

REVIEW TOPIC OF THE WEEK

Cardiac Sarcoidosis



David H. Birnie, MD, MBChB,^a Pablo B. Nery, MD,^a Andrew C. Ha, MD,^b Rob S.B. Beanlands, MD^a

ABSTRACT

Clinically manifest cardiac involvement occurs in perhaps 5% of patients with sarcoidosis. The 3 principal manifestations of cardiac sarcoidosis (CS) are conduction abnormalities, ventricular arrhythmias, and heart failure. An estimated 20% to 25% of patients with pulmonary/systemic sarcoidosis have asymptomatic cardiac involvement (clinically silent disease). In 2014, the first international guideline for the diagnosis and management of CS was published. In patients with clinically manifest CS, the extent of left ventricular dysfunction seems to be the most important predictor of prognosis. There is controversy in published reports as to the outcome of patients with clinically silent CS. Despite a paucity of data, immunosuppression therapy (primarily with corticosteroids) has been advocated for the treatment of clinically manifest CS. Device therapy, primarily with implantable cardioverter-defibrillators, is often recommended for patients with clinically manifest disease. (J Am Coll Cardiol 2016;68:411-21) © 2016 by the American College of Cardiology Foundation.

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology. Accumulating evidence suggests that it is caused by an immunological response to an unidentified antigenic trigger in genetically susceptible persons (1). Noncaseating granulomas are the histopathological hallmark (Figure 1). The lungs are affected in more than 90% of patients, and the disease can also involve the heart, liver, spleen, skin, eyes, parotid gland, or other organs and tissues. Most disease (70%) occurs in patients 25 to 60 years of age (2,3), and it is rare in people <15 or >70 years of age (4). Sarcoidosis is a worldwide disease, with a prevalence of about 4.7 to 64 in 100,000; the highest rates are reported in northern Europeans and African Americans, particularly in women (2,3).

Familial clustering indicates a strong genetic element in sarcoidosis (5). Gene linkage studies suggest that genes influencing clinical presentation of sarcoidosis are likely to be different from those that underlie disease susceptibility (6). Associations have been described with HLA DQB*0601 (7) and the tumor necrosis factor allele TNFA2 (8) in Japanese patients

with cardiac sarcoidosis (CS). Much remains to be learned about genetic/environmental interactions in sarcoidosis in general and in relation to disease phenotypes (e.g., organ predilection).

Clinically manifest cardiac involvement occurs in perhaps 5% of patients with sarcoidosis. In addition, many patients with pulmonary/systemic sarcoidosis have asymptomatic cardiac involvement (clinically silent disease). This finding was initially on the basis of autopsy studies, which estimated the prevalence of cardiac involvement to be at least 25% of patients with sarcoidosis (9,10). These autopsy findings are consistent with recent data using late gadolinium enhanced (LGE) cardiovascular magnetic resonance (CMR) technology (Table 1).

Studies suggest that CS seems to be becoming more prevalent. However, this is likely due to improvements in imaging and/or more thorough investigation, rather than a true increase in prevalence. In Finland, the rate of diagnosis of CS increased more than 20-fold between 1988 and 2012 (11). In the United States, the incidence of patients who underwent transplantation and had CS as the



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From the ^aDivision of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; and the ^bPeter Munk Cardiac Centre, University Health Network and Department of Medicine, University of Toronto, Toronto, Ontario, Canada. Dr. Beanlands has served as a consultant for Lantheus Medical Imaging and Jubilant DRAXImage; and has received research grants from GE Healthcare, Lantheus Medical Imaging, and Jubilant DRAXImage. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
CMR = cardiac magnetic resonance
CS = cardiac sarcoidosis
ECG = electrocardiogram
FDG = fluorodeoxyglucose
ICD = implantable cardioverter-defibrillator
LGE = late gadolinium enhancement
LV = left ventricular
PET = positron emission tomography
VT = ventricular tachycardia

etiology of cardiomyopathy increased from 0.1% (1994 to 1997) to 0.5% (2010 to 2014) (12).

