

Evaluation of Known or Suspected Cardiac Sarcoidosis

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Abstract—Sarcoidosis is a multisystem disorder of unknown cause, and cardiac sarcoidosis affects at least 25% of patients and accounts for substantial mortality and morbidity from this disease. Cardiac sarcoidosis may present with heart failure, left ventricular systolic dysfunction, AV block, atrial or ventricular arrhythmias, and sudden cardiac death. Cardiac involvement can be challenging to detect and diagnose because of the focal nature of the disease, as well as the fact that clinical criteria have limited diagnostic accuracy. Nevertheless, the diagnosis of cardiac sarcoidosis can be enhanced by integrating both clinical and imaging findings. This article reviews the various roles that different imaging modalities provide in the evaluation and management of patients with known or suspected cardiac sarcoidosis. (*Circ Cardiovasc Imaging*. 2016;9:e000867. DOI: 10.1161/CIRCIMAGING.113.000867.)

Key Words: cardiomyopathies ■ echocardiography ■ magnetic resonance angiography
■ positron-emission tomography ■ sarcoidosis

Background

Sarcoidosis is a multisystem disorder of unknown cause, which is characterized by the formation of noncaseating granulomas in multiple organs.¹ The annual incidence of sarcoidosis has been estimated at 5 to 40 cases per 100 000 persons in the United States and Europe with a 3-fold higher risk in blacks than in whites.²

Cardiac sarcoidosis (CS), which affects at least one quarter of patients,³ portends a worse prognosis and accounts for substantial mortality and morbidity from this disease. Although CS is often under diagnosed, increased detection of this condition has recently been described in some populations.⁴ After diagnosis, treatment with corticosteroids may slow the progression of heart failure,⁵⁻⁷ whereas implantable cardiac defibrillators (ICD) may improve survival.⁸ Nevertheless, such therapies have not been evaluated in any clinical trials, have considerable side effects, are costly, and do not benefit all patients. Therefore, there is an important need to accurately diagnose cardiac involvement and also identify patients who are most likely to benefit from treatment.

However, cardiac involvement can be difficult to detect, in part, because of the focal nature of the disease.^{3,9} For instance, cardiac biopsy has a sensitivity of only ≈20% to 30%, because it often misses areas of cardiac involvement.^{5,10} The clinical diagnosis of CS often uses clinical criteria such as the Japanese Ministry of Health and Welfare criteria, which were originally published in 1993¹¹ and then modified in 2007,¹² and more recently the Heart Rhythm Society (HRS) expert consensus statement.¹³ However, these criteria have an imperfect diagnostic accuracy^{14,15} and have not been validated. Nevertheless,

an important and evolving contribution of these criteria is the recognition that the diagnosis of CS relies on integrating both clinical and imaging findings. Yet, even when the diagnosis of CS is established, the appropriate management of those with suspected disease is not clearly defined.¹⁶

This review will provide an overview of the different imaging modalities used in the evaluation of patients with known or suspected CS, focusing on how to use data from these tests in patient management. We will then discuss how to choose between the different available testing options and the different approaches to combine data from multiple modalities.

Diagnosis of CS

Cardiac involvement by sarcoidosis can affect any portion of the heart, including the pericardium, atria, ventricles, papillary muscles, and valves. Rare reports have also described CS causing vasculitis of the coronary arteries.¹⁷

From a clinical perspective, CS may be suspected in patients who present with new and unexplained AV block, atrial arrhythmias, ventricular arrhythmias, or left ventricular dysfunction, particularly if such individuals also have a prior history of non-CS. However, often nonspecific symptoms such as palpitations or presyncope may be the only presenting symptoms. Because such symptoms can be caused by a wide range of conditions, CS may not be initially suspected. Ultimately, the diagnosis sometimes is only established after imaging tests are performed to evaluate for other suspected conditions.

The dilemma faced by many clinicians and imagers is that there is no reliable reference standard to diagnose CS. The

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guidelines for the diagnosis of CS published by the Japanese Ministry of Health and Welfare (JMHW; Table 1) have not been systematically validated and have reduced sensitivity and specificity when compared with imaging techniques.^{14,15} One particular limitation of these guidelines is that in the absence of positive myocardial histology, the diagnosis of CS requires the presence of extracardiac disease, and thus individuals with isolated CS, by definition, will be not be diagnosed. The 2007 update of these guidelines (which requires 2 major criteria or 1 major and 2 minor criteria to establish the diagnosis) has incorporated the presence of late gadolinium enhancement (LGE) or nuclear scintigraphy myocardial perfusion defects as minor criteria. Yet, other criteria that are less accurate—such as gallium uptake in the heart or ejection fraction <50%—were categorized as major criteria.

