Cardiac Sarcoidosis

Jian Liang Tan, MD[a,*], Hee Kong Fong, MD[b], Edo Y. Birati, MD[c], and Yuchi Han, MD, MMSc[c]

Clinical and subclinical cardiac sarcoidosis (CS) remains diagnostically challenging as the sensitivity and specificity of the diagnostic modalities are limited. The Japanese Ministry of Health and Welfare criteria and the Heart Rhythm Society expert consensus statement on CS are the most common guidelines used to diagnose CS. However, they are mostly based on expert opinions and lack clinical trial validation. The emergence and increase use of newer imaging modalities such as cardiac magnetic resonance and positron emission tomography may give valuable information for accurate diagnosis and assessment of treatment response in CS patient. Although immunosuppressive therapies, particularly corticosteroids, have been proposed as the mainstay of treatment in CS, there is paucity of data on the optimal initiation, duration, and dosage of immunosuppressive therapies. Recommendations are mostly based on small observational studies. Further studies are warranted to better characterize the use of immunosuppressive therapies in this patient population. Device therapies such as implantable cardioverter-defibrillators are usually recommended for patient with clinical CS. In conclusion, this article synthesizes the current best evidence of utilizing various imaging modalities to diagnose CS and summarizing the main therapeutic approaches to manage and treat CS. **(Am J Cardiol 2019;123:513−522)**

Sarcoidosis is a rare inflammatory disorder of unknown etiology involving multiple organ system, most commonly, the lymphatic system, lungs, eyes, skin, and nervous system, and rarely the heart. It is characterized by the formation of noncaseating granulomas in the affected organs.[1] In the United States, the reported age-adjusted annual incidence of sarcoidosis was about 10.9 per 100,000 in white Americans and 35.5 per 100,000 in African Americans.[2] In patients with systemic sarcoidosis, it was estimated that 5% of them have symptomatic cardiac sarcoidosis (CS). However, a few autopsy series and imaging studies have reported that the prevalence of subclinical CS is 25%, underscoring a substantially higher rate of CS.[3,4] During the last 2 decades, the disease became more prevalent, likely due to improvement in imaging modalities and higher awareness of the disease.[5,6] Cardiac sarcoidosis accounts for a substantial morbidity and mortality. Hence, early recognition of CS is imperative to prevent detrimental consequences.

Diagnosis of CS

CS may affect any parts of the heart, including atria, ventricles, valves, papillary muscles, pericardium, conduction system, and coronary vessels. CS can have a wide range of clinical symptoms and is often diagnosed late in its clinical stage. Palpitations or presyncope may sometimes be the only initial presenting symptoms. The Japanese Ministry of Health and Welfare (JMHW) criteria (Table 1) and the Heart Rhythm Society (HRS) expert consensus statement (Table 2) are currently the 2 most well-established diagnostic guidelines for CS.[7,8] Nonetheless, the JMHW and HRS diagnostic criteria were mainly based on expert consensus and have yet to be validated by prospective data or clinical trials.

Biomarkers such as angiotensin-converting enzyme, lysozyme, urinary calcium, interleukin, interferon, neopterin, B-type natriuretic peptide, or high-sensitivity troponin levels are often elevated in patients with CS but these tests have low sensitivity and specificity.[1] Although immunological markers such as serum amyloid A proteins, microRNAs, and transforming growth factor-beta are currently being investigated on their potential roles in sarcoidosis, none of them can readily be used to diagnose or assess the disease activity of CS.[9]

Chest x-ray and chest computed tomography (CT) are the most commonly available imaging modalities. Chest x-ray is generally the initial imaging study used to examine for lung and lymph node involvement and is abnormal in >90% of patients with extracardiac sarcoidosis.[10] High-resolution CT of the lung enables a better analysis of the lung parenchymal and interstitial involvement. However, most authors would not exclude CS based on a negative chest imaging study.

Electrocardiogram (ECG) is an appropriate initial screening tool in patients with sarcoidosis. However, ECG abnormalities are only present in around 3.2% to 8.6% of patients with clinically silent CS.[11] Abnormalities such as complete heart block and right bundle branch block are the most common findings.[8] A 24-hour Holter monitoring can be used to detect subclinical arrhythmia that might be

[a]Department of Internal Medicine, Crozer-Chester Medical Center, Upland, Pennsylvania; [b]Department of Internal Medicine, University of Missouri-Columbia, Columbia, Missouri; and [c]Cardiovascular Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Manuscript received August 4, 2018; revised manuscript received and accepted October 31, 2018.

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*Corresponding author: Tel: (267) 818-0489; fax: (610) 447-6373.

E-mail addresses: jianliangoctjl@gmail.com; jian.liang.tan@crozer.org (J.L. Tan).