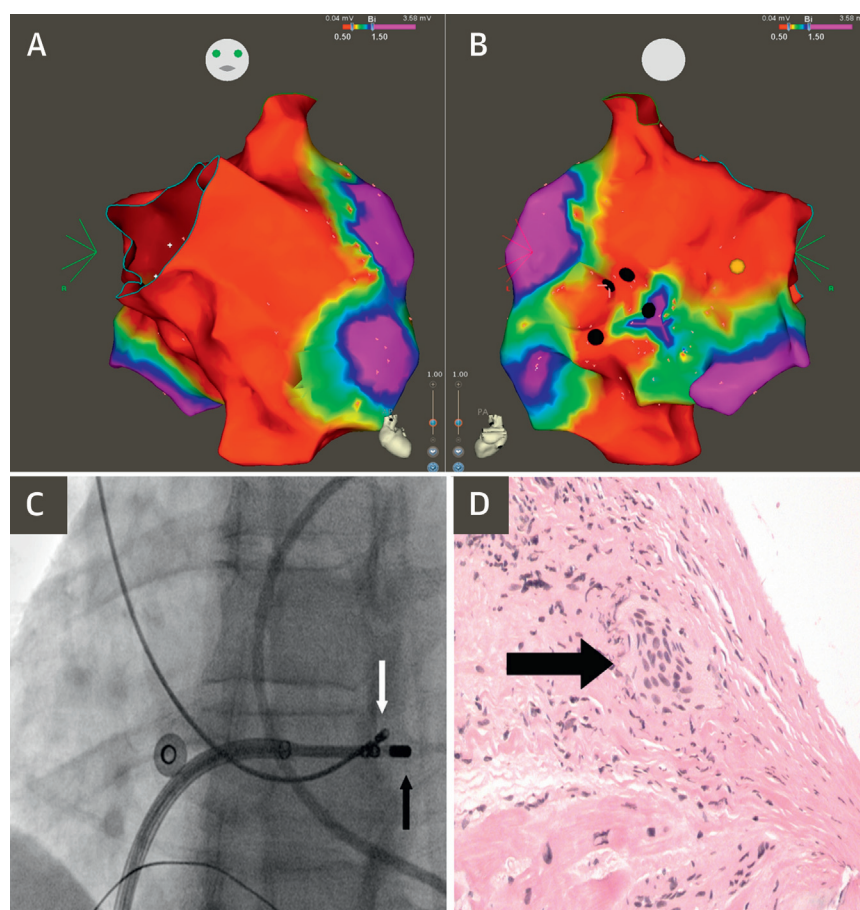
There is a growing realization that CS can be the first manifestation of sarcoidosis in any organ. Between 16% and 35% of patients presenting with complete atrioventricular (AV) block (age <60 years) (13,14) or ventricular tachycardia (VT) of unknown etiology (15,16) have previously undiagnosed CS as the underlying etiology. Also, CS as the underlying cause of heart failure is often missed; for example, core left ventricular (LV) biopsies at the time of LV assist device implantation found previously undiagnosed CS in 6 of 177 patients (3.4%) (17). Roberts *et al.* (18) examined explanted hearts, and 10

of 346 (3%) had undiagnosed CS. Also, CS can present with features similar to arrhythmogenic right ventricular (RV) cardiomyopathy (19).

CLINICAL MANIFESTATIONS

Clinical features of CS depend on the location, extent, and activity of the disease. The principal manifestations are conduction abnormalities; ventricular arrhythmias, including sudden death; and heart failure. These patients are usually highly symptomatic, with the symptom complex dependent on presentation. Furthermore, cardiac symptoms usually dominate over extracardiac symptoms, as patients generally only have low-grade pulmonary and no other organ involvement (14,15,20,21). Indeed, most patients with clinically manifest CS

FIGURE 1 Electroanatomic Bipolar Voltage Map of the Right Ventricle



(A) Anterior and (B) posterior 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 $\times 200$. Reproduced with permission from Nery *et al.* (30).

have minimal extracardiac disease, and up to one-third have isolated CS (14,15,20). Patients with clinically silent CS can have nonspecific chest pain, dyspnea, and fatigue, which are usually due to extracardiac disease. The manifestations of CS are shown in the **Central Illustration**.

DIAGNOSIS

CHEST IMAGING. Chest radiography is performed at the initial presentation of extracardiac sarcoidosis and is abnormal in 85% to 95% of patients (22). High-resolution CT is more accurate than chest radiography in helping with the diagnosis of sarcoidosis. For example, Chung et al. (23) studied 44 uveitis patients with biopsy-proven sarcoidosis; chest radiography was abnormal in 22 (50%) and high-resolution CT was abnormal in 42 (95%). Similar data are lacking in patients with possible CS. Thus, it is currently unclear whether negative high-resolution CT is sufficient to exclude CS as a potential explanation for certain cardiac presentations.

ELECTROCARDIOGRAM. The electrocardiogram (ECG) is usually abnormal in patients with clinically manifest disease. Abnormalities include various degrees of conduction block, such as isolated bundle branch block and fascicular block. Right bundle branch block is consistently more common than left in all CS cohorts (24-29). Also, QRS complex fragmentation, ST-T-wave changes, pathological Q waves (pseudoinfarct pattern), and (rarely) epsilon waves can occur (30). In contrast, the ECG is abnormal in only 3.2% to 8.6% of patients with clinically silent CS (Table 2) (24,25,27,28).

ECHOCARDIOGRAPHY. The echocardiogram is often abnormal in manifest disease, but is usually normal in clinically silent CS (24). Abnormalities are variable and usually nonspecific, although interventricular thinning, especially basal, can be a feature of CS (31). Less frequently, there may be an increase in myocardial wall thickness, simulating LV hypertrophy or resembling hypertrophic cardiomyopathy (32). Other abnormalities include LV and/or RV diastolic and systolic dysfunction, isolated wall motion abnormalities, basal septal thinning, and aneurysms (33,34). Regional wall motion abnormalities are usually seen in a noncoronary distribution. Newer techniques, including strain rate, show promise in the early diagnosis of CS (35).