Recently, the HRS introduced an expert consensus statement, which provides more contemporary criteria for the diagnosis of CS. Similar to the JMHW criteria, the HRS expert consensus statement offers 2 pathways that can be used to diagnose CS: (1) histological diagnosis, using myocardial tissue or (2) a clinical diagnosis. Acknowledging the inherent uncertainty related to diagnosing CS in the absence of myocardial tissue histology, the clinical diagnosis criteria state that “it is *probable* that CS is present” (defined as >50% likelihood) if there is a histological diagnosis of extracardiac sarcoidosis and the patient meets ≥ 1 of several criteria (Table 2).

Echocardiography

Although transthoracic echocardiography is an extremely useful test for assessing the severity of left ventricular systolic or diastolic dysfunction, it is more limited for determining the

cause of cardiomyopathy. Among patients with biopsy-proven extracardiac sarcoidosis, an abnormal echocardiogram may be helpful in suggesting the presence of CS.¹⁸ Indeed, echocardiographic abnormalities (Figure 1) have been reported in 14% to 46% of patients with systemic sarcoidosis, even in the absence of symptoms or ECG abnormalities.^{19–23} Abnormal findings include wall motion abnormalities, diastolic dysfunction, abnormal myocardial wall thickness in a noncoronary distribution, possibly caused by sarcoid granulomas, or thinning, as a late result of the same process.^{20–22} In addition, findings of left ventricular dilatation and left ventricular systolic dysfunction, which can be assessed by echocardiography, are predictors of mortality in CS.^{6,21}

Despite the various abnormalities that can be identified by echocardiography, patients with CS may have a normal echocardiogram, and accordingly echocardiography has a low sensitivity to diagnose early or localized mild disease.²¹ Supporting these concepts, Mehta et al²⁴ found echocardiographic abnormalities in only 25% of the patients who exhibited cardiac magnetic resonance imaging (CMR) or ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomographic (PET) evidence of CS, whereas Freeman et al²⁵ determined a negative predictive value of only 32% for the ability of echocardiographic findings to exclude CS.

Use of Strain Imaging

One parameter that may have an important future role for screening patients with suspected CS is left ventricular global longitudinal strain. Joyce et al²⁶ evaluated 100 patients with systemic sarcoidosis who did not have any overt heart disease or known CS and who underwent echocardiography. They

Table 1. Guidelines for Diagnosis Cardiac Sarcoidosis

The Japanese Ministry of Health and Welfare, 1993	Japanese Society of Sarcoidosis and Other Granulomatous Disorders, 2006
Histological diagnosis group: endomyocardial biopsy specimens demonstrate epithelioid granuloma without caseating granuloma	Histological diagnosis group: endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis
Clinical diagnosis group: in patients with a histological diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is suspected when item a and ≥ 1 items b through e are present, and other causes such as hypertension and coronary artery disease have been excluded.	Clinical diagnosis group: although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid cell granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies either of the following conditions:
<ul style="list-style-type: none"> a. ECG: RBBB, left-axis deviation, AV block, ventricular tachycardia, PVCs (over grade 2 in Lown classification of premature ventricular tachycardia), or abnormal Q or ST-T change b. Echocardiography: abnormal wall motion, regional wall thinning, or dilatation of the left ventricle c. Myocardial scintigraphy: perfusion defect by ²⁰¹Tl or abnormal accumulation by ⁶⁷Ga-citrate or ^{99m}Tc-PYP d. Catheter: abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle e. Endomyocardial biopsy: interstitial fibrosis or cellular infiltration over moderate grade even if the findings are nonspecific 	<ul style="list-style-type: none"> • ≥ 2 of the 4 major criteria are satisfied • 1 in 4 of the major criteria and ≥ 2 of the 5 minor criteria are satisfied
	Major criteria
	<ul style="list-style-type: none"> • Advanced AV block • Basal thinning of the interventricular septum • Positive ⁶⁷Gallium uptake in the heart • Depressed ejection fraction of the left ventricle (<50%)
	Minor criteria
	<ul style="list-style-type: none"> • Abnormal ECG findings: ventricular arrhythmias (ventricular tachycardia, multifocal or frequent PVCs) CRBBB, abnormal axis deviation or abnormal Q wave • Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening) • Nuclear medicine: perfusion defect detected by ²⁰¹Tl or ^{99m}Tc myocardial scintigraphy • Gadolinium-enhanced CMR imaging: delayed enhancement of myocardium • Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade

CMR indicates cardiac magnetic resonance; CRBBB, complete right bundle branch block; ⁶⁷Ga, gallium-67; PVC, premature ventricular contraction; PYP, pyrophosphate; ^{99m}Tc, technetium-99 m; and ²⁰¹Tl, thallium-201.

