# Multimodality Imaging in Cardiac Sarcoidosis: Is There a Winner?

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Abstract: Sarcoidosis is a multisystem granulomatous disease of unknown cause that can affect the heart. Cardiac sarcoidosis may be present in as many as 25% of patients with systemic sarcoidosis, and it is frequently underdiagnosed. The early and accurate diagnosis of myocardial involvement is challenging. Advanced imaging techniques play important roles in the diagnosis and management of patients with cardiac sarcoidosis.

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Keywords: Cardiac sarcoidosis, echocardiography, imaging, magnetic resonance, multimodality, sarcoidosis.
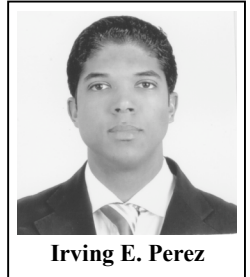
1. INTRODUCTION

Sarcoidosis is an immune-mediated granulomatous disorder of unknown etiology that affects multiple organs [1], such as the lungs, lymph nodes, skin, central nervous system, eyes and heart [2]. It is a global disease, with an incidence of 1.0–35.5 in 100,000 and a prevalence of approximately 4.7–64 in 100,000 per year. Differences in the incidence and prevalence of this disorder in different populations are related to variations in ethnic origin, geographical location, gender and age. The highest rates have been reported in African American and northern European individuals. The female to male ratio of sarcoidosis is 1.20:1.75 [3]. Approximately 70% of patients are 25-45 years of age at initial presentation [3].

Several studies have suggested that genetic and environmental susceptibilities may contribute to the development of sarcoidosis [4, 5]. The disease process may reflect an excessive immune response to unknown antigens. Its response is exaggerated due to a lack of negative immunological feedback signals [6]. Interestingly, the reason why this disease progresses in some individuals and resolves spontaneously in others is thought to involve antigen persistence, which leads to a chronic response [7].

Sarcoidosis manifests in different ways depending on age, gender, and race. The classic manifestations are fatigue, cough and localized disease of the skin (erythema nodosum). The following 3 criteria are used for the diagnosis of sarcoidosis: 1) evidence of non-caseating granulomas; 2) characteristic clinical and radiological features; and 3) no evidence of an alternative disease [8]. The most frequent diagnostic signs are extrapulmonary localizations (skin and eyes), bilateral hilar lymphadenopathy or diffuse micronodular pulmonary infiltration on CXR or the galaxy sign on CT [9].

Cardiac involvement often occurs, leading to increases in morbidity and mortality. Multimodality imaging plays a fundamental role in early the diagnosis of this disorder in association with prompt therapy. However, its accurate detection remains a challenge.

2. CARDIAC SARCOIDOSIS (CS)

The leading cause of death in the United States (US) is cardiovascular disease [10]. The prevalence of CS in the US is approximately 25% for patients with sarcoidosis, and it may be as high as 58% in Japan [11, 12]. CS accounts for an estimated 13%-25% of deaths from sarcoidosis [12]. Based on its variable clinical presentation, an antemortem diagnosis can be very challenging, and only 40%-50% of CS patients who undergo autopsy have clinical manifestations of cardiac disease. Histology findings may include the following: 1) granulomas; 2) edema and inflammation; and 3) scarring and fibrosis [13]. Granulomas may involve any part of the heart [14]. The myocardium is the most frequently affected region, especially the ventricular septum and left ventricular free wall. Sarcoidosis can also involve the coronary arteries (periarterial and media tissue), pericardium and valves [12].

The clinical manifestations of CS are dependent on both the location and extent of the granulomas, inflammation and fibrosis, and this disorder may present with a variety of signs and symptoms, ranging from a lack of symptoms to sudden cardiac death. Presenting symptoms that are nonspecific may include dizziness, palpitations, syncope or near syncope, dyspnea, orthopnea, peripheral edema and chest pain.

Conduction abnormalities occur in 12%-62% of patients and can affect any location of the conduction system. These abnormalities may lead to an atrioventricular block, bundle branch block or sinus node arrest [15, 16]. Supraventricular arrhythmia, particularly atrial fibrillation, atrial flutter and atrial tachycardia, are common in CS. The prevalence of supraventricular arrhythmia has been reported to range from 23%-36% in recent studies [17-19]. This abnormality is thought to be related to left atrial dilation rather than direct

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granulomatous involvement in the atrium [14]. Ventricular arrhythmias are more common than those that are supraventricular, and they occur due to the direct granulomatous involvement of the myocardium [20].