BIOMARKERS. Angiotensin-converting enzyme levels are elevated in 60% of patients with sarcoidosis; however, serum angiotensin-converting enzyme levels lack sensitivity and specificity in diagnosing

TABLE 1 Studies That Examined the Prevalence and Prognosis of Clinically Silent Cardiac Sarcoidosis

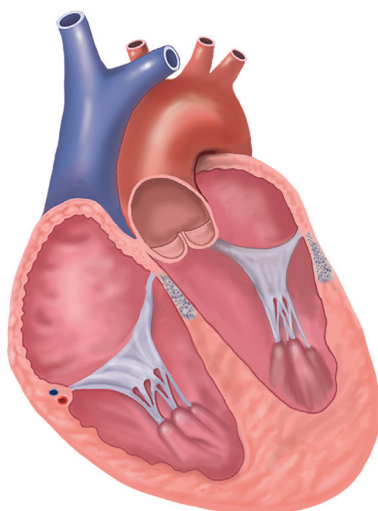
Location (Ref. #)	Year	N	% With CS	Test	FU (Months)	Cardiac Events
France (74)	2002	31	54.9	CMR	3	0%
France (72)	2003	50	14.0	CMR	10	0%
Holland (73)	2005	82	3.7	Mostly CMR	19	0%
United States (24)	2008	62	38.7	PET or CMR	24	0%
Japan (25)	2014	61	13.0	CMR	50	0%
Germany (28)	2016	188	15.4	CMR	No FU	
United States (42)*	2011	152	19.0	CMR	No FU	
United States (27)	2009	81	25.9	CMR	21	4 of 21 cardiac deaths in LGE ⁺ group (26%)
Germany (43)	2013	155	25.5	CMR	31	11 of 39 in LGE ⁺ group (28.2%) had primary endpoint†
United States (44)*	2016	205	20.0	CMR	36	Rate of death/VT per year was >20× higher than LGE (4.9% vs. 0.2%; p < 0.01)

*Likely significant overlap in cohorts. †Primary endpoints were 3 deaths, 4 aborted sudden deaths, and 4 appropriate implantable cardioverter-defibrillator shocks for ventricular tachycardia.
CMR = magnetic resonance imaging; FU = follow-up; LGE = late gadolinium enhancement; PET = positron emission tomography; VT = ventricular tachycardia.

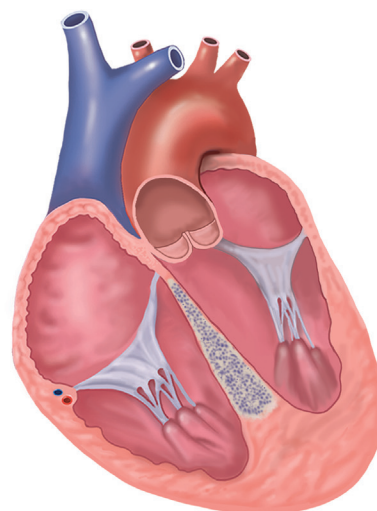
or managing sarcoidosis (36). Hence, studies have focused on finding new biomarkers to assess disease activity. Neopterin and, especially, soluble interleukin-2 receptor levels have been shown to be significantly elevated in active disease (37). Kandolin et al. (38) reported highly sensitive troponin levels in 62 patients with new-onset CS. Troponin was elevated at presentation in 33 patients, and normalized after 4 weeks of steroids in 67% (38). Although promising, none of these biomarkers are ready for clinical use.

CMR IMAGING. There is no specific pattern of LGE on CMR that is diagnostic for CS, although usually it is patchy and multifocal, with sparing of the endocardial border (39,40). LGE is most commonly seen in basal segments, particularly of the septum and lateral wall, and usually in the midmyocardium and epicardium of the myocardium (Figure 2) (27,41,42). However, transmural involvement can occur, and the RV free wall may also be involved in some cases (27).

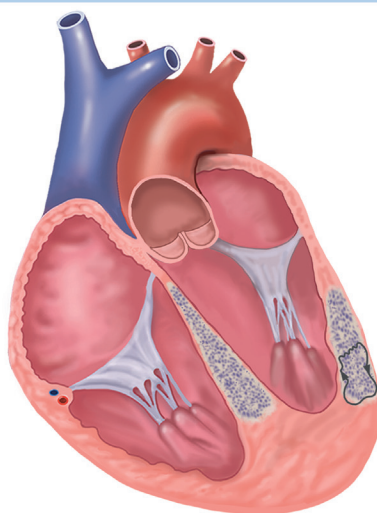
CMR is increasingly utilized for assessment of clinically silent CS, in view of its ability to identify small regions of myocardial damage, even in subjects with preserved LV systolic function (Table 1) (24,25,27,28,42-44). T2 CMR imaging may enable detection of active inflammation, but has some technical challenges (45). Technology has been developed to perform fused positron emission tomography (PET)/CMR, which enables concurrent imaging of the 2 stages of the disease (i.e., inflammation and fibrosis/scar) (Figure 2) (46).