Table 2. Criteria for Clinical Diagnosis of CS Based on Heart Rhythm Society Expert Consensus Statement

It is probable* that CS is present if all 3 of the following conditions are met:

- There is a histological diagnosis of extracardiac sarcoidosis
- One or more of the following is present:
 - Corticosteroid- or immunosuppressant-responsive cardiomyopathy or heart block
 - Unexplained reduced LVEF (<40%)
 - Unexplained sustained (spontaneous or induced) ventricular tachycardia
 - Mobitz type II second-degree heart block or third-degree heart block
 - Patchy uptake (of FDG) on dedicated cardiac PET in a pattern consistent with CS
 - Late gadolinium enhancement on CMR; in a pattern consistent with CS
 - Positive gallium uptake; in a pattern consistent with CS
- Other causes for the cardiac manifestation(s) have been reasonably excluded.

CMR indicates cardiac magnetic resonance imaging; CS, cardiac sarcoidosis; FDG, ¹⁸F-fluorodeoxyglucose; and LVEF, left ventricular ejection fraction.

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*Probable involvement was defined as ≥50% likelihood of cardiac involvement, and was considered adequate to establish a clinical diagnosis of CS.

showed that when compared with age- and sex-matched controls, patients with sarcoidosis had impaired global longitudinal strain, and that this was associated with a higher rate of adverse cardiovascular events.

Although requiring further validation, 1 group suggested that there may be a role for 3-dimensional (3D) speckle tracking radial strain in distinguishing CS from dilated cardiomyopathy²⁷ although in a different study impaired radial strain by 2D speckle tracking was not useful in identifying LGE detected by CMR, whereas circumferential and longitudinal strain exhibited a significant association.²⁸

Ultimately, strain imaging by echocardiography may provide a useful method to assess response to therapy²⁹ although to date there are no studies supporting this application.

Cardiac PET

The use of cardiac PET involves 1 scan to image inflammation (FDG) and 1 scan to assess resting myocardial perfusion imaging (⁸²Rubidium or ¹³N-Ammonia). Although PET imaging is preferred when available, rest myocardial perfusion imaging can also be performed with technetium-99 m using

single photon emission computed tomography, which is more widely available.

Patient Preparation

To shift normal myocardial metabolism to primary fatty acid utilization and, thus, suppress physiological uptake of FDG from normal myocardium, several protocols have been suggested³⁰ (Table 3) We recommend a high-fat/very low-carbohydrate diet for 2 meals before the scan followed by a fast of at least 4 hours.³¹ Alternative options include a high-fat/very low-carbohydrate meal followed by a longer fast of 12 hours, or in patients who are unable to tolerate the dietary preparation, a prolonged fast of at least 18 hours. Patients should be specifically instructed to avoid any sugar-containing foods and not to exercise on the day of the scan. Administration of a high-fat beverage 1 hour before scanning has not been found to improve myocardial FDG suppression.^{32,33} The use of low molecular weight heparin transiently increases serum free fatty acids, but may not be useful for suppressing physiological FDG uptake³⁴ and when used alone as a single bolus after a 12-hour fast was found to be inferior to long-term fasting.³⁵

Image Interpretation

Image interpretation is performed by analyzing both the FDG PET and resting myocardial perfusion images. A normal examination will have complete suppression of FDG from the myocardium and normal rest perfusion. In early stage of disease, focal areas of increased FDG uptake (corresponding to glucose consumption by macrophages) will be present. Resting perfusion defects may be seen in the presence of inflammation, which leads to compression of the microvasculature, or scar related to fibrosis.

In more advanced stages of disease, a resting perfusion defect (ie, scar) may be present without any inflammation. Thus, the absence of FDG uptake cannot be used to rule out the presence of previous CS, and this finding should be interpreted as a sign of no active myocardial inflammation.

Although resting perfusion defects and area of increased FDG uptake can occur in different locations, when these 2 abnormalities occur in the same location, a mismatch between perfusion and metabolism is described (Figure 2). It is notable that such a mismatch pattern can also be seen when using FDG to identify areas of viable myocardium although the patient

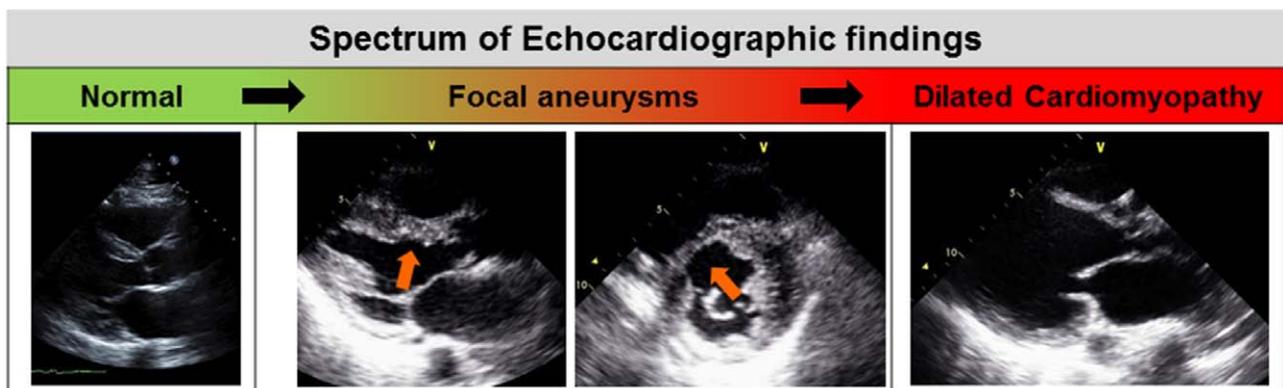


Figure 1. Spectrum of cardiac sarcoidosis by echocardiography.