Heart failure is a common presentation in CS and is a sign of the progression of the disease to an advanced stage and a poor prognosis [11]. Right ventricular dysfunction may be just as common as left ventricular dysfunction [21]. Among all of the possible valvular abnormalities, mitral valve regurgitation is the most common in CS and is most often due to papillary muscle dysfunction as opposed to direct valvular destruction by sarcoidosis [22].

2.1. Cardiac Diagnostic Tools

2.1.1. Electrophysiology

2.1.1.1. Electrocardiogram (ECG)

Patients with a history of extracardiac sarcoidosis should be screened for cardiac involvement, for which a comprehensive cardiac history should be obtained and physical examination, standard ECG, Holter monitoring and/or signal-averaged ECG should be performed. The initial presentation of CS may be lethal due to ventricular tachy-arrhythmias or heart blocks; thus, the early identification of this disorder is crucial for the initiation of therapy. Sarcoidosis can be progressive. Patients with a history of extracardiac sarcoidosis should be screened for CS at least yearly [19]. ECG may reveal cardiac involvement by the following findings: 1) atrial arrhythmias; 2) unifocal or multifocal premature ventricular contractions or ventricular tachycardia; 3) the presence of Q waves in contiguous leads without evidence of myocardial infarction; 4) a fragmented QRS complex in contiguous leads without evidence of myocardial infarction; 5) bundle branch blocks; and 6) atrioventricular blocks (Fig. **1**) [19]. QT dispersion (QTd) can also be observed in CS. QTd is the difference between the maximum and minimum QT intervals on a 12 lead ECG. A study performed by Uyarel has revealed that patients with CS have a significantly greater QTd than those with extracardiac sarcoidosis and healthy individuals [23].
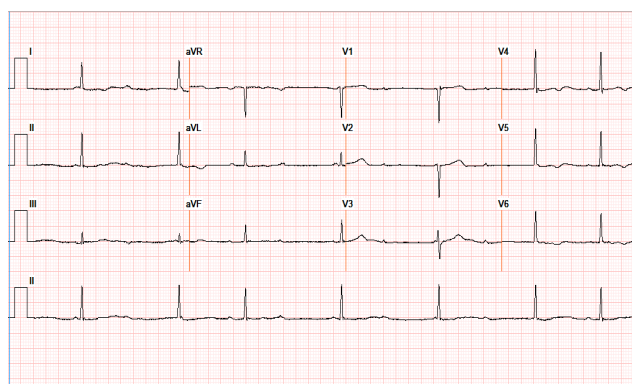

Fig. (1). EKG showing complete heart block (original).

The major mechanism of the conduction abnormality in CS is thought to involve the direct spread of inflammation and/or fibrosis to the atrioventricular node or the His-Purkinje system. Although the degree of atrioventricular block can increase, progressing to a complete block, there is evidence of reversibility after the initiation of therapy [24].

2.1.1.2. Holter Monitoring

Suzuki *et al.* analyzed the utility of 24 hour Holter monitoring to diagnose myocardial involvement in sarcoidosis. This group associated ventricular ectopic beats of more than 100 per day with CS and reported a sensitivity of 67% and a specificity of 62% [25]. Notably, heart rate variability as determined by Holter monitoring is known to be decreased in CS [26].

2.1.1.3. Signal-averaged ECG (SAECG)

SAECG averages multiple QRS complexes to remove interference and to demonstrate subtle electrical late potentials that may predispose an individual to fatal ventricular arrhythmias. SAECG was first developed to reveal intramyocardial conduction delay as a result of myocardial scarring in patients with a history of ischemic heart disease. This tool may have a potential use in screening for cardiac sarcoidosis in asymptomatic patients with known pulmonary sarcoidosis [27]. An abnormal test should prompt further evaluation for CS. SAECG has several limitations, such as a high number of false positives, which have been observed in patients with coronary artery disease and myocardial infarction (due to its effect on fibrosis), and an inability to interpret results in patients with a heart block and conduction system disease, which are present in many patients with CS. In addition, only patients with a narrow baseline QRS duration should be screened with this test [27]. Patients with CS can have one or more abnormal (SAECG) domains [19] In a cohort study performed by Schuller *et al.*, 27 of 88 patients were found to have symptoms and biopsy-proven CS, and SAECGs were abnormal in 14 of those 27 patients in addition to 11 of those that remained, demonstrating a sensitivity of 52% and a specificity of 82% [27].