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Table 1
Japanese Ministry of Health and Welfare criteria for diagnosing cardiac sarcoidosis[4]

Histological Diagnosis	Clinical Diagnosis
1. EMB revealed noncaseating granulomas and 2. Histological or clinical diagnosis of extracardiac sarcoidosis	1. Presence of extracardiac sarcoidosis based on histological or clinical criteria plus either of the following: • ≥2 of the 4 major criteria • 1 major criteria and ≥2 minor criteria Major Criteria: • Advanced atrioventricular block • Decreased left ventricular ejection fraction, < 50 (%) • Positive ^{67}gallium uptake in the heart • Abnormal thinning of the basal interventricular septum Minor Criteria: • Abnormal ECG: ventricular arrhythmias, multifocal or frequent PVCs, complete RBBB, abnormal axis or Q waves • Abnormal echocardiogram: regional wall motion abnormality or morphological abnormality (aneurysm or wall thickening) • Nuclear imaging: perfusion defect on ^{201}Thallium or ^{99m}Technetium single-photon emission computed tomography • Late gadolinium enhancement on cardiac magnetic resonance imaging • EMB: over moderate interstitial fibrosis and monocyte infiltration

EBM = endomyocardial biopsy; ECG = electrocardiogram; PVC = premature ventricular complex; RBBB = right bundle branch block.

missed on ECG in patients with suspected CS. Nonetheless, the abnormalities noted on ECG or Holter monitor are often nonspecific and insensitive to examine cardiac involvement in patient with sarcoidosis.

A 2-dimensional transthoracic echocardiography is recommended as the initial screening test for CS in patient with systemic sarcoidosis. Findings including noncoronary distribution wall motion abnormalities and anterior basal septal thinning with increased echogenicity may be highly suggestive of CS.[12] Other abnormalities such as decreased left or right ventricular (RV) systolic or diastolic function, ventricular dilatation or aneurysms, valvular abnormalities, and pericardial effusion are present in 14% to 46% of patients with CS.[13] Those findings are very nonspecific, and they are often presented late in the clinical stage. Recent study has shown that speckle-tracking echocardiography could potentially be used to detect early stage of CS.[14] The presence of impaired left ventricular (LV) longitudinal strain may be suggestive of early granulomatous cardiac infiltration and higher degree of reduction in LV longitudinal strain is associated with poorer clinical outcomes and increased risk of adverse cardiac events.[15] Nonetheless, LV longitudinal strain impairment cannot differentiate active lesion from fibrotic scar.[14] Hence, this may limit its use for monitoring treatment response in CS patients treated with immunosuppressive therapies.

Cardiac magnetic resonance (CMR) is a noninvasive advanced imaging test which offers high spatial resolution and detailed assessment of LV and RV functions, detection of edema, perfusion defects, and myocardial scar. The typical CS findings noted on CMR are as follows: acute phase of the disease may be characterized by noncoronary distribution wall motion abnormalities, increased myocardial wall thickness, or increased intramyocardial signal intensity

Table 2
Heart Rhythm Society expert consensus statements on criteria for diagnosing cardiac sarcoidosis[5]

Histological Diagnosis	Clinical Diagnosis
1. EMB revealed noncaseating granulomas and 2. No other cause identified for the above histological finding	1. It is probable CS if: • There is presence of extracardiac sarcoidosis based on histological criteria And one or more of the following: • Treatment-responsive cardiomyopathy or heart block with corticosteroid +/- immunosuppressant drug • Unexplained decreased left ventricular ejection fraction <40 (%) • Unexplained sustained ventricular tachycardia; spontaneous or induced • Mobitz type II second-degree heart block or complete heart block • Patchy uptake of ^{18}F-flurodeoxyglycose on cardiac positron emission tomography, typical pattern consistent with CS • Late gadolinium enhancement on cardiac magnetic resonance imaging, typical pattern consistent with CS • Positive gallium uptake, typical pattern consistent with CS and: • Other causes have been reasonably excluded

CS = cardiac sarcoidosis; EBM = endomyocardial biopsy.

on T2-weighted images due to granulomatous lesion and edema associated with inflammation.[4] Chronic phase or inactive CS may be demonstrated by myocardial wall thinning or aneurysm and a low signal on T2-weighted images but high late gadolinium enhanced (LGE) signal intensity suggesting scaring or fibrosis. The locations of multifocal fibrosis can be anywhere in the myocardium and do not conform to any coronary distribution (Figure 1). Smedema et al reported that CMR has high negative predictive value of 100%, sensitivity of 100%, specificity of 78%, and accuracy of 83% in detecting CS compared with the JMHW criteria.[16]