Table 3. Different Approaches to Suppress ¹⁸F-fluorodeoxyglucose From Normal Myocardium

Method	Principle/Rationale
High-fat, low-carbohydrate diet followed by fast	Increasing FFA in serum will promote FFA consumption by the myocardium.
Low-carbohydrate diet followed by fast	
Prolong fast (>18 h) without previous diet restrictions	Lower insulin levels required to suppress glucose consumptions by the myocardium
FFA load	
Administration of UFH	UFH activates lipoprotein and hepatic lipase

See text for recommendations and review of key studies comparing these techniques. FFA indicates free fatty acids; and UFH, unfractionated heparin.

preparation before a viability study (which relies on inducing a state of high insulin levels thereby promoting uptake of FDG by the myocardium) is vastly different. Nevertheless, when considering the diagnosis of CS in individuals found to have a mismatch pattern, ruling out the presence of obstructive coronary artery disease is often required. Although most studies examining the role of PET in diagnosing CS have excluded patients with coronary artery disease, it is noteworthy that these 2 conditions are not mutually exclusive as some patients with CS may have advanced coronary artery disease.

Whole-Body Imaging

In addition to dedicated cardiac perfusion and FDG imaging, whole-body FDG imaging using a large field of view (typically from the base of the skull to the midthigh level) should also be performed to evaluate for extracardiac sarcoidosis. The identification of metabolically active extra cardiac disease could be useful for establishing the diagnosis of sarcoidosis and identifying areas that are more amenable than the heart for biopsy. In addition, the amount and severity of inflammation outside the heart could be used as a factor when considering the potential need/benefit for immunosuppressive therapies.

Diagnostic and Prognostic Value of PET

Although several studies have attempted to determine the accuracy of cardiac PET for diagnosing CS, these studies have all been severely limited because of the fact that the JMHW criteria was used as the references standard. A meta analysis,¹⁵ which included 7 such studies representing 164 patients, calculated a pooled sensitivity of 89% and specificity of 78%; however, these estimates are biased as the lower specificity of PET may reflect the fact that this test is more sensitive for identifying CS than the JMHW criteria.

Recent data from our group showed that among 118 patients referred for cardiac PET because of known or suspected CS, those with abnormal myocardial perfusion and metabolism (ie, focal inflammation) had a 4-fold increase in the annual rate of ventricular tachycardia or death.³¹ These findings persisted even after accounting for the JMHW criteria and left ventricular ejection fraction. Interestingly, we also found that among those with active inflammation, those who had evidence of focal RV involvement had the highest event rate. On the contrary, the presence or absence of active extra-cardiac sarcoidosis was not associated with adverse events. Further supporting the prognostic value of cardiac PET, Ahmadian et al³⁶ evaluated 31 patients with suspected sarcoidosis and found that the majority of adverse cardiac events occurred in individuals with abnormal FDG uptake.

Other Nuclear Cardiology Techniques

Rest myocardial perfusion imaging using single photon emission computed tomography may identify perfusion defects from microvascular compression and fibrosis although the spatial resolution of these techniques is lower than PET. When stress testing is performed, such defects may improve (ie, reverse distribution) although this phenomenon is not specific to CS alone.

Gallium-citrate imaging—although considered one of the criteria used by the JMHW—is of limited value because of its low sensitivity and should only be considered when FDG PET or CMR are not available. Reflecting the poor sensitivity of

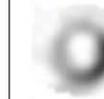
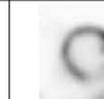
Spectrum of disease by PET/CT to evaluate rest perfusion and metabolism						
	Normal perfusion and metabolism		Abnormal metabolism		Abnormal perfusion and/or metabolism	
Perfusion						
	Normal	Normal	Normal	Abnormal	Abnormal	Abnormal
FDG						
	Normal (Negative)	Diffuse (non-specific)	Focal increase	Focal increase	Focal increase (different areas)	Normal (Negative)
Interpretation	Normal	Non-specific*	Early Disease	Mismatch Pattern	Scar and Inflammation	Scar

Figure 2. Spectrum of cardiac sarcoidosis by cardiac positron emission tomography (PET). *Likely failure to suppress ¹⁸F-fluorodeoxyglucose (FDG) uptake by normal myocardium although rarely can also be seen with diffuse disease. CT indicates computed tomography.