CENTRAL ILLUSTRATION Clinical Features of Cardiac Sarcoidosis

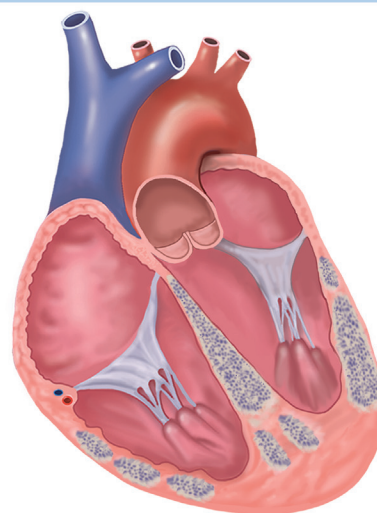
Small patches of basal involvement, usually clinically silent



Large area of septal involvement, often clinically manifest as heart block



Re-entrant circuit involving area of granuloma/fibrosis leading to VT



Extensive areas of LV and RV involvement, often clinically manifest as heart failure +/- heart block +/- VT

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(Top left) Small patches of basal involvement, usually clinically silent disease. **(Top right)** Large area of septal involvement often clinically manifests as heart block. **(Bottom left)** Re-entrant circuit involving an area of fibrosis/granuloma leading to ventricular tachycardia. **(Bottom right)** Extensive areas of LV and RV involvement often clinically manifest as heart failure $\pm$ heart block $\pm$ VT. LV = left ventricular; RV = right ventricular; VT = ventricular tachycardia.

TABLE 2 Studies that have reported ECG abnormalities in patients with clinically silent CS (diagnosed by CMR)							
	Any Abnormality	Complete RBBB	Partial RBBB	Complete LBBB	Partial LBBB	Fascicular Block	Q Waves
US (24)	4/62 (6.5%)	2	0	1	0	1	NR
Japan (25)	2/61 (3.2%)	2	0	0	0	0	0
Germany (28)	10/188 (5.3%)	3	3	0	1	NR	3
US (27)	7/81 (8.6%)	2	0	1	0	NR	3

LBBB = left bundle branch block; RBBB = right bundle branch block; NR = not reported.

FLUORODEOXYGLUCOSE PET IMAGING. Fluorodeoxyglucose (FDG) is a glucose analog that is useful in differentiating between normal and active inflammatory lesions where the activated proinflammatory macrophages show a higher metabolic rate and glucose utilization (47). Although no individual clinical finding is pathognomonic for the diagnosis, focal or focal-on-diffuse FDG uptake patterns suggest active CS (48,49). It has been suggested that PET might be useful as a disease activity marker to guide CS therapy. FDG-PET testing should be performed at a center with experience in CS imaging protocols (50). The suppression of physiological FDG uptake in the cardiac muscle is a key factor in optimizing diagnostic accuracy (51). Various preparation and imaging protocols have been used. In 2014, the Japanese Society of Nuclear Medicine published a consensus guideline (51), and North American guidelines are currently being developed.

ENDOMYOCARDIAL BIOPSY. In patients with extracardiac sarcoidosis, lymph node or lung biopsy is typically targeted first, due to the higher diagnostic yield and lower procedural risk. In cases of negative extracardiac biopsy, endomyocardial biopsy may be required to confirm the diagnosis. However, endomyocardial biopsy has low sensitivity due to the focal nature of the disease, revealing noncaseating granulomas in <25% of patients with CS (52). To increase sensitivity, electrophysiological (electroanatomic mapping) (Figure 1) (30,53) or image-guided (PET or CMR) (20) biopsy procedures are now recommended by consensus guidelines (50,54). These techniques have increased positive biopsy rates to up to 50% (20,53).

CONSENSUS GUIDELINES FOR THE DIAGNOSIS OF CS. In 2014, the first international guideline for the diagnosis of CS, written by experts in the field chosen by the Heart Rhythm Society in collaboration with

