

FOCUS ISSUE: CARDIAC SARCOIDOSIS – FROM THE CME SESSION AT 63rd SNMMI ANNUAL MEETING – REVIEW ARTICLE

Clinical Management of Cardiac Sarcoidosis

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Abstract

Approximately 5% of patients with sarcoidosis will have cardiac involvement clinically manifest as one or more of ventricular arrhythmias, conduction abnormalities and heart failure. Another 20% to 25% have clinically silent disease (asymptomatic cardiac involvement). There is a growing realisation that CS can be the first manifestation of sarcoidosis in any organ. In particular physicians should consider CS in patients with VT of unknown etiology and in patients aged <60 presenting with idiopathic advanced conduction system disease. Immunosuppression therapy (usually with corticosteroids) has been suggested for the treatment of clinically manifest CS despite modest data. Positron Emission Tomography (FDG-PET) imaging is often used to detect active disease and guide immunosuppression. The extent of left ventricular dysfunction seems to be the most important predictor of prognosis. Also the extent of LGE on CMR is emerging as an important prognostic factor. Patients with clinically manifest disease often need device therapy, usually with implantable cardioverter defibrillators. There are still much to be learned as regarding best practices in managing CS patients and multi-center research efforts are underway.

Keywords: Atrio-ventricular block, Cardiac sarcoidosis, Clinically manifest, Clinically silent, Heart failure, Sudden cardiac death, Ventricular arrhythmias

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It is estimated that 5% of patients with sarcoidosis have clinically manifest cardiac involvement. Clinical features of Cardiac Sarcoidosis (CS) are dependent on the location and extent of the disease. The principal manifestations are, ventricular arrhythmias including sudden death, conduction abnormalities and heart failure. These patients are often quite symptomatic with the symptoms dependent on presentation. Furthermore, the cardiac symptoms are usually dominant over extra-cardiac as patients generally only have low grade pulmonary and no other organ involvement (1-4). Indeed most patients with clinically manifest CS have minimal extra-cardiac disease (1-3). Another 20-25% of sarcoidosis patients have clinically silent (i.e. asymptomatic) cardiac involvement. This is based on autopsy data (5) and late gadolinium-enhanced cardiac magnetic resonance (LGE-CMR) studies (6, 7) Patients with clinically silent CS can have non-specific

chest pain, dyspnea and fatigue but this is usually due to extra-cardiac disease.

Diagnosis of cardiac sarcoidosis

Biomarkers

Historical sarcoidosis biomarkers, circulating ACE and lysozyme, are frequently measured in suspected CS, but their utility is limited (8). For this reason, studies have focused on searching for new biomarkers to evaluate disease activity; in 2015, Kandolin et al. measured highly sensitive Troponin levels in 62 patients with new-onset CS. Thirty-three patients showed elevated concentrations at presentation; in 67% of cases, these normalized after steroid use for 4 weeks (9).

Electrocardiogram

The electrocardiogram (ECG) is usually abnormal in

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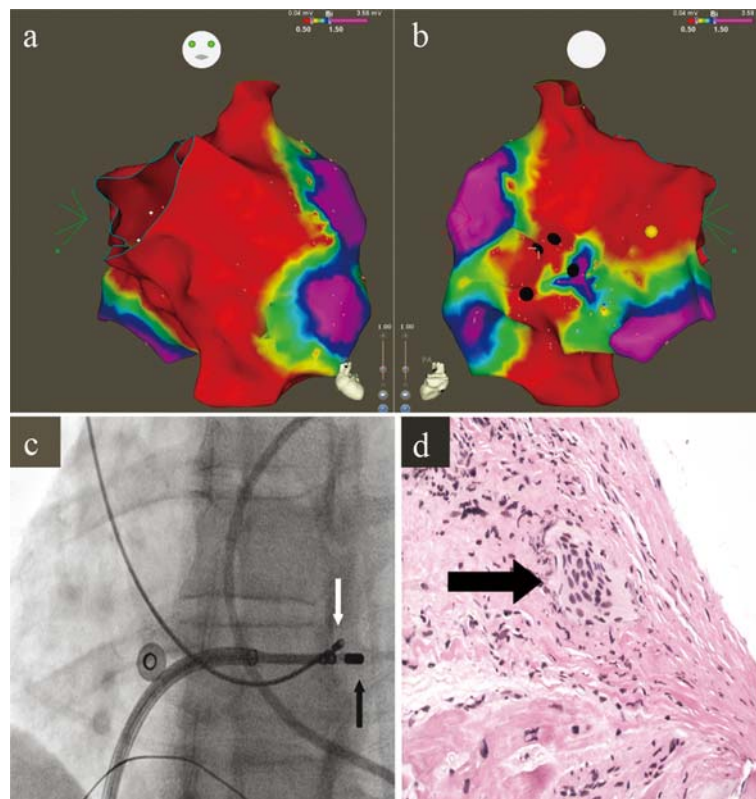


