

# Cardiac Sarcoidosis: Role of Multimodality Imaging for Diagnosis and Treatment

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## Article Info

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## Abstract

The clinical presentation of cardiac sarcoidosis (CS) ranges from an incidentally discovered condition to heart failure and sudden death. The diagnosis of CS is tough, and as a result, CS is often under-recognized in clinical practice. CS is mostly noted in the setting of systemic sarcoidosis, though isolated CS can occur. Frequently clinical criteria require the diagnosis of extracardiac disease in order to establish the diagnosis of CS in the absence of having a positive endomyocardial biopsy. While endomyocardial biopsy provides a high specificity for diagnosing CS, this invasive test has a limited sensitivity. There is incomplete knowledge of disease development and a deficient consensus on the ideal methods for disease recognition. We discuss CS in general, the clinical disease, diagnostic algorithms, latest guidelines and management.

## Abbreviations

CS: Cardiac Sarcoidosis; CMR: Cardiac MRI; PET: Positron Emission Tomography; EMB: Endomyocardial Biopsy; HRS: Heart Rhythm Society; ACC: American College of Cardiology; AHA: American Heart Association; LGE: Late Gadolinium Enhancement.

## Introduction

Sarcoidosis is a disease process with an unidentified cause, which manifests pathologically as noncaseating granulomas with multiorgan involvement. The characteristic pattern is bilateral hilar lymph node involvement, reticular opacities in the lung and joint, eye, peripheral nervous system involvement and/or skin lesions. The incidence and prevalence (estimated at 10 to 20 per 100,000 population) of sarcoidosis are undetermined. The disease has no geographical predominance. It usually involves adolescents and young adults<sup>1</sup>.

The prevalence of Cardiac Sarcoidosis among patients with systemic sarcoidosis is reported to be 20 to 27 percent in the United States and as high as 58 percent in Japan<sup>2</sup>. It has been estimated that the lifetime risk of sarcoidosis in blacks in the United States is 2.4 percent, compared with a lifetime risk of 0.85 percent in whites<sup>27,28</sup>.

## Symptoms

Symptoms of CS include palpitations, presyncope, syncope, fatigue, dyspnea, orthopnea, and sudden cardiac death. Palpitations may be caused by either supraventricular or ventricular arrhythmias. Presyncope or syncope can be caused by AV block, ventricular

tachycardia, or supraventricular tachycardia. Fatigue, dyspnea, and orthopnea can reflect heart failure caused by CS<sup>34</sup>.

First degree AV block is the most common clinical presentation in patients with clinically evident CS. First-degree AV block due to disease of the AV node or bundle of His and intraventricular conduction defect is common and may progress<sup>35</sup>.

Ventricular arrhythmias (sustained or nonsustained ventricular tachycardia and ventricular premature beats [VPBs]) are the second most common clinical presentation of CS, occurring in approximately 30 percent of cases<sup>3</sup>. Supraventricular arrhythmias seen with CS include paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation, and sinus arrest secondary to granulomatous involvement of the sinus node<sup>34</sup>.

Sudden death due to ventricular tachyarrhythmia or conduction block accounts for 25 to 65 percent of deaths caused by CS. Implantation of ICD should be considered in patients with patients at risk for ventricular arrhythmias and sudden cardiac death. A recent study reported reduced mortality rates in patients receiving appropriate immunosuppressant therapy for cardiac sarcoidosis versus those without treatment<sup>20</sup>.

Age and lack of pacemaker or defibrillator were the significant predictors of mortality for CS. Decreased LVEF of less than 40% was associated with worse prognosis<sup>30</sup>. Reduced lung diffusion capacity (<35% of predicted) and 6-minute walk distance of less than 300 meters were associated with reduced survival in the overall precapillary cohort. Preserved FEV1/FVC ratio was also identified as an independent risk factor for worsened outcomes<sup>32</sup>.

CS can cause either a dilated cardiomyopathy or a restrictive cardiomyopathy which can lead to HF with preserved ejection fraction. Few patients with CS present right-sided heart failure, due to sarcoid-related inflammation or scar affecting the right ventricle<sup>36</sup>.