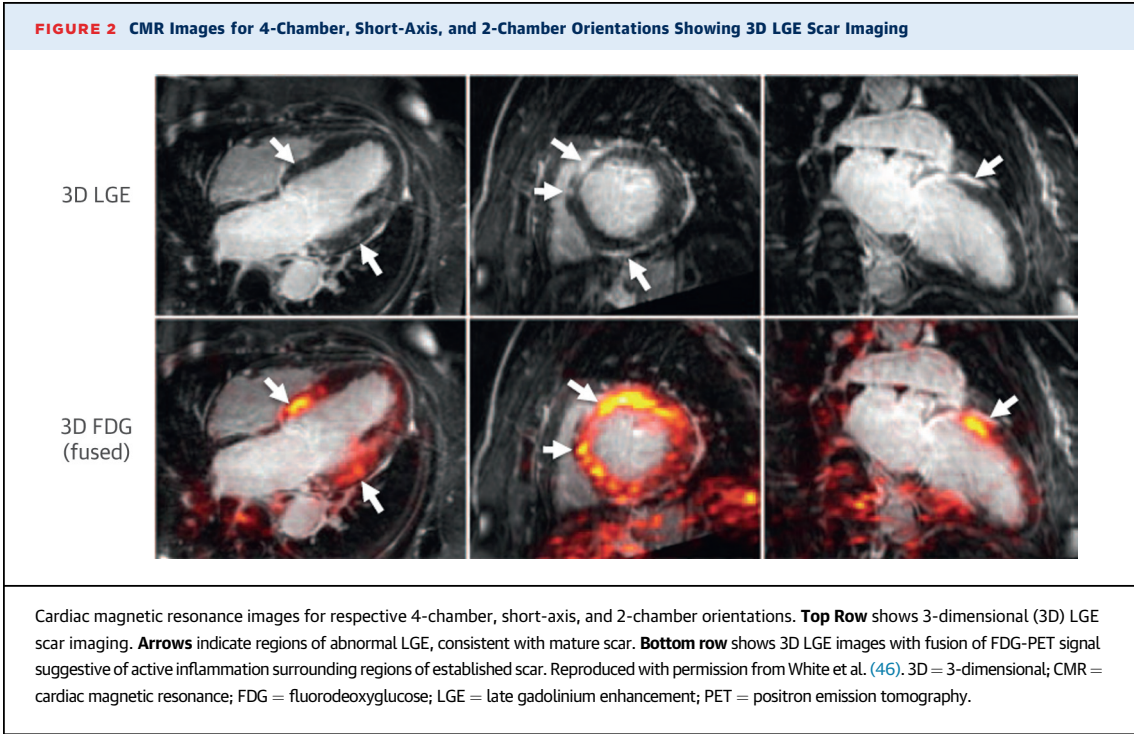


TABLE 3 Expert Consensus Recommendations on Criteria for Diagnosis of CS

There Are 2 Pathways to a Diagnosis of CS	
1. Histological diagnosis from myocardial tissue	CS is diagnosed in the presence of noncaseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains, if applicable).
2. Clinical diagnosis from invasive and noninvasive studies	It is probable that there is CS if: a) There is a histological diagnosis of extracardiac sarcoidosis AND b) 1 or more of following is present: 1. Steroid ± immunosuppressant-responsive cardiomyopathy or heart block 2. Unexplained LVEF <40% 3. Unexplained sustained (spontaneous or induced) ventricular tachycardia 4. Mobitz type II second- or third-degree heart block 5. Patchy uptake on dedicated cardiac FDG-PET (in a pattern consistent with CS) 6. LGE 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
Modified with permission from Birnie et al. (50). CMR = cardiac magnetic resonance; CS = cardiac sarcoidosis; FDG-PET = fluorodeoxyglucose-positron emission tomography; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction.	

multiple other societies, was published (Table 3) (50). Prior to this, the only published diagnostic guidelines were the Japanese Ministry of Health and Welfare criteria (55) and the National Institutes of Health's a Case Control Etiology of Sarcoidosis Study set of criteria published in 1999 (56).

SCREENING FOR CS. There are few data comparing the sensitivity and specificity of various screening tests for cardiac involvement in patients with extracardiac sarcoidosis. Mehta et al. (24) investigated 62 extra-CS patients with detailed cardiac history, ECG, Holter monitoring, and echocardiography. They showed that the presence of 1 or more cardiac symptoms (significant palpitations, syncope, or pre-syncope) and/or an abnormal cardiac test had a sensitivity of 100% and a specificity of 87% for the diagnosis of CS (24). Larger studies are clearly required to define the sensitivity and specificity (and

cost-effectiveness) of various screening strategies/ tests to detect clinically silent cardiac involvement. In addition, there are no data on whether or not interval rescreeing is necessary in patients with an initial negative work-up (50).

CLINICAL MANAGEMENT

IMMUNOSUPPRESSION. Many patients with pulmonary sarcoidosis undergo spontaneous remission without treatment. The usual indication for therapy of pulmonary sarcoidosis is a combination of symptoms, deteriorating lung function, and progressive radiographic changes. Treatment of cardiac, ocular, neurological, or renal sarcoidosis or hypercalcemia is generally recommended. Despite more than 50 years of use, there is no proof of survival benefit from corticosteroid treatment (57).

Sadek et al. (58) published a systematic review of corticosteroids in the treatment of CS. Only 10 papers met the inclusion criteria; there were no randomized trials, and all papers were of poor to fair quality. The highest-quality data were related to AV block; the data quality was too limited to draw clear conclusions for any other outcome (58). Despite the paucity of data, most experts recommend treatment of CS with corticosteroid therapy. It is unknown whether all patients with CS should be treated, or only those with clinically manifest disease.