Transvenous endomyocardial biopsy is a diagnostic tool for CS which has a low sensitivity of <25% due to patchy or focal distribution of the granulomas resulting in sampling error.[17] CMR may be used as a guide for endomyocardial biopsy to increase the diagnostic accuracy.[8] Besides its use in diagnosing CS, CMR may add an important value to prognostication and therapeutic purposes. The HRS supported the use of CMR to further evaluate for CS and sudden cardiac death (SCD) risk stratification. Ise et al studied 43 LGE-positive patients with CS and showed that the extend of LGE was associated with increased risk of cardiac mortality, hospitalization for HF, and life-threatening arrhythmias.[18] Patients with LGE mass ≥20% of LV mass are less likely to have functional LV recovery following steroid treatment. In a small prospective study of 81 patients with biopsy proven extracardiac sarcoid, patients

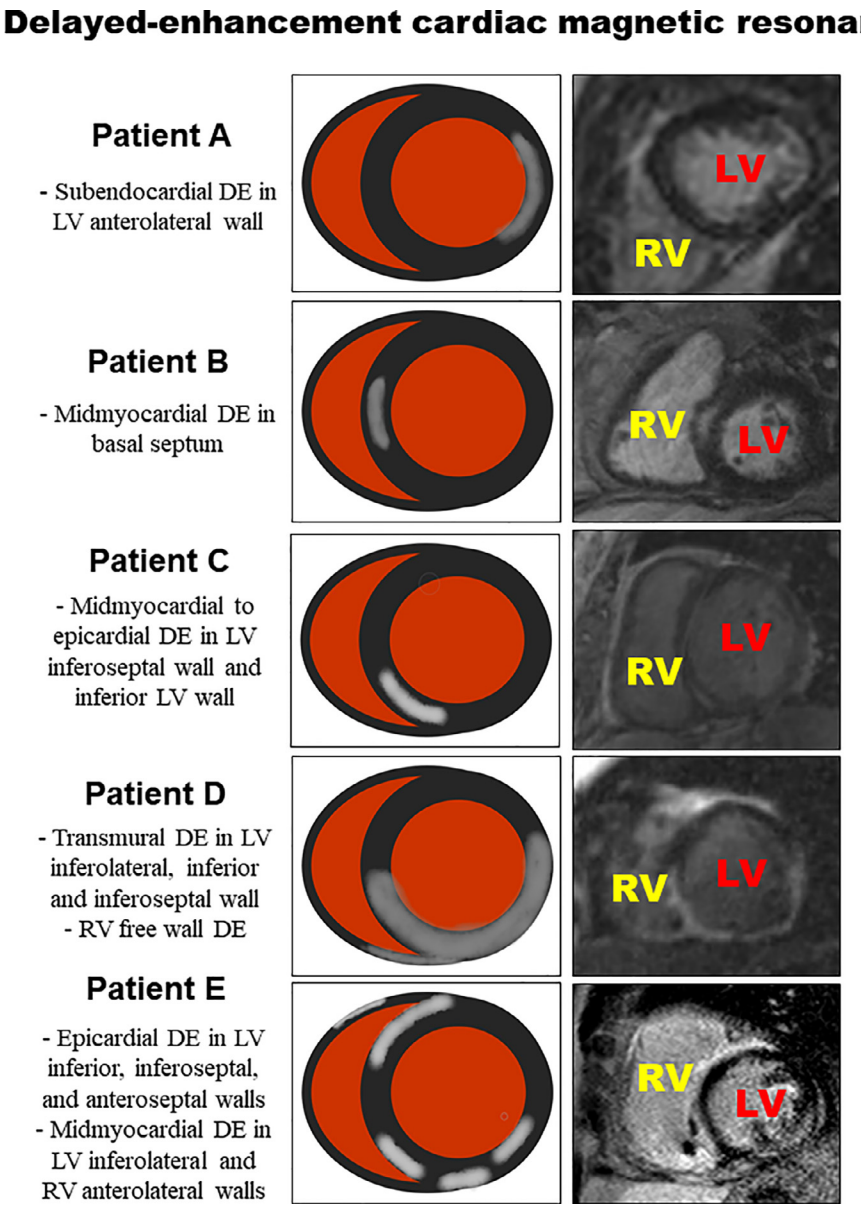

Figure 1. Patterns of delayed-enhancement (DE) on CMR in patients with cardiac sarcoidosis. Images from 5 patients positive for cardiac involvement by DE-CMR are shown. A variety of DE patterns are demonstrated. Cartoon representations of the DE-CMR images are shown immediately adjacent. White regions in the cartoon figures depict areas of cardiac involvement. CMR = cardiac magnetic resonance; DE = delayed-enhancement; LV = left ventricle; RV = right ventricle.

with LGE on CMR had a higher yearly rate of cardiac-related death (11.5% vs 1.0%) and cardiac-related adverse events (17.2% vs 1.9%) compared with patients without LGE on CMR.[19] In a larger study of 155 systemic sarcoidosis patients who were evaluated for CS with CMR, the presence of LGE was a powerful independent risk for fatal events (death, aborted SCD, or implantable cardioverter-defibrillator (ICD) discharge) with a Cox hazard ratio (HR) of 31.6.[20] The extent of LGE, shown on CMR, was associated with increased risk of cardiac-related events.[20]

