Curr Treat Options Cardio Med (2016) 18: 16
DOI 10.1007/s11936-016-0439-9

A Diagnostic and Therapeutic Approach to Arrhythmias in Cardiac Sarcoidosis

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Published online: 13 February 2016

This article is part of the Topical Collection on *Arrhythmia*

Keywords Cardiac sarcoidosis · Ventricular tachycardia · Steroids · Immunosuppression · Ablation · ICD

Opinion statement

Cardiac sarcoidosis is a protean disease, capable of causing nearly any cardiac abnormality. Electrical abnormalities including heart block and ventricular tachyarrhythmias are some of the most feared manifestations of cardiac sarcoidosis. Despite increasing awareness, cardiac sarcoidosis remains underdiagnosed in clinical practice, and as a result, many patients do not receive potentially disease-altering immunosuppressant therapy. In this review, we discuss cardiac sarcoidosis and its management, focusing diagnostic and therapeutic approaches to arrhythmias in cardiac sarcoidosis.

Introduction

Nearly a century after its first report in 1898 by Jonathan Hutchinson [1], sarcoidosis remains a challenging disease to diagnose and treat due to heterogenous presentation and complex multiorgan involvement [2, 3]. Increasingly, cardiologists are considering cardiac sarcoidosis (CS) on the differential diagnosis of a patient presenting with idiopathic heart block, tachyarrhythmias, or cardiomyopathy. In this review, we will consider the pathophysiology, epidemiology, and clinical manifestations of CS, focusing on the electrophysiology abnormalities. We will then consider therapeutic options including corticosteroids and other immunosuppressants, antiarrhythmic

drugs, traditional heart failure therapies, and invasive strategies including ablation therapy, implantable cardioverter defibrillators (ICD), and sympathetic denervation.

Pathophysiology and clinical manifestations

Sarcoidosis continues to be a disorder of unknown etiology, described by pathology, and not by pathophysiology. The accumulation of mononuclear phagocytes and T-lymphocytes into the *sine qua non* pathologic structure of the noncaseating granuloma defines the disease [3, 4] and clearly points to an autoimmune pathway. As mentioned above, any organ system may be involved, with the lung, lymph nodes, skin, eye, and central nervous system being the most common. Given the multisystem nature of the disease, its clinical presentations are myriad and even the cardiac manifestations of the disease vary widely from patient to patient. Most common cardiac presentations can be divided into arrhythmic, cardiomyopathic, and pericardial groups [4–7]. Direct granulomatous involvement of any of the four cardiac valves [8], constrictive pericarditis [9], coronary artery granulomatous disease causing myocardial ischemia [10], and intracardiac masses have all also been described.

Electrophysiologic manifestations of CS can be divided into heart block and tachyarrhythmias. Due to the variability in population studies and diagnostic criteria used, the proportion of the population affected by each manifestation fluctuates widely in published reports. Atrioventricular block is present in 26–62 % of patient with CS and bundle branch block in 12–61 %. Supraventricular and ventricular tachyarrythmias are reports in up to 15 and 42 % of patients respectively. Ominously, 12–60 % of patients with CS present with sudden cardiac death [11].

Epidemiology

In the USA, the annual incidence of sarcoidosis is 10.9 per 100,000 in whites and 35.5 per 100,000 in African-Americans [12]. Women between the ages of 20 and 40 carry the highest incidence of systemic sarcoidosis. However, myocardial involvement carries no predilection for gender. In autopsy series, 20–30 % of all patients with sarcoidosis have pathologic cardiac involvement; though only 3–5 % of all sarcoid patients will have clinically evident cardiac involvement noted prior to death [13]. It is thus likely that many cases of cardiac sarcoidosis are clinically unrecognized. It has been our experience that the discovery of CS in the explanted (native) heart of a patient receiving an orthotopic heart transplant is not rare. The lack of recognition of CS in a patient with extra-cardiac sarcoidosis is not without prognostic implications. Cardiac involvement accounts for as much as 25 % of all deaths from sarcoid in the USA. Curiously, in Japan, CS has an unusually high incidence: up to 58 % of all sarcoid patients in Japan have cardiac involvement, and as

many as 85 % of deaths in Japanese patients with sarcoidosis are due to cardiac involvement [14].

Diagnosis

Given its variable clinical presentations, CS remains a challenging disease to diagnose. Through the years, varying diagnostic criteria have been proposed, all with differing strengths and weaknesses. In 2006, the Japanese Ministry of Health and Welfare published guidelines for diagnosis based on either histology or clinical characteristics (Table 1) [15]. While useful, these guidelines are not universally accepted and are often maligned as lacking specificity and sensitivity and also fail to account for advances in diagnostic techniques [16, 17].

