardiac FDG-PET images** – Limited whole-body images are strongly recommended when there are no prior data regarding the presence or disease activity of extracardiac sarcoidosis.

• From the orbits to the upper thigh, and at minimum should include the **chest, liver, and spleen**, as these are the most frequently affected organs.

**Multiple focal sites of increased FDG activity**
Fluorodeoxyglucose (FDG)-positron emission tomography/computerized tomography imaging in a patient with cardiac and extracardiac sarcoidosis (maximum intensity projection). Multiple focal sites of increased FDG activity in the heart, lungs, pleura, liver, spleen, bones and multiple lymph nodes.
Cardiac Positron Emission Tomography Enhances Prognostic Assessments of Patients with Suspected Cardiac Sarcoidosis

Ron Blankstein, MD, Michael Osborne, MD, Masanao Naya, MD, Alfonso Waller, MD, Chun K. Kim, MD, Venkatesh L. Murthy, MD, Pedram Kazemian, MD, Raymond Y Kwong, MD MPH, Michifumi Tokuda, MD, Hicham Skali, MD, Robert Padera, MD PhD, Jon Hainer, BS, William G. Stevenson, MD, Sharmila Dorbala, MD MPH, and Marcelo F. Di Carli, MD.
Figure 4. Survival free of death or VT stratified by cardiac PET exam results:
Survival free of death or VT stratified by cardiac PET exam results.

Figure 5. Survival free of death or VT stratified by focal RV inflammation:
Survival free of death or VT stratified by the presence or absence of focal right ventricular FDG uptake among individuals with abnormal cardiac PET exam.
**Comparison of CMR with FDG-PET**

- CMR and PET likely provide **complementary information** for many patients with suspected CS

- **CMR** is more likely to provide information regarding the presence and extent of **scar**

- **PET** is more likely to provide information regarding the presence, extent, and severity of myocardial **inflammation**.

- When any one test provides inconclusive results, we suggest **combining data** from both of these exams in order to determine the likelihood of CS

Figure 5. Suggested algorithm for using advanced cardiac imaging to evaluate patients with suspected cardiac sarcoidosis. CMR indicates cardiac magnetic resonance imaging; and PET, positron emission tomography.
Endomyocardial Biopsy

- Is the gold standard for diagnosis of CS
- High specificity, low sensitivity 20%
- False negative results due to patchy distribution of disease.

Photomicrograph of cardiac biopsy in cardiac sarcoidosis (20x objective)
Characteristic histopathologic findings in cardiac sarcoidosis including nonnecrotizing granulomatous inflammation with many multinucleated giant cells (arrows) in a background of dense replacement-type fibrosis.
MANAGEMENT OF CARDIAC SARCOIDOSIS

- The main goals of patient management include preventing disease progression.
- Avoiding the development or worsening of left ventricular (LV) dysfunction.
- Managing atrioventricular (AV) block, arrhythmias and risk of sudden death.
- The following approach applies to patients with **definite or probable CS**.
- **General management** treatment of underlying cardiovascular risk factors, including use of statin therapy as indicated

- Patients with HF (HF with reduced ejection fraction [HFrEF] or HF with preserved ejection fraction [HFpEF]) should receive **standard therapy**

- Patients without HF with left ventricular ejection fraction (LVEF) ≤40 percent should receive standard **treatment for asymptomatic LV systolic dysfunction**
- **Immunosuppressive therapies** – Indications for immunosuppressive therapy in patients with definite or probable CS who have evidence of active myocardial inflammation

- **Management of conduction abnormalities** – Patients with CS with AV block are treated with immunosuppressive therapy and may require a permanent pacemaker.