CMR mapping techniques such as T1, T2, and extracellular volume may be performed in combination with LGE to improve the diagnosis of subclinical CS. Greulich et al examined 61 sarcoidosis patients and 26 healthy subjects and noted that patients with sarcoidosis demonstrated significantly higher native T1 (994 vs 960 ms; $p < 0.001$), T2 (52 vs 49 ms; $p < 0.001$), and extracellular volume (28 vs 25%; $p = 0.001$) compared with healthy groups.[21] However, these differences are within 2 standard deviations of the normal and although there is group difference, it is difficult to choose cut-off values for individuals for diagnosis. In another small retrospective study of 50 patients by Crouser et al, T2 signal was notably higher in patients with sarcoidosis and suspected CS versus healthy groups (60.0 [56.8 to 65.9] ms, vs 51.5 [50.0 to 52.9] ms, $p < 0.0001$).[22] It was again noted that T2 abnormality could be present even without LGE findings. Similarly, Puntmann et al studied 40 patients with extracardiac sarcoidosis (18 of them received anti-inflammatory treatment) who underwent CMR with LGE, T1, and T2 mapping.[23] There was significant improvement of T1 and T2 signal in the treated group (z score: -3.72 and -2.88; $p < 0.01$) compared with the untreated group (z score, -1.42 and -1.38; $p > 0.15$).[23] Hence, serial T1 and T2 CMR imaging may be helpful in assessing treatment response to immunosuppressive agents in patients with active CS.

There are several limitations in the use of CMR to evaluate CS. First, CS is a great mimicker of many other cardiac diseases. The findings of LGE on CMR can be present in other cardiac conditions such as myocarditis.[24] Second, the findings of LGE on CMR cannot differentiate active versus chronic lesions of CS. Although T2 is elevated in active disease, it is not as reproducible as LGE imaging. Third, gadolinium-enhanced CMR imaging study remains contraindicated in patient with significant renal impairment (eGFR < 30 ml/min) due to the risk of nephrogenic systemic fibrosis.

The recent development of hybrid PET-CMR imaging systems (Figure 2) may seem promising to simultaneously obtain cardiac structure and function, detect fibrosis, and examine the degree of active inflammation.[25] Wicks et al studied a total of 51 suspected CS patients with PET-CMR imaging.[26] The authors noted that hybrid PET-CMR was superior for detecting CS with sensitivity of 94%, specificity of 44%, positive predictive values of 76%, and negative predictive values 80%, respectively, when estimated using the JMHW guidelines as a standard reference.[26] This may further increase the diagnostic accuracy and better guide therapy in patients with active CS.

PET is a radionuclide imaging technique that is used in combination with CT scan to detect active metabolic processes in the body. The images produced by PET-CT have a higher spatial resolution compared with other nuclear imaging modalities. PET-CT has also the technical advantages of lower radiation exposure, quantitative analysis, robust built-in attenuation correction, and anatomical localization. Cardiac PET imaging for CS involved the use of FDG to evaluate for myocardial inflammation.

Special patient preparation is required before ^{18}F-FDG-PET/CT imaging to adequately suppress myocardial FDG uptake and increase utilization of free fatty acid by the cardiac muscle, for the detection of focal inflammation within sarcoid granulomas. The current approaches include avoid strenuous exercise for 24 hours, low-carbohydrate and high-fat diets for ≥2 meals, prolonged fasting for ≥12 hours, and concomitant administration of intravenous unfractionated heparin to maximize the suppression of normal myocardial FDG uptake.[27] A newer radiotracer, 3′-deoxy-3′-^{18}F-fluorothymidine, was shown to be a promising PET tracer to examine active lesions of CS.[28] It is easier to be performed and required no special diet or prolonged fasting before the study.[28] However, larger prospective studies are warranted to validate its clinical use in patient with CS before commercializing it.

^{18}F-FDG-PET/CT captured a wide spectrum of disease stage (areas of pathologic glucose uptake and active inflammation) in CS as shown in Figure 2.[25] It has become an essential imaging modality for early diagnosis, management, follow-up, and prognostication in patients with CS. The classical patterns of myocardial FDG uptake in patient with active CS are either diffuse, focal, and focal-on-diffuse patterns.[29] ^{18}F-FDG-PET/CT has a sensitivity of 89%, a specificity of 78%, a positive likelihood ratio of 4.1 (95% confidence interval [CI], 1.7 to 10), and a negative likelihood ratio of 0.19 (95% CI, 0.1 to 0.4) to diagnose CS, using JMHW guidelines as the standard reference.[29] Up to the present, only 1 study by Ohira et al has directly compared the diagnostic accuracy of ^{18}F-FDG-PET/CT with CMR.[30] The authors noted that ^{18}F-FDG-PET/CT has a higher sensitivity (88% vs 75%) but lower specificity (39% vs 77%) than CMR, using JMHW criteria as a standard reference.[30] The capability of ^{18}F-FDG-PET/CT in identifying active lesion (early stage) versus LGE in identifying fibrosis (advanced stage) accurately is the most likely explanation for the differences in the sensitivity and specificity of these 2 imaging modalities.[30]