In general terms, CS should be suspected in a patient with known extracardiac sarcoidosis and any cardiac abnormality—whether electrical, functional, or structural. As noted above, fascicular or atrioventricular (AV) block should particularly raise clinical suspicion, as should ventricular tachyarrhythmias. Even though the Japanese Ministry of Health and Welfare guidelines place emphasis on histologic confirmation with endomyocardial biopsy, advances in imaging have allowed noninvasive diagnostic techniques to take the fore in clinical practice. Echocardiography provides important prognostic and functional

Table 1. 2006 Japanese Ministry of Health and Welfare guidelines for diagnosis of Cardiac Sarcoidosis [15]

Diagnostic category	Criteria
Histologic diagnosis group	Endomyocardial biopsy demonstrates noncaseating epithelioid cell granulomata with histological or clinical diagnosis of extracardiac sarcoidosis
Clinical diagnosis group	• Negative endomyocardial biopsy • Presence of histologic or clinical extracardiac sarcoid
Major clinical criteria	
	Advanced atrioventricular block
	Basal thinning of the interventricular septum
	Positive cardiac gallium uptake
	Depressed left ventricular ejection fraction (<50 %)
Minor clinical criteria	
	Abnormal ECG findings
	• Ventricular arrhythmias
	• Right bundle branch block
	• Axis deviation
	• Abnormal Q-wave
	Abnormal echocardiography
	• Regional wall motion abnormalities
	• Morphologic abnormality
	Nuclear perfusion defect detected
	Delayed gadolinium enhancement noted on cardiac MRI
	Endomyocardial biopsy showing interstitial fibrosis or monocyte infiltration over moderate grade

information and thus remains a cornerstone imaging modality for CS assessment [18, 19]. However, while Doppler assessment of strain and strain rate by tissue Doppler sampling has shown early promise in assessing patients for cardiac sarcoid involvement [20–22] and warrants further investigation, echocardiography cannot provide a definitive diagnosis of CS. With excellent sensitivity, specificity, and spatial resolution, cardiac magnetic resonance (CMR) imaging is considered the diagnostic imaging test of choice for CS in those patients who can undergo magnetic resonance imaging and gadolinium administration [23–25]. For those unable to undergo CMR, 18F-FDG PET remains a highly sensitive, albeit less specific, imaging modality for CS [26, 27]. Other radionuclide tests (201Th, 99mTc, and 67Ga) fall short of the diagnostic capabilities of CMR and PET [26, 28–30]. However, they remain more widely available outside of tertiary referral centers, and all may provide additional diagnostic and prognostic information for CS.

Therapies

Immunosuppressants

- Cardiac involvement with sarcoidosis carries a poor prognosis if untreated and warrants immediate initiation or escalation of immunosuppressive therapy at the time of diagnosis [14]. Corticosteroids remain the mainstay of initial therapy in CS.
- Randomized controlled trial data is scarce, yet it is widely accepted that initial therapy of CS should consist of systemic corticosteroids at moderate to high doses [23, 31]. Small cohort studies indicate that an initial dose of at least 30 mg/day of oral prednisone for 2–3 months with a gradual taper to a maintenance dose of 10–20 mg every other day results in clinical improvement, a reduction in negative ventricular remodeling, and reduced risk of ventricular arrhythmia or heart block [23, 32, 33]. Yazaki et al. found that 75 patients treated with steroids had a significantly better 5-year survival compared with untreated patients (75 vs 10 %), though this study carries all the usual cautions of a retrospective analysis [34].
- Corticosteroid therapy has historically been used only for CS patients with left ventricular (LV) ejection fraction <50 %, advanced AV block, or ventricular tachyarrhythmias. However, new studies suggest that this approach may lead to a harmful delay in therapy. Several retrospective cohort analyses have suggested that corticosteroid therapy holds the most benefit for patients who do not yet have severe LV dysfunction and those patients with signs of active inflammation on imaging [34–36]. Once patients progress to the advanced fibrogranulomatous scarred phase of the disease, immunosuppressant therapy likely holds little benefit. These findings argue for early therapy with corticosteroids in patients with signs of CS and active inflammation, even in the absence of LV dysfunction or high-grade arrhythmias.
- It is not uncommon for CS symptoms and signs to recur during a taper of steroids. In the case of a recurrence, experts recommend an

immediate reinitiation of the initial dose (often as high as 1 mg/kg/day of oral prednisone) until symptoms are again controlled.