2.1.2. Imaging

2.1.2.1. Chest X-ray

In patients with CS, there are no specific findings on chest x-ray. Non-specific findings often include vascular congestion and cardiomegaly secondary to congestive heart failure or dilated ventricles (Fig. **2**) [28]. In pulmonary sarcoidosis, the most common findings are bilateral hilar adenopathy or diffuse micronodular pulmonary infiltrates [3].

Fig. (2). Chest x-ray showing cardiomegaly (original).

2.1.2.2. Echocardiography

Patients should undergo screening echocardiography to assess biventricular function and regional wall motion as part of the initial panel of diagnostic tests [29]. During the early stage of CS, echocardiography may fail to detect mild localized myocardial abnormalities. Two–dimensional (2D) echocardiography abnormalities in CS include dilatation of the left ventricle (Fig. **3**), systolic dysfunction of the left ventricle and abnormal septal thickening or thinning (Fig. **4**). Doppler echocardiography can identify left ventricular diastolic dysfunction, which can be an early sign of cardiac involvement in sarcoidosis [2].
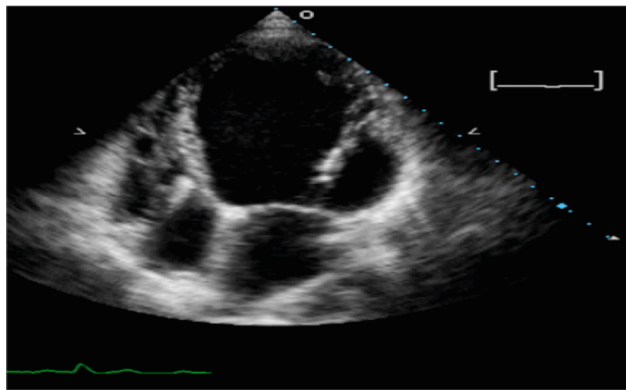

Fig. (3). Left ventricular dilatation observed on echo (original).
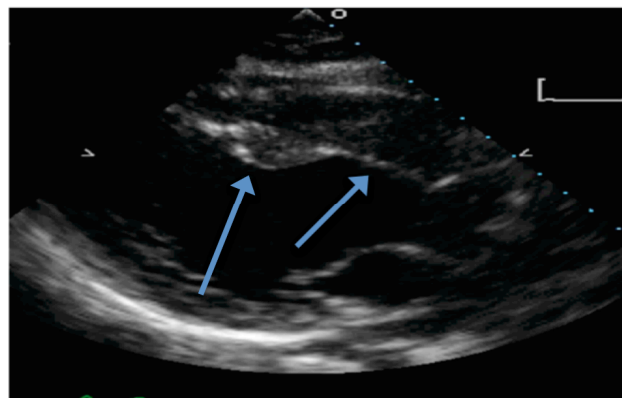

Fig. (4). Echo parasternal long axis view revealing basal septal thinning and aneurysm formation (original).

Sarcoidosis-related pulmonary hypertension (SRPH) is a rare complication and is associated with significant morbidity and mortality [30]. In a recent large cohort with biopsy-proven sarcoidosis, the prevalence of SRPH was estimated to be 12% [31]. In this study, patients with sarcoidosis and a pulmonary arterial systolic pressure (PASP) of more than 40 mmHg as shown by Doppler echo were considered to have SRPH and required right heart catheterization (RHC) for confirmation. There is a considerable correlation between Doppler echo and RHC results [32]. The advantage of Doppler echo is that it is non-invasive [31]. In addition to an elevated PASP, right ventricular abnormalities are significant additional parameters that can be used to reinforce the diagnosis of pulmonary hypertension in patients in which it is highly suspected [30]. Arcasoy *et al.* estimated pulmonary arterial systolic pressures by echo in patients with advanced lung disease who underwent evaluation for lung transplantation. The sensitivity, specificity, and positive and negative predictive values of this method for the diagnosis of pulmonary arterial hypertension were 85%, 55%, 52% and 87%, respectively [32].

Speckle tracking echo (STE) is a useful tool for the quantitative assessment of regional myocardial function and strain pattern. STE and 2D echo are helpful for the detection of early changes in myocardial mechanics before LV systolic dysfunction becomes apparent. In a recent study, STE has been shown to accurately detect subclinical LV, emphasizing the limitations of relying on LVEF as the only parameter of LV systolic performance [33].