### Diagnostic Tests

Echocardiographic findings in patients with CS are varied. Focal areas of edema can result in increased wall thickness mimicking hypertrophic cardiomyopathy and focal areas of akinesis, dyskinesis, wall thinning [Figure 1]. Among patients with CS, LVEF can be either preserved or reduced and there is evidence of diastolic dysfunction.

While echocardiography has a limited sensitivity for detecting CS compared with cardiac magnetic resonance [CMR], it can be useful for evaluating the effects of pulmonary sarcoidosis and CS on hemodynamics and cardiac structure and function including left and right ventricle size and function, valve function, and estimating right heart and pulmonary pressures.

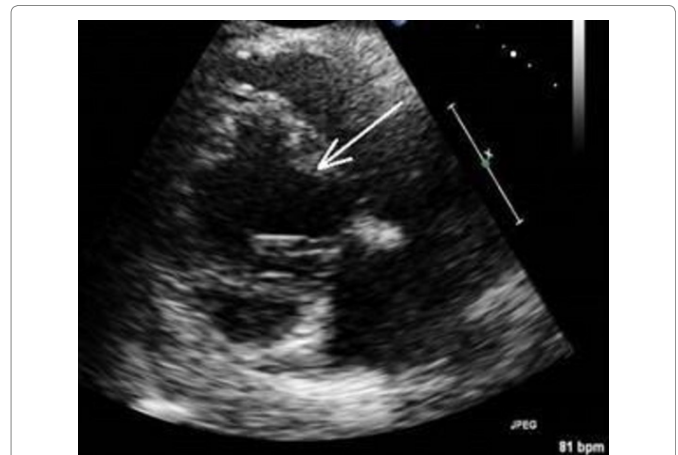


Figure 1: Transthoracic echocardiogram in parasternal long-axis view demonstrating septal thinning and akinesis (white arrow) in systolic frame. [Adapted from Bhandare D et al<sup>14</sup>].

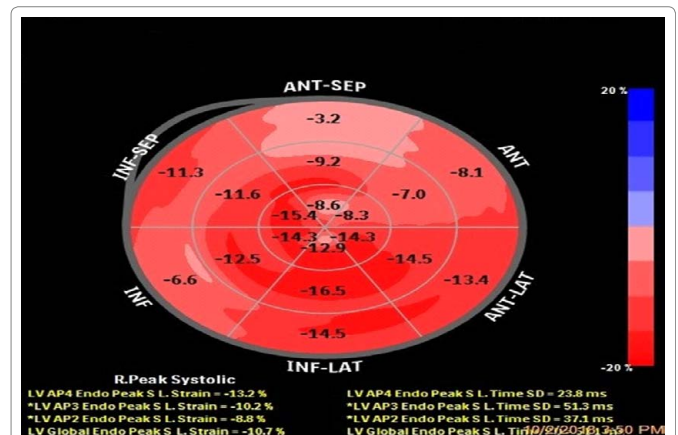


Figure 2: Echocardiographic strain imaging showing decreased longitudinal strain pattern in the anteroseptal region (Philips EPIQ). (Anteroseptal, anterior, anterolateral, inferolateral, inferior, inferoseptal wall). [Adapted from Bhandare et al<sup>14</sup>]

The reduced global longitudinal strain may be present in CS despite preserved ejection fraction, and reduction in longitudinal strain magnitude may vary inversely with late gadolinium enhancement (LGE) burden [Figure 2]<sup>3,14</sup>.