Fig. 1 Electroanatomic bipolar voltage map of the right ventricle displaying anterior (a) and posterior (b) views. Green, yellow, and red indicate low-voltage regions; purple denotes regions of normal voltage, defined as ≥ 1.5 mV. Black circles illustrate areas targeted for biopsy. Yellow circle illustrates location of right bundle. (c) Fluoroscopy images obtained in the left anterior oblique 25° projection showing biptome (white arrow) targeting the low-voltage region in the right ventricular septum, adjacent to mapping catheter (black arrow). (d) Microscopic view of an endomyocardial biopsy specimen obtained from the right ventricular septum showing noncaseating granuloma (arrow). Hematoxylin-eosin; magnification 200 \times . (reproduced with permission from (16))

patients with clinically manifest disease. Abnormalities include various degrees of conduction block including isolated bundle branch block and fascicular block. Right bundle branch block is consistently more common than left in all CS cohorts (10-15). Also pathological Q waves (pseudo-infarct pattern), ST-T wave changes, and rarely epsilon waves can occur (16). In contrast the ECG is abnormal in only 3.2-8.6% of patients with clinically silent CS (10, 11, 13, 14).

Echocardiography

Abnormalities tend to be non-specific; basal interventricular thinning is the most typical feature of CS. Less commonly an increase in myocardial wall thickness may be seen, simulating left ventricular hypertrophy or hypertrophic cardiomyopathy (17). There may be other abnormalities, such as aneurysms, left ventricular (LV) and/or right ventricular (RV) diastolic and systolic dysfunction, and isolated wall motion abnormalities.

Cardiac magnetic resonance imaging

LGE is most often seen in basal segments (particularly of the septum and lateral wall) and typically in the epicardium

and mid myocardium (18, 19) Typically it is multi-focal and patchy in distribution, with sparing of the endocardial border; and no specific pattern of LGE is diagnostic for CS (20).

Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging

A glucose analog, FDG, is useful in distinguishing inflammatory lesions, in which the activated pro-inflammatory macrophages show a higher metabolic rate and glucose utilization (21). FDG uptake indicating inflammation, can be evident earlier than scar formation findings on LGE CMR (22). Appropriate diet preparation is important to overcome challenges of myocardial activity for image interpretation (23). There have been suggestions that PET could be a useful disease activity marker for guiding CS therapy (24).

Tissue biopsy

In view of the lower procedural risk and higher diagnostic yield, lymph node or lung biopsy is targeted first in patients with extra-cardiac sarcoidosis. In negative extra-cardiac biopsy cases and in patients having no extracardiac disease endomyocardial biopsy (EMB) is necessary to confirm the

Table 1 Expert consensus recommendations on criteria for the diagnosis of Cardiac Sarcoidosis (modified from (26) with permission)

There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. Histological diagnosis from myocardial tissue
CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).
 2. Clinical diagnosis from invasive and non-invasive studies
It is probable* that there is CS if:
 - a) There is a histological diagnosis of extra-cardiac sarcoidosis
AND
 - b) One or more of following is present
 1. Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
 2. Unexplained left ventricular ejection fraction <40%
 3. Unexplained sustained (spontaneous or induced) ventricular tachycardia
 4. Mobitz type II second degree heart block or third degree heart block
 5. Patchy uptake on dedicated cardiac FDG-PET (in a pattern consistent with CS)
 6. Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
 7. Positive gallium uptake (in a pattern consistent with CS)
 AND
 - c) Other causes for the cardiac manifestation(s) have been reasonably excluded
-

CS: cardiac sarcoidosis, FDG-PET: fluorodeoxyglucose- positron emission tomography, CMR: cardiac magnetic resonance

diagnosis. To increase the positive biopsy rate, electrophysiological (electro-anatomic mapping, see Fig. 1) (16, 25) or imaging (PET or CMR) (1) guided biopsy procedures have been described, and are now recommended by consensus guidelines (26). Using these techniques positive biopsy rates have been reported as up to 50% (1, 25, 27).

Consensus guidelines for diagnosing CS

There are a number of published guideline documents; most recently in 2014 by the Heart Rhythm Society in collaboration with multiple other societies. (see Table 1) (26). Previous diagnostic guidelines were published by the National Institutes of Health's A Case Control Etiology of Sarcoidosis Study (ACCESS) (28) and the Japanese Ministry of Health and Welfare criteria (29).