Serial ^{18}F-FDG-PET/CT may be used to determine treatment option (intensification vs tapering of corticosteroid therapy) and monitor treatment response in patient with CS, mainly due to its ability to measure and quantify the metabolically active lesion (using maximum standard uptake value and standard uptake value volume).[31] Osborne et al evaluated 23 patients (91% treated with corticosteroids) for the intensity and extent of active lesions of CS with at least 2 ^{18}F-FDG-PET/CT exams at different time points (median time of 2.0 years).[31] There was a significant inverse relation between LV ejection fraction (EF) and maximum standard uptake value. It was noted that nonresponders to therapy had a significant decrease in EF compared with responders and vice versa.[31]

^{18}F-FDG-PET/CT has also been proven to be helpful in providing important prognostic information in patient with

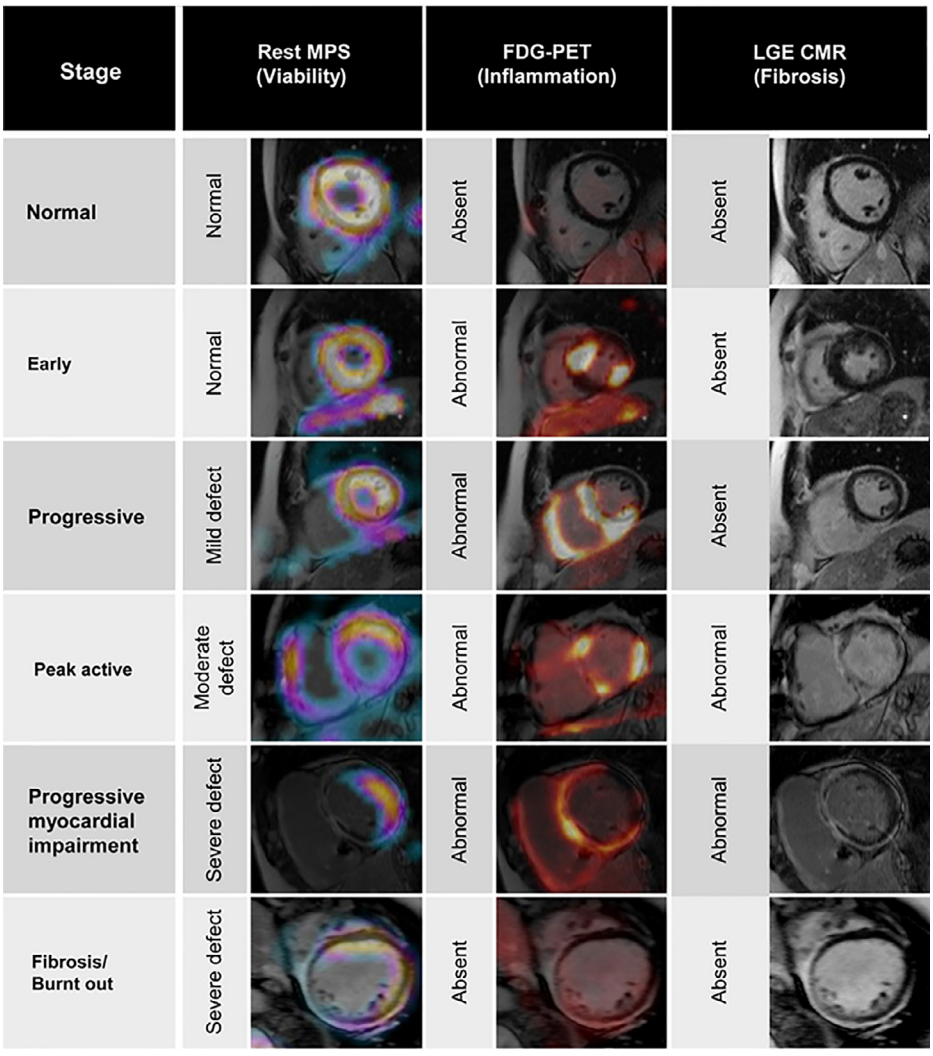

Figure 2. Staging of cardiac sarcoidosis, originally proposed by Skali et al using resting MPS to show increasing depth and extent of scarring as disease advances and worsening of LV function. Corresponding FDG-PET shows a heterogeneous pattern of inflammation in the intermediate stages except in the normal and burnt-out stages where there is no FDG activity. Therefore, it cannot be used alone for staging. The corresponding late gadolinium enhanced (LGE) CMR images are also shown both fused with MPS and PET and alone. Reproduced with permission from ref. [25] CMR = cardiac magnetic resonance; FDG-PET = 2-fluorodeoxyglucose positron emission tomography; LV = left ventricle; MPS = myocardial perfusion scintigraphy.