- **Management of ventricular arrhythmias and risk of sudden cardiac death (SCD)** – Management includes risk stratification to determine when ICD implantation is appropriate.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Medication</th>
<th>Mechanism</th>
<th>Potential benefit</th>
<th>Potential harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical immunosuppressive therapy</td>
<td>Prednisone</td>
<td>Anti-inflammatory, start 40-60 mg per day</td>
<td>No RCT data. An observational study of 23 cardiac sarcoid subjects suggests that $^{18}$F-FDG PET may guide steroid therapy (LVEF of 3.8% per reduction in SUV volume of 100 cm$^3$ above a threshold value, $P=0.022$) (18)</td>
<td>Diabetes, weight gain, hypertension, insomnia, depression and irritability, fractures, infection</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>Anti-metabolite and immune-modulator</td>
<td>Steroid-sparing. No RCT data. In a three year open-label study comparing 7 vs. 10 CS subjects treated with steroid or steroid + MTX, respectively, steroid + MTX had improved LVEF (44.5%±13.8% vs. 60.7%±14.3%, $P=0.04$) (19)</td>
<td>Thrombocytopenia, anemia, immunosuppression, pulmonary and liver toxicity, neurologic toxicity, infection</td>
</tr>
<tr>
<td>Other immune-modulators</td>
<td>Varied</td>
<td>Steroid-sparing. Case reports only have included Infliximab, Azathioprine, Cyclosporine, Anti-malarials, Pentoxifylline, Azathioprine, Thalidomide</td>
<td>Anemia, immunosuppression, other specific toxicities</td>
<td>Anemia, immunosuppression, other specific toxicities</td>
</tr>
<tr>
<td>Medical therapy for heart failure</td>
<td>ACE/ARB</td>
<td>Improves adverse cardiac remodeling</td>
<td>Class I to reduce mortality and morbidity of HFrEF. Class Ila for structural heart disease without impaired LVEF or symptoms (20)</td>
<td>Renal impairment, electrolyte abnormality, allergy, angioedema, cough</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>Negative inotrope, delays AV conduction</td>
<td>Class I to reduce mortality and morbidity for HFrEF (20)</td>
<td>Fatigue, cardiac conduction block, mood effects, erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Diuretics and restricted dietary</td>
<td>Fluid and sodium excretion</td>
<td>Class I for HFrEF and symptoms (20)</td>
<td>Renal impairment, electrolyte abnormality, orthostasis</td>
</tr>
<tr>
<td></td>
<td>sodium excretion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^{18}$F-FDG PET, $^{18}$F-fluorodeoxyglucose positron emission tomography; LVEF, left ventricular ejection fraction; SUV, standardized uptake values; CS, cardiac sarcoidosis.
Indications for immunosuppression

- For patients who have evidence of **active myocardial inflammation** (by [FDG-PET] or myocardial histology), reduce onset or progression of LV dysfunction or HF.

- Patients with evidence of **focal inflammation involving the right ventricle** detected by FDG-PET, have a worse prognosis.

- For **asymptomatic patients with CS with normal LVEF and right ventricular ejection fraction (RVEF)**, we suggest an **individualized assessment of the potential risks and benefits of treatment**.

- Evaluation of the burden of inflammation in other organs, as determined by a limited whole-body FDG-PET.
In patients with significant inflammation, FDG-PET imaging at approximately six months of therapy may be reasonable to assess treatment response.
- Retrospective studies suggest that glucocorticoid therapy can improve AV block.

- Limited data suggesting that glucocorticoid therapy may prevent LV dysfunction, particularly if treatment is initiated before the onset of moderate or severe systolic dysfunction.

- The effect of glucocorticoid therapy on ventricular arrhythmias is even less certain.
Management of conduction disease and arrhythmias

Among patients with CS, sudden death due to ventricular tachyarrhythmias or conduction block accounts for 30 to 65 percent of deaths.

High rate of recurrence of ventricular tachycardia (VT) or sudden death with antiarrhythmic drug therapy, even when guided by electrophysiologic (EP) testing.

Roberts WC, McAllister HA Jr, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy cases (group 2). Am J Med 1977