Screening for cardiac sarcoidosis

Cardiac sarcoidosis screening in patients with specific cardiac presentations

1. Unexplained Mobitz II or third degree atrioventricular (AV) block

In a Finnish study of patients aged <55, biopsy-verified CS was found in 14/72 (19%) and "probable" CS was found in 4/72 (6%); and giant cell myocarditis was found in 4/72 (6%) (30). In a similar study from a tertiary Canadian centre CS was diagnosed in 11/32 (34%) patients aged <60 (3). In both studies the prognosis for CS patients was poorer versus those who had idiopathic complete AV block (3, 30).

2. Sustained monomorphic ventricular tachycardia (VT) of unknown etiology

In a prospective study that screened consecutive patients with VT of unknown etiology (excluded patients with outflow tract or fascicular VT) for sarcoidosis, 4 of 14 patients (29%)

were diagnosed with CS (2). In a study by Tung of 103 patients (85% Caucasian, 7% African American and 8% Asian with VT and non-ischemic cardiomyopathy, 17/103 (16.5%) had undiagnosed CS (31).

3. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC and CS may have overlapping clinical features. Phillips et al. described 15 patients who met task force criteria for a diagnosis of ARVC but were subsequently found to have CS (32).

Screening for cardiac involvement in patients with biopsy-proven, extra-cardiac sarcoidosis

There are few data to compare the utility of screening tests for cardiac involvement in patients with extra-cardiac sarcoidosis (10). It is apparent that larger studies are needed to define the sensitivity and specificity (and cost effectiveness) of various screening strategies and tests to detect clinically silent cardiac involvement.

Clinical management

Role of immunosuppression

Sadek et al. published a systematic review of corticosteroids for the treatment of CS (33). Ten manuscripts met the criteria for inclusion and all publications ranged from poor to fair in quality. The best data related to AV block and LV dysfunction; otherwise in view of the poor in data quality, no clear conclusions could be established for other outcomes (33). Twenty seven of 57 patients (47.4%) treated with corticosteroids had improvements in AV conduction while in contrast, out of 16 patients not treated with corticosteroids, 0/16 improved (33). The data summary for LV dysfunction from 73 patients, of whom 60 were treated with steroids and 13 were not, suggested that corticosteroid therapy is associated