CS. Sperry et al performed a retrospective analysis of 269 patients who underwent perfusion and ^{18}F-FDG-PET/CT imaging.[32] All subjects were suspected with CS and were followed for a mean period of 1.8 years. The authors concluded that segments with myocardial perfusion-metabolism mismatch (adjusted HR of 1.12; 95% CI, 1.01 to 1.24; $p = 0.029$) and coefficient of variation of FDG uptake (adjusted HR of 1.05; 95% CI, 1.01 to 1.10; $p = 0.041$) were associated with adverse prognosis (ventricular arrhythmia, heart transplantation, or all-cause mortality).[32] Blankstein et al conducted a large prospective study of 118 consecutive patients who were referred for ^{18}F-FDG- and ^{82}Rb-PET/CT for assessment of CS, 60% had abnormal FDG-PET scans and were followed for a mean period of 1.5 years.[33] The authors concluded that patient with focal myocardial perfusion defect and increased myocardial FDG uptake had a significant risk of ventricular tachycardia (VT) and death (HR of 3.9, $p < 0.01$), and patient with focal RV FDG uptake was associated with worse prognosis (HR of 2.8, $p = 0.04$).[33]

Hence, cardiac ^{18}F-FDG-PET/CT imaging can be a helpful imaging study for early diagnosis, prognostication, and follow-up in patients with CS. However, more prospective studies are warranted to better characterize the role of ^{18}F-FDG-PET/CT in CS.

Management of CS

Management of CS is challenging as the clinical manifestations of isolated CS tend to vary widely and there is no reliable method to diagnose isolated CS in its early stage. There are 2 main therapeutic approaches in the management of CS: (1) pharmacological management of CS includes immunosuppressive therapy for active lesions of CS, guideline-directed medical therapy (GDMT) for HF, and antiarrhythmics drug therapy for arrhythmias; (2)

invasive management includes permanent pacemaker, ICD, cardiac resynchronization therapy, catheter ablation of refractory ventricular arrhythmic foci, and cardiac transplantation.[8] The primary goals of early treatment for CS are to decrease inflammation and prevent fibrosis or scarring associated with granuloma formation, to preserve cardiac function, and to reduce SCD risk associated with conduction abnormalities or ventricular arrhythmias.[34]

Most of the data regarding the role of immunosuppression therapies (Table 3) in patient with CS are based on small observational studies and there is currently no reference standard to guide the timing, duration, or intensity of the immunosuppressive therapies in patient with clinically active or symptomatic CS.[35] Despite the paucity of evidence, corticosteroids remained the cornerstone in the treatment of clinically active or symptomatic CS and are recommended by most authors.

Sadek et al performed a systematic review of 10 manuscripts ranged from poor to fair quality to study the role of corticosteroids in CS.[35] The authors reported that corticosteroids might be helpful for AV nodal recovery, but no clear conclusion could be drawn about other outcomes (LV function, ventricular arrhythmias, and mortality) due to insufficient power of the studies.[35] Data from several studies support the benefit of starting corticosteroids at an early stage of CS. Padala et al conducted a retrospective analysis of 30 patients with CS. The authors noted that early initiation of corticosteroids may be associated with better clinical outcomes (improvement in mean EF [from 25% to 46%, $p < 0.001$], no ventricular arrhythmias recurrences, and complete recovery of AV conduction).[34] Yodogawa et al studied 31 CS patients treated with corticosteroids (initial dose of 30 mg/day of prednisone, and tapered over a period of 6 months to a maintenance dose of 10 mg/day) who had premature ventricular complexes >300/day.[36] Patients with LVEF ≥35% had a significant lower prevalence of nonsustained VT (6% compared with 41%, $p = 0.04$), a lower number of premature ventricular complexes/24 hours (from 742 compared with 1,820), and a higher prevalence of ^{67}Ga uptake compared with LVEF <35% group.[36]

The optimal duration and dose of corticosteroids in the treatment of CS have not been well defined. Yazaki et al analyzed 75 Japanese patients treated with corticosteroids and noted no significant difference in survival curves of patients treated with an initial prednisone dose of >30 mg/day and those treated with ≤30 mg/day.[37] Most experts recommended an initial dose of 30 to 40 mg of prednisone per day followed by a repeat cardiac imaging (^{18}F-FDG-PET/CT) after 1 to 6 months to assess for treatment response and guide subsequent prednisone dose.[11,38] Patients should be monitored for at least 3 years after reducing or stopping corticosteroids as relapse occurs in about 40% of the patients.[39] Study has shown that long-term maintenance dose of corticosteroid therapy leads to a better clinical outcome (lower HF admission and greater preservation of LV systolic function).[40] However, more prospective studies are warranted to make any definitive recommendation.