this technique, in 1 small study of patients with CS who had positive myocardial FDG uptake by PET, only 23% showed abnormal Gallium uptake in the heart.³⁷

Cardiac MRI

Although CMR can detect morphological abnormalities such as areas of wall thinning or aneurysm, the principal method for detecting of CS by CMR relies on identifying areas of midwall and subepicardial LGE (Figure 3). Gadolinium is an extracellular contrast agent, which has slow washout (and therefore positive enhancement) from areas of fibrosis and inflammation, both disease processes result in expansion of the extracellular space.³⁸ Nevertheless, the presence of LGE in a noninfarct pattern can often be a nonspecific finding, which is also seen in other disease such as scar from previous myocarditis or from fibrosis in idiopathic cardiomyopathy. Rarely, CS can also cause subendocardial LGE, thus mimicking an infarct pattern. From our experience and others, features of LGE that favor the diagnosis of CS include multifocal involvement and involvement of the basal anteroseptum and inferoseptum, which demonstrates contiguous extension into the right ventricle. The presence of increased T2-weighted signal—a marker of increased water content—can be used to identify areas of increased inflammation although this technique is technically challenging³⁹ and has not been evaluated among patients with CS. Current T2 mapping techniques may overcome some of these challenges and provide a more robust method to identify and quantify myocardial inflammation.⁴⁰

Smedema et al²³ evaluated the diagnosis accuracy of CMR against the JMHW criteria in a cohort of 58 patients with biopsy-proven pulmonary sarcoidosis. They found that CMR had a 100% sensitivity because it was able to diagnose all 12 (21%) of patients that were positive by the JMHW criteria. However, the specificity of LGE by CMR was only 78% (with positive predictive value of 55%), likely reflecting the poor sensitivity of the JMHW criteria and the ability of CMR to identify small area of scar, which were not associated with any ECG, echocardiography, or single photon emission computed tomography abnormalities.

Prognostic Value of CMR

Patel et al¹⁴ compared the prognostic value of LGE by CMR with the JMHW criteria. They followed up 81 patients with biopsy-proven extracardiac sarcoidosis over a mean of 21 months, during which 6 patients died (5 were attributed

to cardiac causes), 2 had ventricular tachycardia, and 1 patient required a pacemaker for AV block. The event rate was 9-fold higher in patients who had LGE as only 2 events (1 cardiac death and 1 noncardiac death) occurred in patients that had no LGE. Interestingly, more events occurred among the JMHW negative group than among the JMHW positive group (5 versus 3). This study concluded that the presence of LGE by CMR is associated with future adverse events and also highlighted the poor sensitivity of the JMHW criteria.

The largest study to date on use of CMR for CS was published by Greulich et al⁴¹ who followed up 153 patients with systemic sarcoidosis. Over a median follow-up of 2.6 years, 12 (8%) patients experienced the combined end point of death, aborted sudden cardiac death, or appropriate ICD therapy. Among the 39 (25%) who had LGE, the hazard ratio for death or aborted sudden cardiac death was 32. On the contrary, only 1 noncardiac event (death caused by a pulmonary infection) occurred among the 114 patients without LGE.

Nadel et al⁴² followed up 106 patients referred for CMR who had previous biopsy-proven extracardiac sarcoidosis or who were found to have CS based on CMR. Overall, 32 (30%) individuals were found to have CMR findings consistent with CS. Over a mean follow-up of 37 months, 12 patients experienced sudden cardiac death or a ventricular arrhythmia. Notably, patients with CS by CMR had a significantly higher event rate (38% versus 1%; $P < 0.001$). In addition, 19 patients with CS underwent ICD implantation after CMR, and 7 of them had appropriate therapies. None of these patients died but 3 patients with CS who did not undergo ICD implantation died. Although retrospective in nature, this study found an association whereby patients with CS by CMR who were treated with ICD were less likely to die of SCD than those who had CS but who did not undergo device implantation.⁴²

Comparison of PET With CMR

There is a paucity of data comparing the utility of PET and CMR for evaluating patients with suspected CS. Ohira et al⁴³ evaluated 21 consecutive patients with suspected CS who underwent both PET and CMR. Among the 21 patients studied, 5 were negative by both modalities and 8 were positive by both although the distribution of findings differed among all 8. In addition, 8 patients had discordant findings: 7 had only