**Table 4** Studies assessing the role of VT ablation in cardiac sarcoidosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>EF (%)</th>
<th>Noninducible post, n/N (%)</th>
<th>Partial success, n/N</th>
<th>Recurrence, n/N (%)</th>
<th>Follow-up period (mo=months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koplan et al</td>
<td>8</td>
<td>34</td>
<td>2/8 (25)</td>
<td>4/9</td>
<td>6/8 (75)</td>
<td>6–84</td>
</tr>
<tr>
<td>Jefic et al</td>
<td>9</td>
<td>42</td>
<td>5/9 (56)</td>
<td>3/9</td>
<td>4/9 (44)</td>
<td>19.8</td>
</tr>
<tr>
<td>Dechering et al</td>
<td>8</td>
<td>36</td>
<td>5/8 (63)</td>
<td></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Class IIa 1. Assessment of myocardial inflammation with FDG-PET can be useful in CS patients with ventricular arrhythmias.
2. Immunosuppression can be useful in CS patients with frequent ventricular ectopy or nonsustained VT and evidence of myocardial inflammation.
3. Immunosuppression can be useful in CS patients with sustained ventricular arrhythmias and evidence of myocardial inflammation.
4. Antiarrhythmic medication therapy can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy.
5. Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive and antiarrhythmic therapy.
6. Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive and antiarrhythmic therapy.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism</th>
<th>Potential benefit</th>
<th>Potential harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device therapy</td>
<td></td>
<td></td>
<td>Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock</td>
</tr>
<tr>
<td>ICD, secondary prevention</td>
<td>Defibrillation of potential</td>
<td>Class I recommendation to reduced mortality in patients with structural heart disease and syncope, VT/VF, or sustained VT/VF inducible by EP study. Class III if life-expectancy &lt;1 year.</td>
<td>Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock</td>
</tr>
<tr>
<td>(level of evidence C) (7)</td>
<td>recurrent VT/VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD, primary prevention</td>
<td>Defibrillation of potential</td>
<td>Class I recommendation to reduce mortality in patients with structural heart disease and EF &lt;30-35% despite medical therapy. Class Ila for those needing pacemaker, unexplained syncope, or sustained VT/VF inducible by EP study. LGE on CMR may be used to consider EP study. Class IIb for LVEF 36-49% or RVEF &lt;40% despite medical therapy. Class III if life-expectancy &lt;1 year.</td>
<td>Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock</td>
</tr>
<tr>
<td>(level of evidence C) (7)</td>
<td>VT/VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td>Prevention of immediately fatal</td>
<td>Class I recommendation to reduce mortality and symptoms from complete heart block and bradyarrhythmia (7,21).</td>
<td>Pain, infection, cost, lead fracture, re-implantation, device removal complex if heart block resolves</td>
</tr>
<tr>
<td>(level of evidence C) (7)</td>
<td>fatal arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>Surgical transplant</td>
<td>Surgically replace organs affected by sarcoidosis with donor organs when end-stage organ dysfunction that may include refractory cardiogenic shock, IV inotrope dependence, peak VO₂ &lt;10 mL/kg per min with achievement of anaerobic metabolism, refractory VT/VF (20)</td>
<td>Infection, need for chronic immunosuppression, risk of surgery, acute and chronic rejection, chance of recurrence (17)</td>
</tr>
<tr>
<td>Heart and lung transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(level of evidence C)</td>
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ICD, implantable cardiac defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; EP, electrophysiologic; EF, ejection fraction; LGE, late gadolinium enhancement; CMR, cardiac magnetic resonance.
Several studies have shown that patients with CS have event rates that exceed many populations studied in secondary prevention trials, supporting the concept that patients with CS, as a group, have a high rate of VT.

Abnormal findings based on FDG-PET or CMR, the association between EF and subsequent events is no longer significant.

LVEF alone should not be used to decide on ICD therapies.

- For patients with inducible sustained VT or clinically relevant VF (this excludes VF with triple premature beats of <220 ms since that response is nonspecific) on EP study, we suggest ICD implantation.

- For patients requiring pacemaker placement for high-grade AV block, we suggest implanting an ICD, rather than a pacemaker system alone.

- For patients with LVEF of <50 percent or RVEF <40 percent despite optimal HF therapy and immunosuppression for active inflammation, and/or abnormal LGE on CMR or perfusion/metabolism mismatch on FDG-PET and who lack a general indication for an ICD, we refer to an electrophysiologist for an individualized assessment of the risks/benefits of ICD implantation. Presence of both depressed EF and imaging criteria is a factor favoring ICD implantation in this setting.
1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest AND/OR
2. The LVEF is ≤35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)

Yes → ICD recommended

No

1. An indication for permanent pacemaker implantation AND/OR
2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology AND/OR
3. Inducible ventricular arrhythmias (>30 seconds of monomorphic VT, or clinically relevant polymorphic VT/ventricular fibrillation)

Yes → ICD can be useful

No

LVEF 36-49% and/or RV ejection fraction <40%, despite optimal medical therapy and a period of immunosuppression, if appropriate. (CMR +/- an electrophysiological study may be considered to help with risk stratification of these patients)

No → CMR may be considered

CMR

No Late Gadolinium Enhancement → ICD Not recommended

Patient should be followed for deterioration in ventricular function

Late Gadolinium Enhancement → An electrophysiologic study may be considered

Negative → ICD can be useful

Positive
Figure 3 Use of CMR and 18F-FDG PET for the diagnosis and monitoring of cardiac sarcoidosis. Patients with normal CMR are unlikely to have significant cardiac involvement and may be monitored clinically. Select patients with high clinical suspicion of cardiac sarcoidosis and normal CMR might be considered for 18F-FDG PET. CMR may be preferable to 18F-FDG PET as a first line test to minimize ionizing radiation, although local institutional expertise may influence test choice. Patients with inflammation by 18F-FDG PET should be considered for anti-inflammatory therapy and repeat 18F-FDG PET imaging in 3–6 months to evaluate response to therapy. EF, ejection fraction; CMR, cardiac magnetic resonance; 18F-FDG PET, 18F-fluorodeoxyglucose positron emission tomography; ICD, implantable cardiac defibrillator.