2.1.2.3. Myocardial Perfusion Assessment with Technetium^{99m}, Thallium^{201} and Gadollinium^{67}

Two studies (Le Guludec *et al.* and Eguchi *et al.*) have demonstrated that technetium^{99} is superior to thallium^{201} for detecting myocardial perfusion abnormalities [34, 35]. However, the sensitivities of technetium^{99} and thallium^{201} are not as high as that of PET. Technetium^{99m} is used to assess myocardial perfusion due to its rapid distribution in the myocardium and slow clearance and redistribution. A phenomenon termed washout has been described from early to delayed imaging in myocardial infarction, hypertrophic cardiomyopathy, complete left bundle branch block and cardiac sarcoidosis. A recent study conducted by Kudoh *et al.* has demonstrated a relationship between this washout phenomenon and left ventricular recovery after steroid therapy in patients with CS [36].

Myocardial perfusion can show a reverse distribution pattern, in which perfusion defects at rest decrease under stress conditions [37]. Therefore, abnormal perfusion in CS is different from that in coronary artery diseases because sarcoid granuloma is not associated with the region of coronary artery perfusion [38]. It is thought that reverse distribution in CS is secondary to focal reversible microvascular constriction in coronary arterioles surrounding granulomas [38].

Thallium^{201} myocardial scintigraphy has been used to diagnose patients with CS. Areas containing defects correspond to the fibrogranulomatous replacement of myocardial tissue [39]. Thallium-^{201} is sensitive but non-specific because it detects cardiac sarcoidosis with and without active inflammation. Another radionuclide test is gadollinium^{67} scintigraphy. The uptake of gadollinium^{67} is interpreted as evidence of active inflammatory disease. It is believed that gadollinium^{67} is actively taken up by macrophages in lesions with active sarcoidosis [40]. Steroid therapy markedly decreases gadollinium^{67} uptake; thus, gadollinium^{67} is used to assess the response to this type of therapy [40]. CMR and PET/CT have largely replaced other radionuclide imaging techniques due to their higher accuracies for CS [41].

2.1.2.4. ^{18}F-FDG PET

The cellular uptake of ^{18}F-FDG PET in sarcoidosis is correlated with the activity of inflammatory cell infiltrates. These cells have high glycolytic activities to satisfy their high energy demands. After crossing the cellular membrane, glucose and ^{18}F-FDG PET are phosphorylated. Although glucose is further metabolized, ^{18}F-FDG PET remains trapped within the cells and can be visualized with this radionuclide technique; therefore, active sarcoid lesions in several organs can be visualized by PET imaging (Fig. **5**) [42, 43]. The reduction in myocardial ^{18}F-FDG PET uptake may be related to the fibrosis of affected lesions or the resolution of inflammation [44].

Yamagishi *et al.* selected 17 patients with biopsy-proven sarcoidosis and CS diagnosed according to the Japanese Ministry of Health and Welfare criteria. Their study compared ^{13}N-ammonia/^{18}F-FDG vs. ^{201}thallium vs. ^{67}gallium. Fifteen patients demonstrated an increased myocardial uptake of ^{18}F-FDG, whereas the rates of uptake of thallium and gallium were only increased in 6 and 3 patients, respectively. Therefore, these results demonstrate that ^{13}N-ammonia/^{18}F-FDG is the most sensitive tool to identify CS and assess disease activity [40].

A recent meta-analysis performed by Yousesef *et al.* has demonstrated that ^{18}F-FDG PET has a sensitivity of 89% and a specificity of 78% compared with JMHWG [45].

All CS patients scheduled for ^{18}F-FDG PET should undergo myocardial perfusion studies with technetium^{99m}, thallium^{201}, rubidium^{82} or ^{13}N-ammonia to compare perfusion images with ^{18}F-FDG PET images to identify changes in the active sarcoid, scar tissue in the normal myocardium and the response to therapy [44]. A recent study by Blankstein *et al.*

has demonstrated the relationship between ^{18}F-FDG uptake and focal perfusion defects as shown by cardiac PET for identifying patients who are at higher risks of lethal arrhythmias and death [46].