- Side effects are prevalent during long-term therapy with corticosteroids, making the use of steroid-sparing agents attractive. Furthermore, some CS patients have worsening arrhythmias or myocardial inflammation by imaging that indicates refractoriness to steroid therapy [37]. At our institution, many practitioners will employ steroid-sparing agents if the total daily dose of prednisone required to achieve therapeutic effect is greater than 20 mg.
- Several other immunosuppressant agents have been used with varying reports of success; none have been tested in clinical trial. Cyclophosphamide, methotrexate, mycophenalate mofetil, and cyclosporine have all been reported in the treatment of CS, however with little evidence-based data on efficacy and superiority to date [37–39]. These agents all have a relatively prolonged onset of action. Thus, it is recommended to start therapy in conjunction with concomitant steroids, with the eventual weaning of steroids as sparing agents demonstrate efficacy in symptom abatement.
- Recently, tumor-necrosis factor-α (TNF-α) has been implicated in the formation of granulomata, prompting trials of infliximab (a TNF-α antagonist) in CS. Early studies report an improvement in myocardial inflammation by imaging as well as improved clinical outcomes [40, 41]. Infliximab poses a not insignificant risk of infection, and in fact, a case of fatal disseminated cryptococcosis has been reported with the use of infliximab in a CS patient.

Anti-arrhythmic drugs

- Anti-arrhythmic drugs (AADs) have been historically and still currently included in the management of ventricular arrhythmia in CS, often in conjunction with immunosuppression (see above) [42–45].
- Increasingly, medication therapy is being used as adjuncts to radiofrequency ablation or ICD implantation. According to the recent HRS consensus [46••], AAD use is recommended as part of a step-wise strategy to treat ventricular arrhythmias after failure of standard immunosuppression therapy (class IIa recommendation), with amiodarone and sotalol as the recommended agents [44, 45], although others such as dofetilide, flecainide [47], and mexiletine have also been used [45].
- Whether amiodarone or sotalol can effectively suppress VT in the absence of ablation is unclear, although one study has estimated that they can be effective for up to 50 % of patients [48•], there is no evidence supporting one agent over another.
- Of note, amiodarone has been discouraged for patients with clinically active pulmonary sarcoidosis due to concern for worsening pulmonary function [49]. The new guidelines also recommend against class I AAD for CS, citing the Cardiac Arrhythmia Suppression Trial (class III

recommendation), although no clear evidence has yet shown that class I agents cause harm specifically in CS.

Traditional heart failure therapy

- Because conduction abnormalities are the most common sequelae of CS and thought to underlie sudden cardiac death (the most common cause of mortality in CS), the bulk of existing research has focused on treatment of arrhythmias. However, congestive heart failure secondary to dilated cardiomyopathy can also occur and cause death in up to 25 % of CS patients [14].
- Conventional medications for systolic heart failure such as angiotensin converting enzyme (ACE)-inhibitors and beta-blockers have been used for CS patients with symptomatic heart failure and/or reduced ejection fraction [34, 35]. Although the most recent HRS guidelines do not address heart failure, prior expert recommendations advocate the use of these heart failure medications for appropriate patients, including diuretics in addition to immunosuppression [50, 51].

Invasive strategies

- Within the past decade, there has been increasing interest in the role of invasive interventions, including implantable cardioverter defibrillators (ICDs), radiofrequency ablation, and sympathectomy as potential treatments for refractory arrhythmias in CS.
- ICD implantation has become the go-to therapy for recurrent and symptomatic arrhythmias to reduce the risk of sudden cardiac death [51], especially since ventricular arrhythmias in some patients prove resistant to immunosuppression [52, 53]. Arrhythmias originating from the ventricles are thought to be induced by a combination of ongoing inflammation and subsequent scarring, which can form a complex substrate for reentry in both the LV and right ventricular (RV) [45, 54•]. Based on three recent multicenter retrospective studies [55–57], the newest HRS guidelines support using ICDs as definitive therapy in patients with spontaneous sustained ventricular arrhythmias or reduced LV ejection fraction (EF) ≤35 % (class I recommendation). However, results from two out of the three studies suggest that even a relatively small reduction in LVEF or RV dysfunction by itself is a significant risk factors for sudden cardiac death [55, 56]; thus, LV EF <50 % or RV dysfunction (RV EF <40 %) are class IIb recommended criteria for ICD implantation. Annual rate of appropriate ICD therapy ranged from 8.6 [57] to 14.5 % [55]. Lower LVEF and younger age have been associated with higher rates of appropriate ICD therapy in one study of 33 male CS patients [44].
- Programmed ventricular stimulation may provide risk stratification in CS patients. A prospective 5-year study of 76 CS patients who underwent programmed stimulation showed that ventricular

arrhythmia or death occurred in the majority of patients with inducible sustained ventricular arrhythmia (induced in 8 out of 76 patients) [58]. The newest HRS consensus accordingly recommends ICD therapy for inducible sustained VT or VF during programmed ventricular stimulation (class IIa recommendation). It should be noted that the patients in this study with stimulation-induced arrhythmia had a mean LVEF of 36.4 %, suggesting that using EF alone may be sufficient to determine appropriateness of ICD implantation.