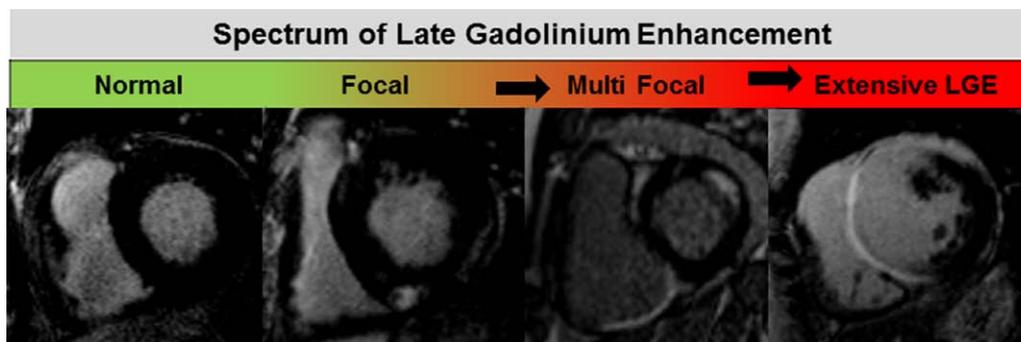


Figure 3. Spectrum of cardiac sarcoidosis by late gadolinium enhancement (LGE) using cardiac magnetic resonance imaging.

PET abnormalities, whereas 1 had only CMR abnormalities. Among the 8 (38%) patients who were categorized as having CS by the JMHW criteria, 3 had abnormal findings by only 1 modality whereas 5 had abnormalities on both. This study was underpowered to detect significant differences between these techniques but has been incorrectly cited by to suggest that PET may have a higher sensitivity based on a nonsignificant, numerically higher sensitivity for PET (7 of 8) than for CMR (6 of 8).

A subsequent study by Ohira et al⁴⁴ evaluated 30 corticosteroid-naïve patients with conduction system disease and CS by the JMHW criteria that underwent both FDG PET and CMR. Patients were classified into 2 groups based on the degree of conduction system disease: group A (18 patients)—chronic mild conduction system disease that included right bundle branch block and axis deviation; or group B (12 patients)—new-onset AV block. Among group A patients, all (18/18) had positive CMR and 72% (13/18) had positive studies by both modalities. Among group B patients, 58% (7/12) had positive findings by both modalities; 8% (1/12) were positive only by CMR; and 33% (4/12) were positive only by FDG PET. Based on these findings, the authors suggested that among patients with new-onset AV block, PET may have increased sensitivity to detect active CS.

Orii et al⁴⁵ evaluated a subset of 32 patients who had both FDG PET and CMR and were diagnosed as having CS. As also supported by the experience of others, they found that assessment of inflammation by FDG PET was more sensitive than CMR-based T2-weighted imaging. In their study, 6 patients with heart block and FDG uptake involving the septum had recovery after steroid therapy, whereas 2 patients with FDG uptake along the septum did not respond but were found to have thinning of the septum. This study suggested that PET FDG may identify patients who are more likely to recover from heart block after steroid therapy.

There are several important considerations to keep in mind when evaluating patients with suspected CS. Among patients who are already on steroid therapy, both CMR and PET may have reduced sensitivity to detect CS although CMR may have a higher sensitivity than PET in such scenarios.⁴³ Because of differences in technique, CMR and PET findings often show different distribution of disease. CMR identifies expansion of the extracellular space, which is most prominent when fibrosis is present, and thus may be better seen in later stages of disease. On the contrary, focal areas of increased FDG may be seen in early stages of disease before any fibrosis is present. Although resting perfusion defects can be seen with both fibrosis and marked inflammation, CMR has higher spatial resolution than PET, and thus small areas of fibrosis are better visualized by CMR than by PET.

When deciding between various imaging modalities, it is always important to consider the expertise of the center performing the tests. For instance, some centers may have significant experience in performing CMR but not PET, and vice versa. Because the use of imaging in the evaluation of CS relies on advanced techniques, which are not routinely available in all centers, referral for a center that has imaging expertise in these areas is often necessary.

Key Questions Relating to Effective Utilization of Imaging CS:

Should Asymptomatic Patients With Extracardiac Sarcoidosis Undergo Routine Screening Using Cardiac Imaging?

Most patients referred for cardiac imaging for the evaluation of CS have signs or symptoms that raise the possibility of cardiac involvement. Therefore, the frequency of cardiac involvement—which has ranged from 4% to 39%²⁴ in various studies—may be overestimated in some cohorts. A useful estimate is provided by Patel et al¹⁴ who found that among 152 consecutive patients with extracardiac sarcoidosis who were mostly asymptomatic and had preserved ejection fractions ($\geq 50\%$), 19% had evidence of LGE.⁴⁶

Although all patients with extracardiac sarcoidosis should undergo cardiac evaluation including ECG as well as a history and physical examination, routine use of advanced imaging techniques should likely be reserved for patients who exhibit signs or symptoms which are suspicious for CS. Although some centers perform screening with echocardiography, it should be emphasized that echocardiography is an insensitive technique to detect CS. Establishing that a patient has a normal ejection fraction or no wall motion abnormalities cannot be used to rule out the presence of CS.