2.1.2.5. Cardiac Magnetic Resonance (CMR)

CMR is a useful tool for the diagnosis and evaluation of CS. This technique detects areas of active and chronic disease. CMR imaging provides high sensitivity and specificity for the diagnosis of myocardial sarcoidosis [47]. Edema or infiltration is observed during the inflammatory phase and is characterized by increased focal wall thickness combined with wall motion abnormalities (focal hypokinesis or akinesis) observed on cine imaging, increased signal intensity on T2-weighted images and early gadolinium enhancement [48]. The chronic phase mainly exhibits delayed gadolinium enhancement (Fig. **6**), representing fibrosis and scarring and wall thinning. Late gadolinium enhancement has emerged as the dominant CMR sequence for the evaluation of cardiac sarcoidosis because it is associated with adverse events and cardiac death [49]. The areas of late gadolinium enhancement in the myocardium are usually localized to the septum (Fig. **7**), the basal and lateral segments of the left ventricle and the papillary muscles [50, 51]. In contrast, patients with myocardial infarction due to coronary artery disease show the late enhancement of the subendocardium or the transmural distribution of the coronary arteries [52]. The location of the abnormalities on CMR might be useful for guiding endomyocardial biopsy to increase the yield and sensitivity. Preliminary observations suggest that monitoring gadolinium enhancement may also be helpful in the assessment of the efficacy of steroid therapy [53, 54].

Late gadolinium enhancement CMR was compared with the modified Japanese Ministry of Health and Welfare
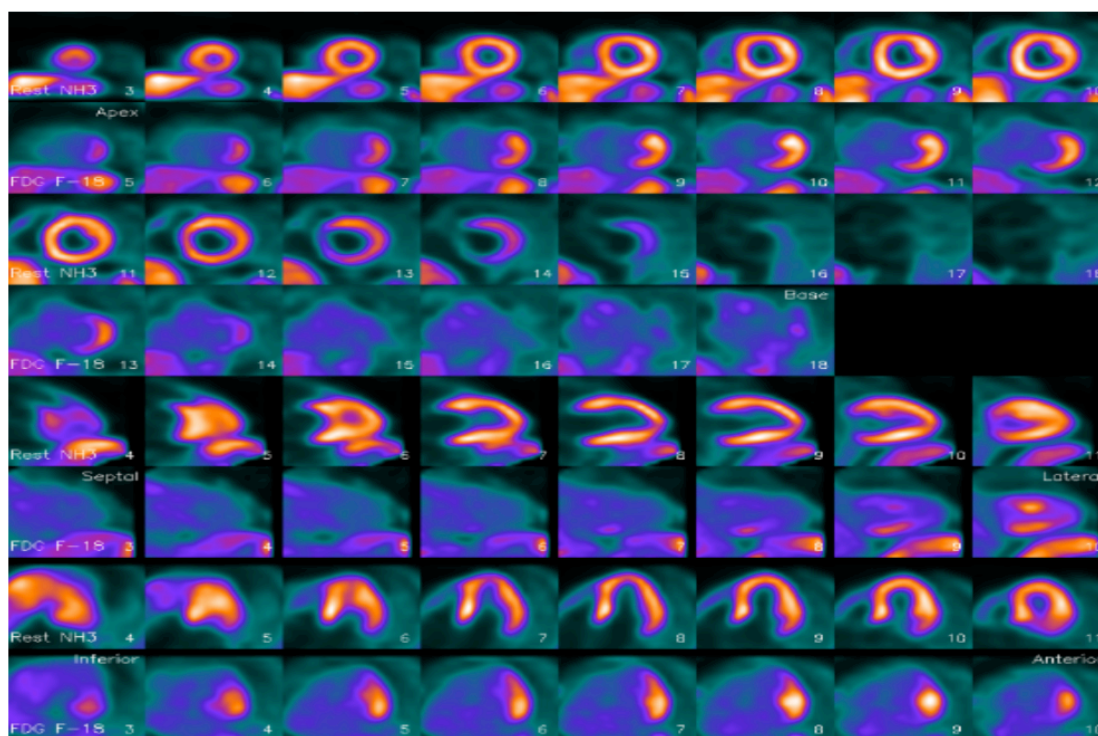
Fig. (5). 18F-FDG PET scan demonstrating basolateral wall uptake (original).
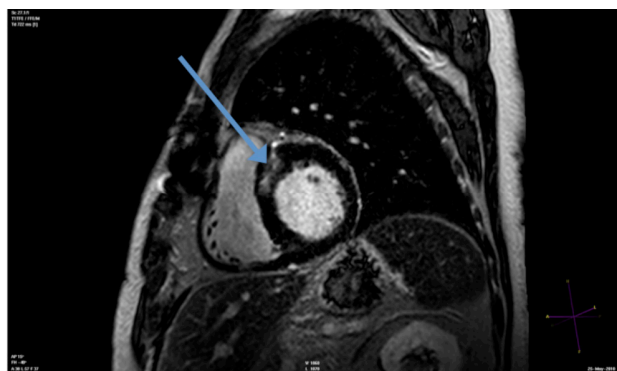
Fig. (6). CMR showing delayed enhancement (original).