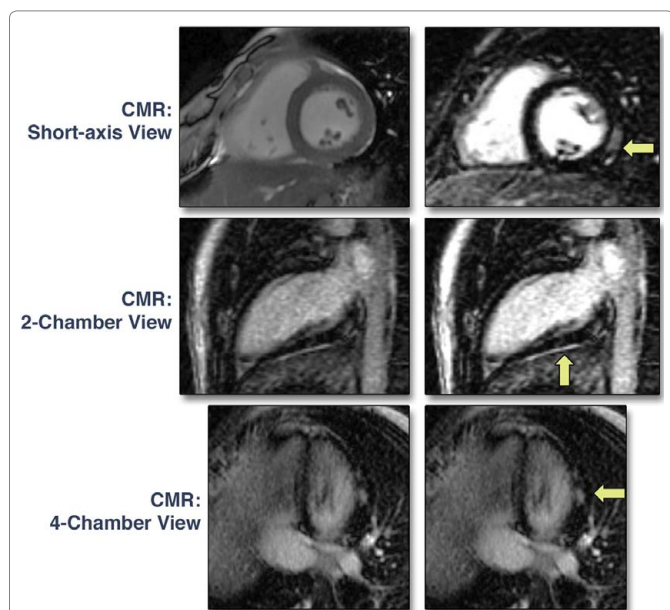
Echocardiography has low sensitivity of 25 to 65 percent for detection of CS as compared to CMR or 18F-fluorodeoxyglucose Positron Emission Tomography (FDG PET)<sup>21</sup>. Despite a high positive predictive value (84 percent), echocardiography had a low sensitivity (27 percent) to detect CS and, when added to the initial screening based on cardiac history and ECG, did not provide any improvement in sensitivity. Based on the above results, 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<sup>22</sup>.

The CMR method for detecting CS is the identification of late gadolinium enhancement [LGE], which is most commonly multifocal and involves the midventricular wall or

subepicardium [Figure3]. Of note, no specific pattern of LGE is pathognomonic for CS, therefore, careful interpretation in the context of other clinical features is required.

The following are typical although not specific LGE patterns in patients with CS:

- Multifocal areas of LGE<sup>4</sup>
- Sub-epicardial and mid-myocardial LGE, although some patients may have sub-endocardial involvement in a pattern like myocardial infarction<sup>23</sup>



**Figure 3:** Cardiac magnetic resonance (CMR) in a patient with sarcoidosis showing subepicardial late gadolinium enhancement in the left ventricular lateral wall in 2-chamber, 4-chamber, and short-axis views and matching steady-state free precession cine imaging (arrows) [Adapted from Kournaos V et al<sup>3</sup>]

- Areas of increased T2 signal often representing inflammation<sup>23</sup>
- Direct LGE extension from the left ventricle, across the interventricular septum, into the right ventricle<sup>24</sup>

The main strength of CMR is the high negative predictive value for excluding CS when no LGE is detected<sup>5</sup>. Moreover, contrast MRI is useful for outcome prediction and risk stratification regarding need for ICD-implantation. Presence and extent of ventricular Gadolinium enhancement is associated with increased risk for ventricular arrhythmias/ventricular fibrillation and sudden cardiac death<sup>15</sup>. This risk is even further increased if right ventricular Gadolinium enhancement is present in MRI<sup>16</sup>.

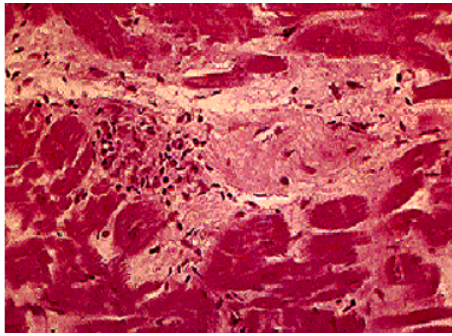
Ischemic cardiomyopathy, which is a common differential diagnosis, is characterized by subendocardial and/or transmural LGE. In comparison, isolated mid-wall or epicardial enhancement is strongly suggestive of sarcoid cardiomyopathy. The territorial vascular distribution of ischemic is quite typical versus the varied distribution pattern in cardiac sarcoidosis

<sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET) can detect active myocardial inflammation, which, in the appropriate clinical context, can be used to determine the likelihood of CS<sup>37</sup> [Figure 4]. FDG uptake by the heart is non-specific for CS and can be seen in other inflammatory myocardial diseases and hibernating myocardium. Extra cardiac FDG-PET images are strongly recommended when there are no prior data regarding the presence or disease activity of extra cardiac sarcoidosis<sup>6</sup>.

CMR and FDG-PET are the two imaging modalities that appear to have the highest sensitivity for detection of CS.