Corticosteroid-sparing agents have shown to be effective in systemic sarcoidosis. However, the use of corticosteroid-sparing agents, alone or combined with corticosteroid in treating CS, remain controversial. The most commonly used corticosteroid-sparing agent in treating CS is methotrexate. Nagai et al described a small open-label study of 17 CS patients.[41] The authors found that patient treated with methotrexate and low-dose corticosteroids was more effective in stabilizing EF and LV end-diastolic diameter and had fewer adverse effects compared with corticosteroids alone.[41] Sperry et al recommended methotrexate, leflunomide, or azathioprine as the first line corticosteroid-sparing agents in CS patients who required long-term immunosuppression to reduce the steroid-associated side effects and complications.[38]

CS patient with LV systolic dysfunction should receive the standard GDMT for HF, including angiotensin-converting enzyme inhibitors, angiotensin receptor II blockers or angiotensin receptor-neprilysin inhibitor, aldosterone inhibitors, and diuretics, in addition to corticosteroid therapy.[8] Beta blockers should be used cautiously due to the risk of high-grade AV block. It is prudent to avoid digoxin in active stage of CS due to the increased risk for heart block and arrhythmias.[42] Patients with refractory disease may be eligible for device therapy, including cardiac resynchronization therapy and LV assist device implantation, and orthotopic cardiac transplantation.[8]

AV block is a common clinical manifestation of CS and it can often be the initial presentation of isolated CS.[43] It is due to the formation of scar tissue or granulomas at the basal septum or near the nodal artery inflicting ischemic injury to the conduction system.[8] The 2014 HRS consensus recommendations for permanent pacemaker implantation in patient with CS are summarized in Table 4.[8] It is generally recommended to implant the device before initiating immunosuppressive therapy due to increased risk of device infection.

In a 10-year follow-up prospective study by Te et al, patients with CS are at increased risk of ventricular arrhythmia and SCD.[44] Although sotalol and amiodarone are commonly prescribed to treat ventricular arrhythmias in patients with CS, the efficacy of antiarrhythmic agents remains variable and breakthroughs can happen.[8] It is generally recommended to avoid amiodarone in patient with pulmonary sarcoidosis. Sotalol is the alternative antiarrhythmic agent in such patient population. Class I antiarrhythmic agents are contraindicated in patients with CS due to their proarrhythmogenic potential in fibrotic myocardium.

HRS expert consensus statement has issued several recommendations for ICD implantation in patients with CS as described in Table 4. Despite this potential life-saving treatment, close to 25% of the CS patients with ICD device received inappropriate shocks.[45] This is not uncommon as up to 32% of them have supraventricular arrhythmias.[46] Further research is necessary to study the potential benefit and outcomes of ICD implantation in CS patients with LVEF >35% and/or nonsustained ventricular arrhythmias for such patient population.

Catheter ablation can be considered in CS patients with incessant VT or persistent VT despite antiarrhythmic agent and immunosuppressive therapies.[8] Nonetheless, the successful use of the standard mapping and entrainment technique for VT catheter ablation in CS patients can be challenging as the circuit may sometimes originate from the tissue deep in the intraventricular septum, tissue near

Table 3
Immunosuppressive therapies in cardiac sarcoidosis

Medication	Dose	Mode of action	Side effects	Monitoring
Prednisone	5-40 mg daily (oral)	Glucocorticoid	Cushing's syndrome, osteoporosis, cataract, hypertension, hyperglycemia, infections, mood swings, psychosis, insomnia	*monitors body weight, blood pressure, blood glucose, bone mineral density
Methotrexate	5-20 mg weekly (oral)	Folate anti-metabolite, anti-inflammatory agent and immunomodulatory agent	Renal toxicity, hepatotoxicity, bone marrow suppression, interstitial pneumonitis, stomatitis, diarrhea, alopecia, infections	*requires dose adjustment for serum creatinine > 1.5 mg/Dl *requires CBC, renal and hepatic function tests every 1-3 months
Azathioprine	50-200 mg daily (oral)	Purine anti-metabolite	Opportunistic infections, hepatotoxicity, leukopenia, thrombocytopenia, lymphoma, skin cancer, oral ulcers, myalgia	*checks TPMT levels prior to the first dose *requires CBC, renal and hepatic function tests every 1-3 months
Leflunomide	10-20 mg daily (oral)	Immunomodulatory agent, pyrimidine synthesis inhibitor	Hepatotoxicity, headache, skin rash, hypertension, teratogenicity, alopecia, diarrhea	*requires monthly CBC for the first 3 months
Mycophenolate mofetil	500-1500 mg twice daily (oral)	de novo guanosine nucleotide synthesis inhibitor	Opportunistic infections, lymphoma, skin cancer, teratogenicity, skin rash, bone marrow suppression, insomnia, renal toxicity, hepatotoxicity	*requires CBC, renal and hepatic function tests every 1-3 months
Cyclophosphamide	500-1000 mg over 30-60 minutes once every 2-4 weeks (intravenous) or *500 mg/m^2 of body surface area every 4 weeks, (intravenous)	Alkylating agent,	Teratogenicity, hemorrhagic cystitis, transitional-cell carcinoma bladder, alopecia, bone marrow suppression, infection, mucositis, amenorrhea	*requires CBC, renal and hepatic function tests every 1-3 months *urinalysis every month due to risk of urinary bladder cancer *adequate rehydration
Infliximab	3-5 mg/kg initially and at week two, then every 4-8 weeks (intravenous)	TNF-alpha inhibitor, chimeric monoclonal antibody	Infections, lymphoma, infusion reactions (anaphylaxis), rash, headache, pharyngitis, sinusitis, dyspepsia, fatigue, hypertension	*requires negative tuberculin skin test or interferon release assay prior to use *Monitor CBC, hold infliximab in the event of active infection