Fig. (7). Delayed enhancement observed in the septum in CMR (original).

(JMH) criteria in a series of 81 patients with biopsy-proven extracardiac sarcoidosis [55]. Clinical evaluation included an ECG and at least one non-CMR cardiac imaging study. Coronary disease was excluded by coronary angiography in all patients with CMR evidence of myocardial damage. Late gadolinium enhancement CMR identified cardiac involvement in 21 patients, while the JMH criteria only identified cardiac disease in 10 patients, with 8 overlaps. During the mean 21 months of follow-up, the patients with CMR evidence of myocardial damage had a 9-fold higher rate of adverse events (17.2 versus 1.9% per year) and an 11.5-fold higher rate of cardiac deaths compared to those with no CMR evidence of damage (11.5 versus 1.0% per year). The JMH-positive patients had a 3.5-fold higher rate of adverse events and a 3.9-fold higher cardiac death rate compared with the JMH-negative patients. Similar findings have also recently been reported in another larger study. Greulich *et al*. have demonstrated that the presence of late gadolinium enhancement (LGE) is a predictor of death and other adverse events in patients with suspected cardiac sarcoidosis in a study of 155 patients with systemic sarcoidosis who underwent a workup for suspected cardiac sarcoid involvement [49]. LGE was present in 39 patients (25.5%). The presence of LGE yielded a hazard ratio (HR) of 31.6 for death, aborted sudden cardiac death, or appropriate ICD discharge, and an HR of 33.9 for any event that occurred after a median follow-up time of 2.6 years. LGE is superior to functional or clinical parameters, such as LVEF, LV end-diastolic volume, or the presentation of heart failure, for the prediction of potentially lethal or other adverse events, respectively. Except

for 1 patient who died of a pulmonary infection, no patient without LGE died or experienced any adverse events during follow-up, even if the LV was enlarged and the LVEF was severely impaired.

Smedema *et al.* assessed whether gadolinium-enhanced cardiac MRI (CMR) is of additional diagnostic value compared with the standard assessment in patients with sarcoidosis who were evaluated for cardiac involvement [51]. They reviewed the findings of 58 patients with pulmonary sarcoidosis who were assessed with ECG, Doppler echocardiography, thallium[201] scintigraphy, and CMR. The standard evaluation led to the diagnosis of cardiac involvement in 13 patients, while CMR resulted in the diagnoses of myocardial scarring and impaired systolic left ventricular function in an additional 6 patients. The extent of delayed enhancement was found to be correlated with the disease duration, ventricular dimensions and function, the severity of mitral regurgitation, and ventricular tachycardia.

Patients in whom cardiac involvement was diagnosed only with CMR had less myocardial scarring and functional impairment compared with those with a diagnosis made by the standard assessment.

Thus, CMR provides an accurate estimation of the extent of cardiac involvement and may reveal signs of early infiltration that are not detected by the standard assessment. In addition, it may also be useful for the assessment of the steroid therapy response [2, 53, 56].

DE-CMR is more than twice as sensitive for the assessment of cardiac involvement compared with the current consensus criteria in patients with sarcoidosis. The extent of late enhancement with gadolinium is related to the severity of cardiac involvement and may therefore have prognostic implications. Further, it is associated with future adverse events, including cardiac death. These data support the necessity for future large, longitudinal follow-up studies to definitively establish CMR LGE as an independent predictor of cardiac death in sarcoidosis, as well as to evaluate the incremental prognostic values of additional parameters.

2.1.2.6. CMR vs. ^{18}F-FDG

While different imaging techniques have been used to evaluate CS, the two that are currently the most accurate are CMR and ^{18}F-FDG PET. Few studies have compared these techniques (Table **1**) [47, 57]. Ohira *et al*. evaluated 21 patients with suspected CS and compared CMR with ^{18}F-FDG PET. Eight of the twenty-one patients were diagnosed with CS according to the Japanese Ministry of Health and Welfare criteria (JMHW). In their study, CMR showed a sensitivity of 75% and a specificity of 76.9%, while 18F-FDG PET had a sensitivity of 87.5% and a specificity of 38.5% [47]. However, Mehta *et al*. have demonstrated that ^{18}F-FDG has a higher sensitivity (86%) than CMR (36%) and that the modified JMHW criteria are associated with a low sensitivity (33%) and a high specificity (97%) [57].