Based on the previous literature^{24,25} and the HRS expert consensus statement, we recommend using CMR and PET for screening for CS in either (1) patients with biopsy-proven or clinically diagnosed extracardiac sarcoidosis who have signs or symptoms of possible cardiac involvement or (2) patients with no previous history of sarcoidosis who have unexplained Mobitz II or third-degree AV block and sustained monophonic ventricular tachycardia of unknown cause (Figure 4).

In light of the morbidity and mortality associated with CS, additional studies are needed to evaluate whether wider screening with imaging is cost effective. Although such screening will undoubtedly identify some individuals that have CS, the main questions to address include (1) does screening identify high-risk findings or different (eg, earlier) subtypes of disease

Biopsy proven extra-cardiac sarcoidosis

Screen with CMR and/or FDG PET if any of the following:

- ◆ Symptoms: -- significant palpitations
-- pre-syncope / syncope
- ◆ Abnormal EKG
- ◆ Abnormal echocardiogram

Specific presentations with no prior history of sarcoidosis

Screen with CMR and/or FDG PET if any of the following:

- ◆ Unexplained Mobitz II or 3rd degree AV lock in adults aged < 60 years
- ◆ Sustained Monomorphic VT of Unknown Etiology

Figure 4. Suggested criteria for screening for cardiac sarcoidosis. Abnormal echocardiogram defined as regional wall motion abnormality, wall aneurysm, basal septum thinning or left ventricular ejection fraction <40%. Abnormal ECG defined as complete left bundle branch block or right bundle branch block, unexplained pathological Q waves in ≥ 2 leads, sustained second- or third-degree AV block, or sustained or nonsustained ventricular tachycardia (VT). Reprinted from Birnie et al¹³ with permission of the publisher. Copyright ©2014, Elsevier.

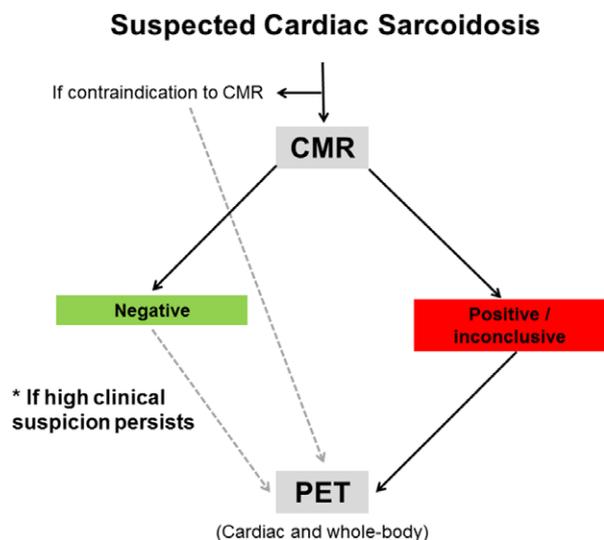


Figure 5. Suggested algorithm for using advanced cardiac imaging to evaluate patients with suspected cardiac sarcoidosis. CMR indicates cardiac magnetic resonance imaging; and PET, positron emission tomography.

that are less likely to be associated with adverse events? (2) What is the number needed to screen to prevent an adverse event? (3) What are the economic and medical implications of false-positive findings? (eg, nonspecific LGE, or FDG uptake, which may lead to downstream testing and anxiety but ultimately may have no bearing on patient outcomes)

How Should Patients With Suspected CS Be Evaluated?

Based on our experience and above presented data, in the absence of any contraindications (implanted devices, glomerular filtration rate <30 mL/min per 1.73 m²), we recommend CMR as a useful initial testing option for patients with suspected CS (Figure 5). In such individuals, the absence of LGE has a sufficiently high negative predictive value and reassuring event-free survival that no further testing would be required for the majority of patients. However, some patients referred for CMR may have nonspecific LGE findings. In such cases, or in a small subset of patients with negative CMR, if sufficiently high likelihood of CS is present, cardiac PET may be useful for further evaluation. The absence of any FDG uptake or perfusion defects would significantly decrease the likelihood of CS and determine that there is no need for any anti-inflammatory therapies (at least for the heart). On the contrary, positive PET findings will increase the likelihood of CS. In such cases, PET can also provide important information on whether there is any active extra cardiac disease, or perhaps disease that is more amenable to a percutaneous biopsy than an endomyocardial biopsy (if no tissue biopsy has been previously established).

How Should Imaging Be Used to Influence Patient Management?

Based on the aforementioned data on the prognostic value of CMR and PET, patients with CS who have abnormal CMR or PET results have a substantially higher rate of sudden cardiac death and ventricular tachycardia and thus should be

considered for ICD therapy, even when not indicated by usual ejection fraction criteria. Higher risk likely exists in patients who have a greater burden of disease by either PET or CMR. Anti-inflammatory therapies should only be considered in patients who have a significant amount of myocardial inflammation, and consequently we suggest imaging with FDG PET for all patients who have abnormal LGE who are being considered for such therapies if there is uncertainty on the presence of active inflammation.

How Should Imaging Be Used to Evaluate Treatment Response?