CBC = complete blood count; kg = kilogram; m = meter; mg = milligrams; PPD = purified protein derivative; TNF = tumor necrosis factor; TPMT = thiopurine S-methyltransferase.

Table 4
Device therapies in cardiac sarcoidosis[5]

Device	Indication	Class
Permanent pacemaker implantation	- Guided by the ACC/AHA/ HRS 2012 guidelines (see sections on Acquired AV Block and Chronic Bifascicular Block) for decisions regarding permanent pacing in CS patients	1
	- Can be useful in CS patients with an indication for pacing even if the AV block reverses transiently	IIa
Implantable cardioverter-defibrillator	- Recommended in patients with CS and ≥one of the following: 1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest; 2. LVEF ≤35 (%), despite optimal GDMT and a period of immunosuppression (if there is active lesion)	I
	- Can be useful in patients with CS, independent of ventricular function, and ≥ one 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 (>30 seconds of monomorphic VT or polymorphic VT) or clinically relevant VF.	IIa
	- May be considered in patients with LVEF 36 −49 (%) and/or an RVEF <40 (%), despite optimal GDMT for heart failure and a period of immunosuppression (if there is active lesion)	IIb

ACC = American College of Cardiology; AHA = American Heart Association; AV = atrioventricular block; CS = cardiac sarcoidosis; EF = ejection fraction; GDMT = guideline-directed medical therapy; HRS = Heart Rhythm Society; LV = left ventricular; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

the His bundle, the ramus intermedius or the left anterior descending coronary artery, and intramural free wall.[47] The recurrence rate of VT, despite successful initial catheter ablation, is reported at 86%.[47]

Cardiac transplantation should be considered in CS patients with intractable ventricular arrhythmias, end-stage heart failure, or refractory cardiogenic shock. Although sarcoidosis may recur in the transplanted heart, the risk of recurrence remained low (<10%) when the patient is kept on low-dose corticosteroids.[48] Perkel et al reported that the 5-year post-transplant survival rate in patient with CS was 79%, comparable to 83% 5-year survival in heart transplant recipients of other causes.[48] In a larger retrospective study conducted by Zaidi et al who studied the outcomes of 65 heart transplant recipients with CS over an 18-year period.[49] The authors reported that 1-year and 5-year survival rates were 87.7% and 80.5%, which was higher compared with the controls (84.5% and 70%, respectively).[49]

In general, patients with isolated CS tend to carry a poorer prognosis compared with systemic sarcoidosis due to increased risk of ventricular arrhythmias and worse event-free survival.[50] Kandolin et al revealed that patients with heart failure have a lower 10-year transplantation-free cardiac survival of 53%.[5] It is evident that the extent of LV systolic dysfunction remained as the most important independent predictor of survival.

Conclusion

During the last decade, numerous advancements have been made to examine the use of noninvasive imaging modalities for early diagnosis of CS, risk stratification, and monitoring treatment response. However, the available studies examining their use in CS patient are mainly based on single-center small retrospective studies. Although there is a pathophysiological rationale for the use of corticosteroid, alone or in combination with corticosteroid-sparing agents to treat CS, there appears to be lack of data from prospective studies or clinical trials to prove their efficacy in reversing conduction abnormality, preserving LV systolic function or improving mortality. The validation process is another challenge because active lesion of CS is uncommon and often detected late in its clinically stage. Hence, the gaps remained in our knowledge about the appropriate use of noninvasive imaging modalities to diagnose and monitor patient with CS, and the appropriate dose and duration of immunosuppressive therapies for CS patient. More research is necessary to better characterize their use in patient with CS.

Conflict of Interest/Disclosure

The authors have no conflicts of interest to disclose.

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