2.1.2.7. Hybrid PET-MR

Wicks *et al*. have provided the first description of the feasibility and improved diagnostic accuracy of hybrid cardiac PET-MR imaging in CS. Their study has shown that hybrid imaging has an improved sensitivity (89%) for identi-

Table 1.   Comparison between CMR and 18F-FDG.

CMR Advantages
1) No radiation exposure
2) Spatial resolution
3) 18F-FDG is expensive and is not widely available
4) 18F-FDG specificity can be reduced by the inability of patients to follow dietary instructions
5) Steroid use can impair 18F-FDG interpretation by altering glucose and insulin levels
18F-FDG PET Advantages
1) Offers assessment of perfusion patterns
2) Offers assessment of disease activity based on specific uptake values
3) Whole-body 18F-FDG PET can be used to evaluate the extent of systemic disease
4) Can be utilized in patients for whom CMR is contraindicated, such as those with implantable metallic devices and impaired renal function

fying presumed CS and a low specificity (42%) and a perfect sensitivity (100%) for detecting confirmed CS [58].

3. CLINICAL DIAGNOSIS (JAPANESE MINISTRY OF HEALTH) VS. DEFINITIVE DIAGNOSIS (BIOPSY)

The diagnosis of cardiac sarcoidosis is challenging and usually involves combining clinical and imaging findings. Features observed on PET or CMR are suggestive of cardiac involvement but are not diagnostic. Currently, the Japanese Ministry of Health and Welfare (JMHWG) guidelines serve as the standard for the clinical diagnosis of CS. In 2006, these guidelines were revised so that this disease could be identified by either one of two methods, including histological diagnosis (by granulomas found on myocardial biopsy) plus the histologic or clinical diagnosis of extracardiac sarcoidosis. The second method includes the histologic or clinical diagnosis of extracardiac sarcoidosis plus a combination of at least 3 major criteria or at least 1 major criteria and 3 minor criteria (Table **2**) [59].

In reality, endomyocardial biopsy (EMB) has a low sensitivity of approximately 20%-30% due to the fact that it often misses areas of myocardial involvement and patchiness associated with this disease [60]. Likewise, the modified JMHW criteria have an imperfect diagnostic accuracy [55].

4. TREATMENT

Currently, there are no guidelines for the treatment of patients with CS, but as soon as a diagnosis is made, there is a consensus that treatment must be promptly started to prevent fatal arrhythmias and subsequent death. In addition, the purpose of prompt treatment is to control inflammation and prevent fibrosis [61].

Corticosteroid therapy is the pillar and first-line treatment for CS to reduce inflammation and suppress its progression to fibrosis [62]. Kato *et al.* studied 20 patients with an atrioventricular block and preserved left ventricular ejection fraction and compared two groups, one treated with steroids and the other treated without steroids, over a period of 79 months. They found that the patients treated without steroids had a decreasing EF and were prone to ventricular tachycardia [24]. In another retrospective study performed by Chapelon *et al.*, the responses of 39 CS patients to a corticosteroid with or without an additional immunosuppressive treatment were evaluated. This group found that 87% of the patients showed improvement and that 54% were cured, as determined both clinically and by imaging, concluding that corticosteroids should be administered as soon as possible to patients with CS and that another immunosuppressive treatment should be initiated in the absence of a therapeutic response [63]. Yodogawa *et al.* have demonstrated that even a complete heart block can be reversed with corticosteroid therapy [64]. Corticosteroids can lead to the resolution of arrhythmias and conduction and electrocardiographic abnormalities [61]. Starting therapy before left ventricular dysfunction results in an excellent clinical outcome and is the mainstay in the treatment of CS [65]. Chiu *et al.* have shown that long-term steroid use during the early or middle stage of CS might be protective or therapeutic but that it is not as effective during the late stages [66].

The precise effective dose and duration for corticosteroid therapy is not yet known. Choosing the optimal dose requires balancing side effects with the likelihood of a response [67]. Chapelon-Abric *et al.* have recommended an initial dose of prednisone of 1 mg per kilogram per day for 6-8 weeks followed by a tapering dose [63]. In contrast, Yazaki *et al.* have

Table 2.   Major and minor criteria of the Japanese Ministry of Health and Welfare for the clinical diagnosis of cardiac sarcoidosis.