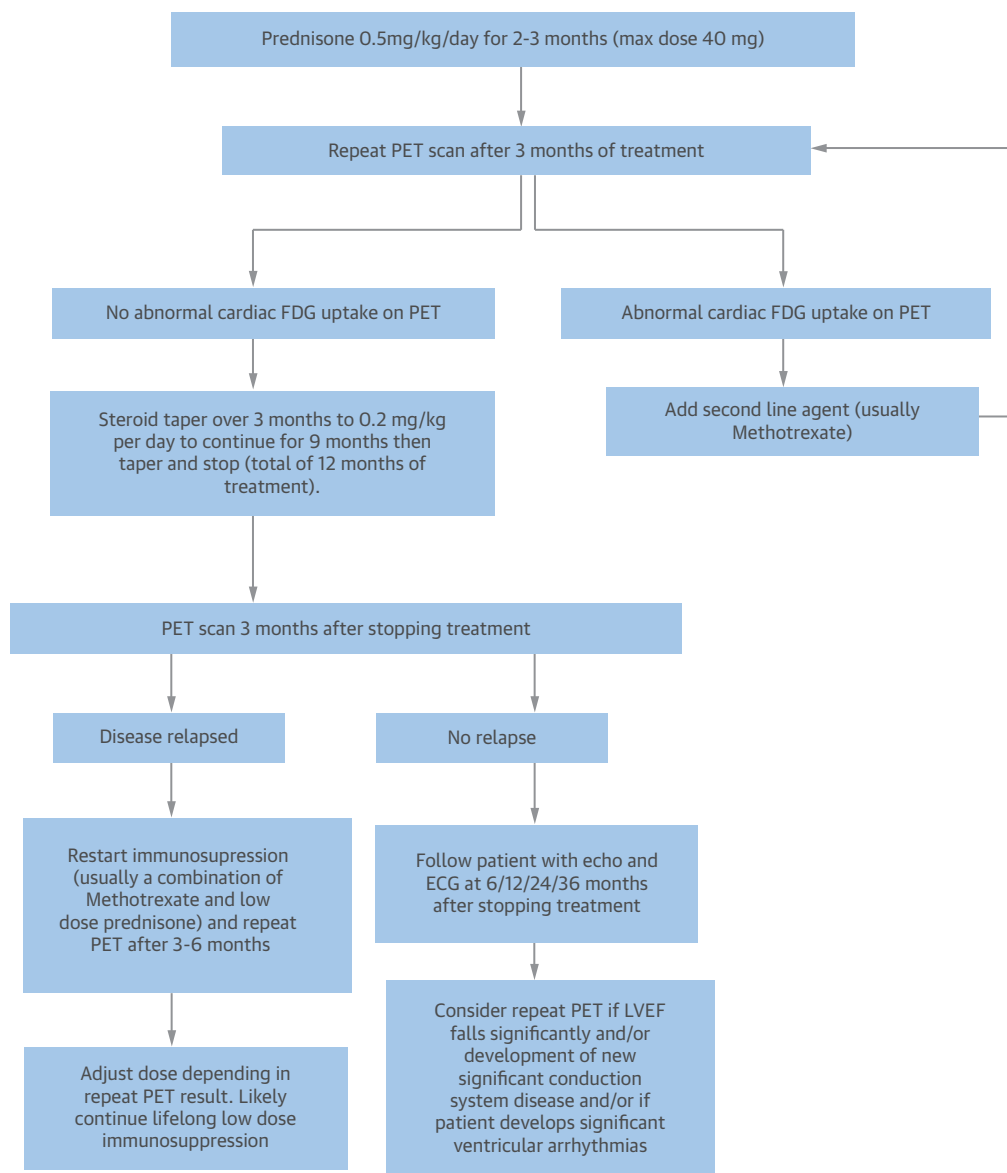
Table 4 summarizes clinical situations where immunosuppression should be considered. Patient preferences and input are important to the process of deciding when and how to treat. The optimal doses of corticosteroids, and how best to assess response to therapy, are also not known. One study showed no significant difference in prognosis in patients treated with prednisone >40 mg/day compared with those treated with ≤30 mg/day (59). Hence, most experts suggest an initial dose of 30 to 40 mg/day (36). The response to treatment should be evaluated after 1 to 3 months. If there has been a response, the prednisone dose should be tapered to 5 to 15 mg/day, with treatment planned for an additional 9 to 12 months (36). Patients should be followed for at least 3 years after discontinuing treatment to assess for relapse (4). Methotrexate is often used as a second-line agent in refractory cases and/or if there are significant steroid side effects (60). Other therapies that have been used in CS include azathioprine (61), cyclophosphamide (62), and infliximab (63). Figure 3 shows the treatment algorithm used at our institution.

HEART FAILURE. The effect of corticosteroids on LV function has been reported in a number of small,

TABLE 4 Clinical Situations Where Immunosuppression Should Be Considered in Patients With Cardiac Sarcoidosis

Mobitz II or 3rd degree heart block and evidence of myocardial inflammation
Frequent ventricular ectopy or nonsustained ventricular arrhythmias and evidence of myocardial inflammation
Sustained ventricular arrhythmias and evidence of myocardial inflammation
Left ventricular dysfunction and evidence of myocardial inflammation

FIGURE 3 Suggested Treatment Algorithm for Patients With Clinically Manifest Cardiac Sarcoidosis



ECG = electrocardiogram; echo = echocardiography; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 2.

single-center observational studies. The summary of the data (58) from a total of 73 patients (60 treated with steroids and 13 who were not), suggests that corticosteroid therapy is associated with:

1. Maintenance of LV function in patients with normal function at diagnosis.
2. Improvement in ejection fraction in patients with mild to moderate LV dysfunction.
3. No improvement in patients with severe LV dysfunction.

On the contrary, a study of 102 patients found LV function improvement after immunosuppression in patients with ejection fraction <35% but no change in patients with lesser extent of dysfunction (11).