Spectrum of disease by PET/CT to evaluate rest perfusion and metabolism							
		Normal perfusion and metabolism		Abnormal metabolism		Abnormal perfusion and/or metabolism	
Perfusion							
	Normal	Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
FDG							
	Normal (Negative)	Diffuse (non-specific)	Focal increase	Focal increase	Focal increase (different areas)	Normal (Negative)	
Interpretation	Normal	Non-specific*	Early Disease	Mismatch Pattern	Scar and Inflammation	Scar	

**Figure 4:** Spectrum of cardiac sarcoidosis by cardiac positron emission tomography (PET). \*Likely failure to suppress <sup>18</sup>F-fluorodeoxyglucose (FDG) uptake by normal myocardium although rarely can also be seen with diffuse disease. CT indicates computed tomography [Adapted from Blankstein R et al<sup>33</sup>].



**Figure 5:** Non caseating granulomatous inflammation within the myocardial wall [Adapted from UpToDate].

CMR is more likely to provide information regarding the occurrence and degree of edema and scar and PET offers information regarding the presence, extent, and severity of myocardial inflammation<sup>7</sup>.

An endomyocardial biopsy [EMB] is recommended when histologic confirmation of non-caseating granulomas from extra cardiac source is lacking [Figure 5] EMB has a low sensitivity of less than 30 percent and its use is limited by false negative results owing to sampling error that may occur due to the patchy distribution of disease<sup>8</sup>.

### Diagnosis of Cardiac Sarcoidosis

A definite diagnosis of CS is established by detection of noncaseating granuloma on histologic examination of myocardial tissue with no alternative cause identified. The term probable CS denotes a likelihood of CS  $\geq 50$  percent. This term recognizes the inherent uncertainty that is often clinically present when evaluating patients with suspected CS<sup>5</sup>.

Since the histologic findings are not pathognomonic, some experts consider the diagnosis of CS “highly probable” if myocardial noncaseating granulomas are detected<sup>22,30</sup>.

The diagnosis of CS is frequently uncertain. Categories (highly probable, probable, and possible CS) may be used in cases in which there is uncertainty regarding the diagnosis of CS. This classification system, while not widely used for evaluating the likelihood of CS, has been developed based on the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) organ assessment instrument, which is used to determine the probability of sarcoidosis organ involvement<sup>29</sup>.

For patients with uncertain diagnosis of CS, the presence of one or more of these clinical findings suggests a higher likelihood of CS<sup>5</sup>.

- Unexplained reduced LVEF (<40 percent)
- Unexplained sustained VT (spontaneous or induced)
- AV block: Mobitz type II second degree or third degree

### Comparison of Major Society Guidelines

The most commonly used clinical criteria for diagnosing CS are the revised Japanese Ministry of Health and Welfare (JMHW) criteria<sup>9,10,20</sup> and the HRS Expert Consensus Statement<sup>5</sup>. Both guidelines provide a histologic pathway whereby a definitive diagnosis of CS can be established by an EMB, which reveals noncaseating granulomas. In patients who do not have a positive EMB, these criteria require a diagnosis of extracardiac sarcoidosis (for the JMHW, this can be either clinical or histologic, while for the HRS criteria, histologic diagnosis of extracardiac sarcoidosis is required) in conjunction with other criteria.

This led to a diagnostic conundrum for isolated CS due to the low sensitivity and associated risks of EMB regardless of developments in image mediated protocols. The Japanese Ministry of Health and Welfare guidelines for sarcoidosis in 2015 proposed a novice guideline in 2015 that replaces histologic confirmation with PET and cardiac MRI as a major criterion<sup>11</sup>. The criteria have been classified as Major and Minor and require the presence of two of the five major or one major and 2 minor for the diagnosis of CS.

The major criteria are:

- a. Late myocardial enhancement on contrast MRI.
- b. Abnormal cardiac uptake in FDG-PET
- c. Impaired ventricular function with regional wall motion abnormality.
- d. Basal thinning of the septal wall or morphologic ventricular abnormality (ventricular aneurysm, wall thinning)
- e. Advanced AV block or sustained ventricular tachycardia

The minor criteria were noted to be the following.

- a. Nonsustained ventricular tachycardia, multifocal PVCs, bundle branch block, axis deviation.
- b. Defect on myocardial perfusion scintigraphy
- c. Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade.