- ICDs are not recommended for patients with normal EF, normal RV function, and for those presenting with incessant ventricular arrhythmia or NYHA class IV heart failure (class III recommendation) [46••].
- Ablation therapy has been shown to be effective for arrhythmias in CS, especially supraventricular arrhythmias. In a study by Willner et al., 32 CS patients received catheter ablation for atrial flutter and fibrillation, with reported 30 out of 32 patients having no recurrence of arrhythmia during follow-up of 1.8 years [59]. Ablation in conjunction with immunosuppression has also been reported to terminate a case of VT storm [60], although a larger study of 21 CS patients with VT storm showed that while the storm event could be treated with ablation, there was still a high rate of VT recurrence at 1 year (63 % recurrence) [54•]. Other ablation strategies include applying voltage mapping as guidance for ablation, which is a technique previously utilized for post-infarct scar-mediated VTs [61]. Jefic et al. showed that ablation targeting scarred regions significantly improved outcomes in nine patients with VT/VF refractory to immunosuppression and AAD (the peri-tricuspid region being the most frequently identified site of reentry) [45].
- Severely depressed LV EF and LV dysfunction likely reflects extensive myocardial involvement and scarring from a more advanced disease process. Ablation may be less effective in patients who have not received early immunosuppression or if they present with extensive systolic dysfunction [62]. Comparison between two similarly-sized studies demonstrating overall successful vs. unsuccessful ablation for VT in CS had an average cohort LV EF of 42 vs 34 %. For the subset of patients with incessant arrhythmia or ventricular arrhythmia refractory to both immunosuppression and AADs, the HRS consensus states that ablation can be a useful therapy (class IIa) and furthermore recommends that if ICD implantation is indicated, it should occur after ablation (class IIa) [46••].
- Patients who are not candidates for other therapies or with ventricular arrhythmias poorly managed with ICD may benefit from cardiac sympathetic denervation. Vaseghi et al. reported significant reduction in ICD shock burden after sympathectomy performed in 41 patients with cardiomyopathy (2 out of 41 had CS), which involves the removal of a portion of the stellate ganglia and thoracic T2–T4 ganglia [63]. Another case series suggested that there may be short-term benefit from bilateral sympathetomy in reducing the need for defibrillation or anti-tachycardia pacing in a CS patient with VT storm unresponsive to medical and ablation therapies [64]. However, given the absence of

large-scale studies on sympathetomies, specifically in CS, and the risk of serious complications associated with the procedure, including hemothorax, pneumothorax, and neuropathic pain, it is unclear what benefit sympathectomy provides and therefore should be considered only after attempting all other interventions [63].

Conclusion

Cardiac sarcoid is a deadly, and likely under-recognized, disease. While sarcoid can lead to almost any cardiac abnormality, heart block and ventricular tachyarrhythmias are likely its most dire manifestations. The presence of any suspicious cardiac symptom or abnormality in a patient with known extra-cardiac sarcoidosis should prompt further investigation with imaging studies such as echocardiography, cardiac magnetic resonance imaging, or 18F-FDG PET. Similarly, the presence of unexplained AV block or ventricular tachyarrhythmias in any patient should prompt suspicion for cardiac sarcoidosis. Corticosteroids remain the backbone of therapy for active CS and should be started early in the disease course to prevent progression to the fibrotic or "burned out" stage of the disease. For patients with progressive disease requiring high doses of corticosteroids, steroid-sparing agents have shown promising efficacy. Tradition heart failure therapies focusing on neuro-hormonal blockade (ACE-inhibitors, beta-blockers) should not be ignored in patients with reduced LV systolic function. ICDs should be employed for secondary prevention or for primary prevention for patients with severely reduced LV systolic function (EF <35 %) and may be offered to patients with even mild reductions in LV and/or RV systolic function. For patients with ventricular arrhythmias refractory to immunosuppressant therapy, ablation therapies can reduce the arrhythmia burden, though recurrence is often the rule instead of the exception.

Compliance with Ethical Standards

Conflict of Interest
Brian A. Houston, Carolyn Park, and Monica Mukherjee each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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