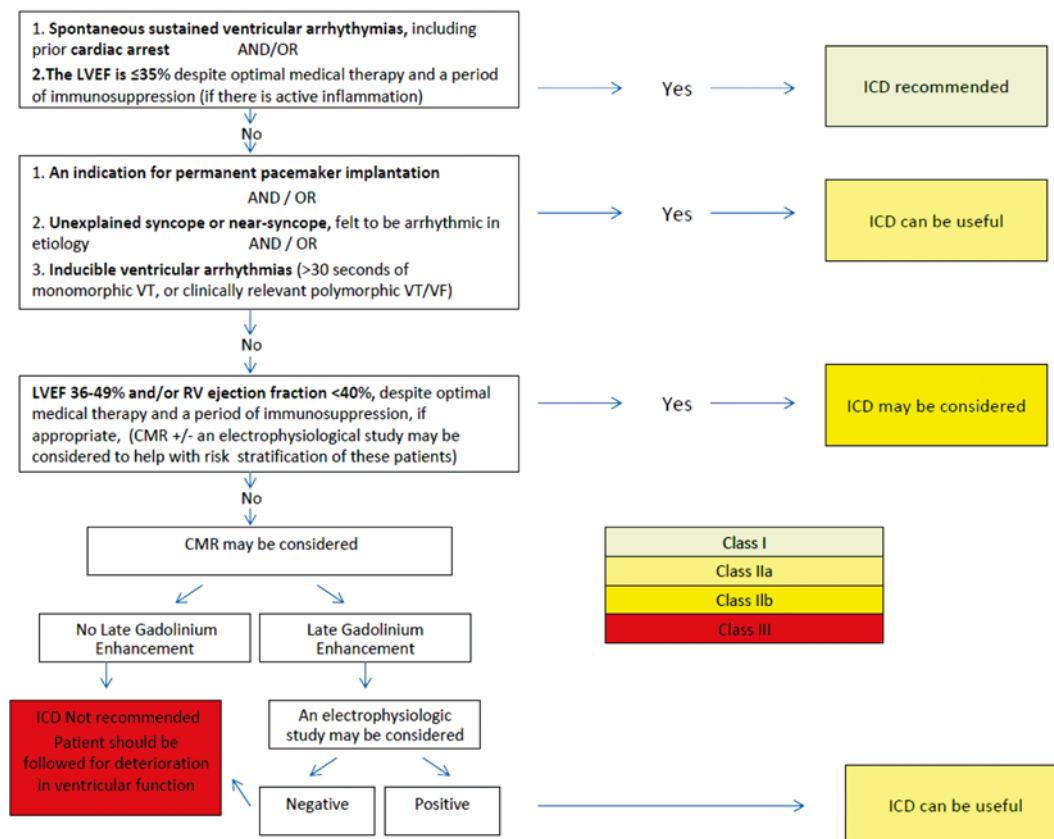


Fig. 2 Consensus recommendations for sudden death risk Stratification and ICD implantation in patients diagnosed with Cardiac Sarcoidosis. (reproduced with permission from (26))

with maintenance of LV function in patients who have normal function at diagnosis, with improved ejection fraction in those with mild to moderate LV dysfunction and no improvement was found in patients with severe LV dysfunction (33). In contrast a more recent study of 102 CS patients, showed improved LV function after steroid therapy in patients with severely depressed ejection fraction (<35 %) but no change in patients with moderately depressed ejection fraction (34).

Most experts have been proponents of treating CS despite this scarcity of data. Other unknowns include the optimal dose and duration of corticosteroids; most experts recommend a starting dose of 30 mg to 40 mg daily (35). FDG-PET imaging is increasingly being used to assess direct therapy. Due to the possibility of relapse, physicians should follow patients for minimum 3 years after completing treatment (8). In refractory cases or in if significant steroid side effects develop, methotrexate is often used as a second line drug (36). Azathioprine, cyclophosphamide, and infliximab are also sometimes used to treat CS (37).

Heart failure

Patients who have CS and LV dysfunction should also be treated with standard medical and device therapies for heart failure, including heart transplantation in refractory cases. Recurrent disease has been reported in the transplanted heart but long-term patient outcomes are similar to outcomes for

control groups (38).

Atrio-ventricular block

Recovery of AV block with steroids is unpredictable in these patients and hence permanent pacing is recommended. Also ICD implantation is generally recommended for patients with second or third degree atrio-ventricular block as these patients have a substantial risk of VT/VF in follow-up (39).

Ventricular arrhythmias

The most common mechanism of ventricular arrhythmia is macro re-entry around areas of scar/fibrosis (40, 41). Reported ablation outcomes are generally modest; in one study, the multiple procedure VT-free survival rate was 37% at 1 year (41), another study found a success rate of 56%. (40). A stepwise approach, therefore, is recommended with initial therapy with immunosuppression, if ongoing inflammation is evident, and anti-arrhythmic drugs; then ablation if this is unsuccessful (26).

Risk stratification for sudden cardiac death and when to consider implantable cardioverter defibrillator (ICD) implantation

CS carries a risk of sudden death, but there are few data to aid with risk stratification. Importantly CS may not behave like other types of non-ischemic cardiomyopathy with regard

to ventricular arrhythmias, ejection fraction, and sudden death risk. This is possibly due to the mixture of scar and active inflammation in many patients. As an example, CS patient cohorts seem to have higher rates of ICD therapies than other patients (42, 43). The 2014 Heart Rhythm Society consensus document (Fig. 2) (26) illustrates one possible approach.

Prognosis

In the current era of heart failure therapy, including ICDs and active transplant surgery, deaths from CS have become rare. The best data is from a recent Finnish nationwide study which found 10-year survival was 92.5% in 102 patients (34). The extent of LV dysfunction is commonly regarded as the most important predictor of survival (33). Several recent CMR studies have, however, raised the presence and extent of myocardial LGE as an even more important overall prognostic factor than LV function (6, 44).

Conclusions and future directions

Approximately 5% of patients with sarcoidosis will have cardiac involvement clinically manifest as one or more of ventricular arrhythmias, conduction abnormalities and heart failure. Another 20% to 25% have clinically silent disease asymptomatic cardiac involvement. There is a growing realisation that CS can be the first manifestation of sarcoidosis in any organ. In particular physicians should consider CS in patients with VT of unknown etiology and in patients aged <60 presenting with idiopathic advanced conduction system disease. Immunosuppression therapy (usually with corticosteroids) has been suggested for the treatment of clinically manifest CS despite modest data. The extent of left ventricular dysfunction seems to be the most important predictor of prognosis. In addition the extent of LGE is emerging as an important prognostic factor. Patients with clinically manifest disease often need device therapy, typically with implantable cardioverter defibrillators. There are still many unknowns in terms of best practices in diagnosing and managing CS patients and multi-center research efforts are underway.

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Conflicts of interest

None.

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