### Differential Diagnosis

An essential part of the diagnosis of sarcoidosis is the exclusion of alternative possibilities, and several settings are particularly prone to diagnostic difficulty. Mycobacterial infection, fungal infections (histoplasmosis, blastomycosis, *Pneumocystis jirovecii*), HIV infection, Löffler’s syndrome, hypersensitivity pneumonitis, pneumoconiosis, drug-induced hypersensitivity, pulmonary histiocytic disorders, foreign body granulomatosis, diseases associated with vascular inflammation (granulomatosis with polyangiitis (Wegener’s), eosinophilic granulomatosis with polyangiitis

(Churg-Strauss), and pulmonary lymphomatoid granulomatosis<sup>25,26</sup>.

CS needs to be distinguished from myocarditis, Arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is often isolated to the right ventricle and spares the septum, while patients with CS and right heart myocardial involvement often also have significant septal and/or left heart infiltration. While some patients can have left-sided arrhythmogenic cardiomyopathy, the pattern of late gadolinium enhancement (LGE) on MRI between this condition and CS is different (left-sided arrhythmogenic cardiomyopathy often has a large amount of circumferential and often contiguous subepicardial LGE)<sup>31</sup>.

## Management

Glucocorticoid therapy has been the most commonly used immunosuppressive agent. The optimal dose of glucocorticoid therapy for CS is not known, and choosing a dose requires balancing the risk of side effects with the likelihood of response<sup>12</sup>. In patients with significant inflammation, FDG-PET imaging at approximately six months of therapy may be reasonable to assess treatment response.

Patients are typically started on 60 mg/day of prednisone and gradually lowered to a maintenance dose of 10 to 15 mg/day over one year. Patients who have resolution of inflammation can develop recurrence. Hence, a low dose of glucocorticoid therapy like Prednisone 5 mg for at least one year may be recommended, especially if low-dose glucocorticoid therapy is well tolerated. Thus, glucocorticoid treatment should be continued for at least one to two years. In patients with significant inflammation, FDG-PET imaging at approximately six months of therapy may be reasonable to assess treatment response. If serial evaluations demonstrate that the disease is dormant, glucocorticoids may be tapered and eventually discontinued. Strict vigilance must be kept on the rest of the patient's life, as relapses are common after tapering of glucocorticoid therapy. Any evidence of recurrence may be handled by reinstating or increasing prednisone to 40 to 60 mg/day.

The common side effects of prolonged steroid use are hypertension, diabetes, lower resistance to infection, myopathy, depression and osteoporosis.

Steroid-sparing agents such as methotrexate, azathioprine, infliximab, or mycophenolate mofetil have been used as add-on therapy or as an alternative owing to the side effect profile of glucocorticoids. These agents may worsen heart failure, and thus should be used with great caution in patients who have volume overload. Appropriate immuno-suppressant therapy for cardiac sarcoidosis is associated with slowed disease progression and reduced long-term mortality rates<sup>20,21</sup>. Establishing an appropriate

immunosuppressant drug therapy in individual patients should be performed under repeated PET control studies, aiming the disappearance of inflammatory cardiac sites with increased FDG-uptake.

A permanent pacemaker is indicated in patients with complete AV block, or other high-grade conduction system disease, even if transient. In such cases, implantation of an ICD, rather than a pacemaker alone can be considered<sup>13</sup>. Several studies revealed the independent predictors of life-threatening ventricular arrhythmias and sudden cardiac death as the following: extent of myocardial late gadolinium enhancement<sup>15,21</sup> previous/presentation with ventricular tachycardia, and impaired left ventricular ejection fraction<sup>17</sup>. This risk for sudden cardiac death is even further increased if right ventricular Gadolinium enhancement is present in MRI<sup>16</sup>.

The 2014 HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias associated with CS<sup>5</sup> recommended that for patients with one or both (i) LVEF 36% to 49% and (ii) LVEF < 40% ICD implantation is recommended [class II B recommended]. In patients with normal LVEF consider CMR and if LGE is noted then do electrophysiological study [EPS]. If EPS is positive, then consider ICD implantation (class IIa recommendation). ICD implantation is not recommended in patients with normal LVEF/RVEF and a negative electrophysiology study (regardless if LGE is noted on CMR).

The 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death recommend ICD implantation (class IIa recommendation) in patients with evidence of extensive myocardial scar by cardiac MRI or PET scan with LVEF greater than 35%<sup>18,19</sup>.

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