Much remains to be learned about the role of corticosteroids in improving/preserving LV function. However, most physicians use steroids in patients with LV dysfunction and evidence of ongoing myocardial inflammation. Patients with CS and LV dysfunction should also be treated with all standard

TABLE 5 Expert Consensus Recommendations on Management of Arrhythmias Associated With Cardiac Sarcoidosis

Diagnosis and Screening	
It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be asked about unexplained syncope/pre-syncope/significant palpitations.	I
It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be screened for cardiac involvement with a 12-lead electrocardiogram.	I
Screening for cardiac involvement with an echocardiogram can be useful in patients with biopsy-proven extracardiac sarcoidosis.	IIa
Advanced cardiac imaging, CMR, or FDG-PET at a center with experience in CS imaging protocols can be useful in patients with 1 or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.	IIa
Screening for CS in patients age <60 yrs with unexplained second-degree (Mobitz II) or third-degree atrioventricular block can be useful.	IIa
Advanced cardiac imaging, CMR, or FDG-PET is not recommended for patients without abnormalities on initial screening by symptoms/electrocardiogram/echocardiogram.	III
Management of Conduction Abnormalities	
Device implantation can be useful in CS patients with an indication for pacing, even if the atrioventricular block reverses transiently.	IIa
Immunosuppression can be useful in CS patients with second-degree (Mobitz II) or third-degree atrioventricular block.	IIa
ICD implantation can be useful in patients with CS and an indication for permanent pacemaker implantation.	IIa
Management of Ventricular Arrhythmias	
Assessment of myocardial inflammation with FDG-PET can be useful in CS patients with ventricular arrhythmias.	IIa
Immunosuppression can be useful in CS patients with ventricular arrhythmias and evidence of myocardial inflammation.	IIa
Antiarrhythmic drug therapy can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy.	IIa
Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive AND antiarrhythmic therapy.	IIa
Risk Stratification for Sudden Cardiac Death	
An electrophysiological study for the purpose of sudden death risk stratification may be considered in patients with LVEF >35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation).	IIb
CMR for the purpose of sudden death risk stratification may be considered	IIb
ICD Implantation	
Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest.	I
LVEF ≤35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation).	I
ICD implantation can be useful in patients with CS, independent of ventricular function and 1 or more of the following: 1. An indication for permanent pacemaker implantation. 2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology. 3. Inducible sustained ventricular arrhythmias.	IIa
ICD implantation may be considered in patients with LVEF 36% to 49% and/or an RV ejection fraction <40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).	IIb
Modified with permission from Birnie et al. (50). ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; RV = right ventricular; other abbreviations as in Table 3.	

heart failure medical and device therapies, including heart transplantation (64).

CONDUCTION ABNORMALITIES. Advanced AV block can be the first presentation of sarcoidosis in any organ (13,14). Generic device guideline documents generally apply to patients who have CS and advanced heart block. The recent consensus document has 2 additional CS-specific recommendations (Table 5).

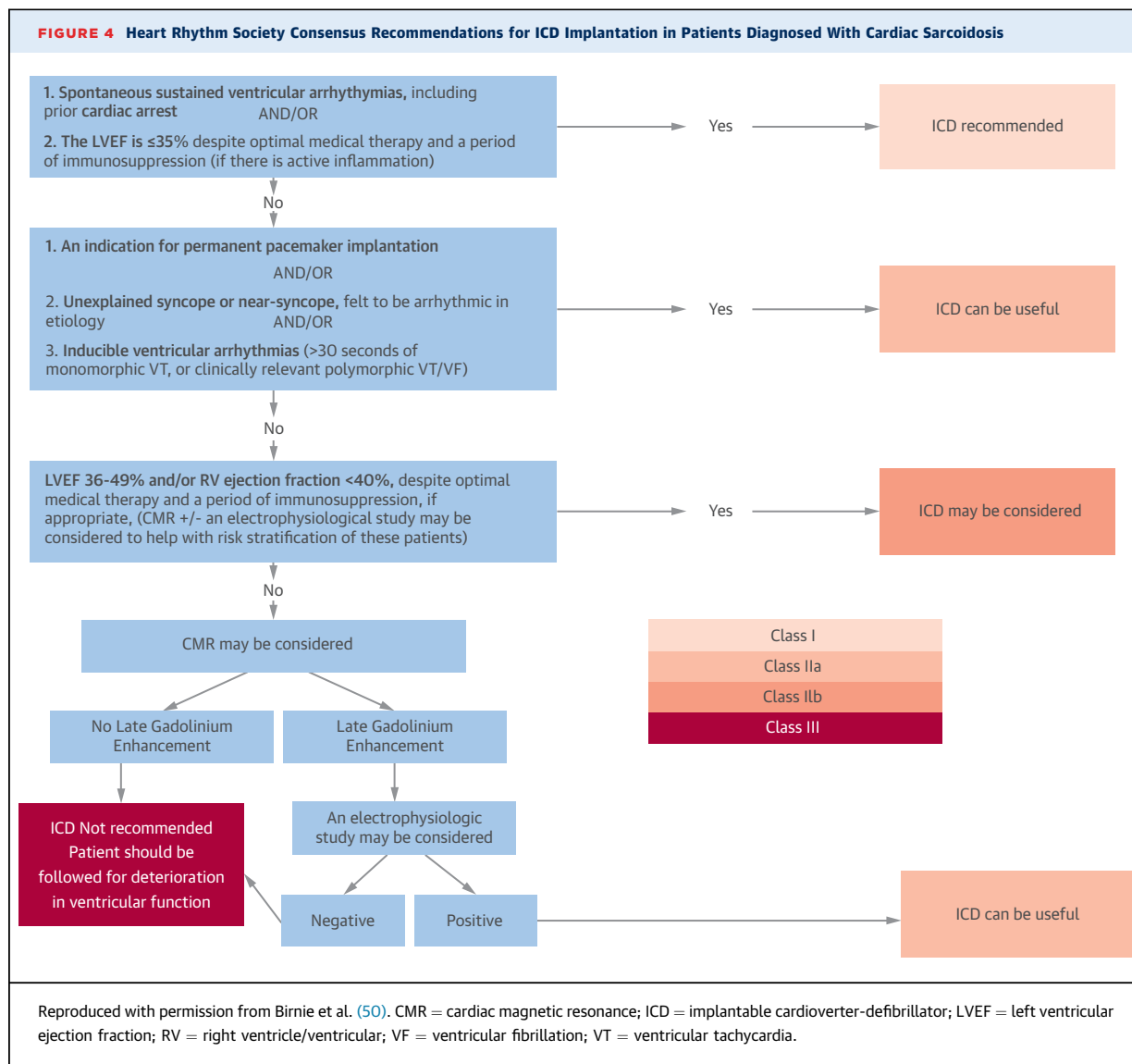
VENTRICULAR ARRHYTHMIAS. The most common mechanism is macro-re-entrant arrhythmias around areas of granulomatous scar (65,66). Kumar et al. (65) studied 21 patients, observing multiple inducible VTs in all patients with a mechanism consistent with scar-mediated re-entry in all VTs. Active inflammation may also play a role in promoting monomorphic VT due to re-entry, either by triggering it with ventricular ectopy, or by slowing conduction in diseased tissue within granulomatous scar.