Major Criteria	Minor Criteria
1) Advanced AV block 2) Basal thinning of the interventricular septum 3) Positive cardiac 67 Ga uptake 4) Depressed LVEF (<50%)	1) Abnormal ECG findings: ventricular arrhythmias (VT or multifocal or frequent PVCs), CRBBB, axis deviation or abnormal Q wave 2) Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm or wall thickening) 3) Nuclear medicine: perfusion defect detected by thallium 201 myocardial scintography or technetium 99 myocardial scintigraphy 4) Gadolinium-enhanced MRI: delayed enhancement of myocardium 5) Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade.

found that there is no apparent survival benefit of high-dose over lower-dose prednisone; therefore, it is recommended that prednisone be administered at a dosage of 60 mg every other day and then tapered (over several months) to 10 mg every other day [67]. Although corticosteroid therapy discontinuation is associated with an approximately 25% relapse rate, steroid therapy may be discontinued [28].

ICD implantation in patients with known CS is a component of an aggressive primary prevention strategy. When these patients present with sustained ventricular arrhythmias, the implantation of a defibrillator is crucial [21]. Based on the widespread scarring caused by CS and its progressive nature, catheter ablation at the site of origin is not indicated. Soejima and Yada have suggested an algorithmic approach to pacemaker and ICD implantation. They have recommended the following: A) pacemaker implantation alone for patients presenting with an advanced atrioventricular block without heart failure or left ventricular dysfunction; B) defibrillator implantation alone for those with spontaneous ventricular arrhythmia and a narrow QRS; and C) defibrillator implantation with cardiac resynchronization therapy for spontaneous ventricular arrhythmias with a wide QRS and impaired ventricular function [59]. Pacemaker implantation is recommended in patients with a high-grade or complete atrioventricular block even if the block reverses transiently due to the concerning fact that their CS may progress [68].

Other immunosuppressive therapies have been used in patients whose condition is refractory to corticosteroids or in those who cannot tolerate their side effects. Treatment with methotrexate, azathioprine or cyclophosphamide can also be used as a steroid-sparing agent. In patients for whom corticosteroids are contraindicated, immunosuppressive agents are chosen for the initial treatment [2, 69].

Interestingly, CS patients undergoing heart transplantation have a higher one-year survival rate than those undergoing transplantation for all other diagnoses [70]. A retrospective study performed by Zaidi *et al.* analyzed 65 CS patients who underwent heart transplantation over an 18-year period. This study revealed that the one-year post-transplantation survival rate was higher for the sarcoidosis patients compared with all others who had undergone transplantation (87.7% vs. 84.5%), and the five year post-transplantation survival rate for the CS patients was 80% [70]. Although CS can recur in post-transplantation patients, its incidence is unknown [71]. Cardiac transplantation in patients with known CS is reserved for those with end-stage disease who are unresponsive to medical therapy, especially younger patients [72]. A smaller study recently published by Perkel *et al.* has demonstrated similar results to the study performed by Zaidi *et al.,* showing that none of the patients experienced recurrence while on minimal immunosuppression, which is the primary concern for deferring transplantation [73].

5. PROGNOSIS

Cardiac sarcoidosis is an unpredictable disease with a variable clinical presentation, natural history and therapeutic response; thus, it is very difficult to assess its prognosis. CS is associated with a poorer prognosis compared with sarcoidosis without cardiac involvement. The mortality rate may exceed 40% within five years and 55% within ten years. The most powerful prognostic predictor is the severity of congestive heart failure. Surprisingly, the presence of pulmonary involvement has been associated with a higher survival rate, which may be explained by a better follow-up [61, 67]. More recently, several studies have demonstrated the relationship between ^{18}F-FDG uptake and a focal perfusion defect on cardiac PET and LGE on CMR, which are present in patients at higher risks of lethal arrhythmias and death. Nevertheless, larger, prospective clinical studies are needed to determine the value of imaging for therapy monitoring and the delineation of risk stratification. Data on the detailed systemic assessment of each imaging modality, including PET perfusion, PET metabolism imaging, cardiac MRI T2-weighted imaging for edema, early GDE, wall thickness and wall motion on cine imaging and LGE, will be useful for obtaining pathophysiologic information on irreversible scar/fibrosis versus reversible inflammation, which can be treated with steroid and other anti-inflammatory therapies.

6. CONCLUSION

Cardiac sarcoidosis should be considered in all cases of unexplained cardiomyopathy with a high-degree atrioventricular block, especially in young patients. Endomyocardial biopsy lacks sensitivity and is invasive. Advances in cardiac imaging improve the diagnosis and prompt treatment of patients, avoiding fatal arrhythmias and death. Unfortunately, a major problem in the diagnosis of CS is the lack of a gold standard imaging modality.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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