Ablation outcomes are modest, reflecting the usual extensive scarring and multiple inducible morphologies. In the study by Kumar et al. (65), multiple-procedure VT-free survival was 37% at 1 year, but VT control was achievable in the majority of patients with fewer antiarrhythmic drugs. In other studies, recurrence rates were 44% (66) and 75% (67). Hence, a stepwise approach is generally recommended (Table 5) (50). Despite limited data, if there is evidence of active inflammation, immunosuppression with corticosteroids is the first suggested step. Antiarrhythmic medications are often started at the same time, with catheter ablation if VT cannot be controlled (50,66).

RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH AND WHEN TO CONSIDER IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR INSERTION. Patients with CS are at risk of sudden death, and there are few data to help with risk stratification. Figure 4, adapted from the 2014 consensus document (50), shows the suggested approach to risk stratification and when to consider implantable cardioverter-defibrillator (ICD) insertion. CS, perhaps because of its element of active granulomatous inflammation, and perhaps because of variable LV and/or RV involvement, may not behave in the same fashion as other types of nonischemic cardiomyopathy. For example, CS patient cohorts appear to have more frequent ICD therapies than other populations (68-70). All 3 studies examined associations with appropriate ICD therapies. The only consistent finding was that a lower ejection fraction was associated with appropriate ICD therapy. However, patients with mildly impaired LV function also had a substantial risk of arrhythmia (68-70).

PROGNOSIS

Patients with CS have a poorer prognosis than patients without cardiac involvement. Cardiac death is due to either heart failure or sudden death. In patients with clinically manifest disease, the extent of LV dysfunction is the most important predictor of survival (58). For example, Chiu et al. (71) found that all patients with normal ejection fraction were alive at



10 years; in patients with severe dysfunction (ejection fraction <30%), the survival rate was 91% after 1 year, 57% after 5 years, and 19% after 10 years (71). However, these data were published in 2005 (71), and contemporary outcomes are likely to be better with modern heart failure therapies and wider use of ICDs.

A total of 8 studies have looked at the prognosis of clinically silent CS (Table 1). Five studies including a total of 286 patients found that patients with clinically silent CS have a completely benign course (no cardiac events over an average of 23 months) (24,25,72-74). However, 3 studies have reported starkly contrasting findings (27,43,44). Hence, there is considerable controversy as to the prognosis of patients with clinically silent CS, and larger studies are needed.

CONCLUSIONS

Studies suggest that CS seems to be becoming more prevalent. However, this is likely due to improvements in imaging and/or more thorough investigation, rather than a true increase in prevalence. There is also a growing realization that CS can be the first manifestation of sarcoidosis in any organ, and that the diagnosis is often delayed or missed altogether. In patients with clinically manifest CS, the extent of LV dysfunction seems to be the most important predictor of prognosis. There is considerable controversy in published reports as to the outcome of patients with clinically silent CS. In 2014, the first international expert consensus for the diagnosis and management

of CS was published. Much remains to be learned about how to best diagnose and manage patients with CS.

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REPRINT REQUESTS AND CORRESPONDENCE:

Dr. David H. Birnie, Division of Cardiology, University of Ottawa Heart Institute, 40 Rue Ruskin Street, Ottawa, Ontario K1S 2K4, Canada. E-mail: dbirnie@ottawaheart.ca.

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