Cardiac PET imaging is the preferred imaging test for determining response to immunosuppressive therapy. When performed using the same technique, both a visual and quantitative comparison of myocardial FDG uptake can be performed. Although some patients experience complete resolution of inflammation (ie, no further FDG uptake on follow-up), others may demonstrate no significant change or even interval worsening (Figure 6). Because there are no data on the ideal drug, dose, or duration of therapy, and given the toxic side effect profiles of all anti-inflammatory agents, imaging may allow clinicians to more precisely select agents, which have a beneficial response while limiting the duration of therapy and considering alternative agents when no significant benefit is observed.

Indeed, minimizing the duration and intensity of therapy (which is usually continued for at least several months until all inflammation has resolved) represents an important goal for both patients and physicians. However, even when complete resolution of inflammation can be visualized by PET FDG, it is unknown whether continuation of therapy at a lower dose has any role in preventing recurrence of disease.

The optimal time interval between serial PET FDG studies is unknown, and, in part, depends on the rate at which anti-inflammatory therapy is being tapered down. Potential factors that can be used to determine the need for subsequent imaging include (1) severity of inflammation on initial scan (eg, smaller areas of inflammation may not require as close of a follow-up); (2) response to inflammatory markers; (3) changes in patient symptoms. In general, in patients with CS who have a severe amount of myocardial inflammation, repeat PET FDG may be reasonable after 3 to 6 months of anti-inflammatory therapy to assess whether the amount and extent of inflammation is lower (which would support taper down of steroids) or whether disease activity is unchanged (which could prompt continuation of therapy or consideration of different agents).

Supporting the role of FDG imaging in following response to therapy, Osborne et al⁴⁷ analyzed 91 PET scans from 23 patients who underwent serial PET examinations during treatment for CS and found that a reduction in the intensity of standardized uptake value (ie, SUV_{max}) or extent (ie, volume of inflammation above a prespecified SUV threshold) was associated with improvement in left ventricular ejection fraction. These results suggest that anti-inflammatory therapies may have an important role in minimizing or preventing left ventricular dysfunction; however, future randomized trials should further establish the potential benefits of imaging-guided

		Examples of response to therapy			
		Baseline		After treatment	
No Response	Whole Body FDG				
	Myocardial Perfusion				
	Inflammation (FDG)	Short axis 	Horizontal Long axis 	Short axis 	Horizontal Long axis
Marked Response	Whole Body FDG				
	Myocardial Perfusion				
	Inflammation (FDG)	Short axis 	Horizontal Long axis 	Short axis 	Horizontal Long axis

Figure 6. Example of using positron emission tomography/computed tomography to assess for response to therapy. FDG indicates ¹⁸F-fluorodeoxyglucose.

therapy and whether treatment is associated with a reduction in adverse events. In the meanwhile, when considering the role of therapy, is probable that not all patients are equally likely to benefit from immunosuppressive therapies, and, in addition to the severity and amount of myocardial inflammation, parameters such as the amount of scar and degree of left ventricular dysfunction and remodeling should be considered.

Although comparison between serial PET studies has often relied on visual assessment, quantitative techniques offer a more precise method to assess treatment response.^{36,48} We suggest using (1) SUV_{max} —maximum standardized uptake value that represents the severity of inflammation. The SUV_{max} is adjusted for decay-corrected injected activity and patient weight; (2) a measure of the extent/amount of inflammation above a prespecified SUV threshold.⁴⁷ Further research is needed to identify appropriate and clinically meaningful quantitative techniques that can be compared over time. In addition, additional studies are needed to determine whether more readily available imaging techniques (eg, strain by echocardiography) or biomarkers can be used to follow response to therapy.

What Are Potential Pitfalls for Diagnosing CS?

The following tests cannot be used to exclude the possibility of CS: normal echocardiogram, normal resting myocardial

perfusion single photon emission computed tomography or PET study, normal chest CT (ie, absence of pulmonary sarcoidosis does not exclude the possibility of cardiac involvement), negative JMHW or HRS criteria, and negative endomyocardial biopsy.

Conversely, abnormal findings should also be interpreted with caution. Abnormal FDG uptake by the myocardium can be seen by conditions such as myocarditis, hibernating myocardium, or from rheumatologic conditions, which cause inflammation in the heart.

Abnormal LGE by MRI can be seen in various conditions such as myocarditis, nonspecific fibrosis from various cardiomyopathies, or artifacts related to poor nulling of the myocardium.

Conclusions

Advances in cardiovascular imaging techniques have contributed to our ability to diagnose CS, identify subgroups that have a higher risk of adverse events, and assess the response to immunosuppressive therapies. Nevertheless, several challenges relating to this disease process exist. First, because of the absence of an appropriate reference standard, the true accuracy of various imaging findings will likely remain unclear. Second, more data are needed to compare the findings of different imaging techniques, as well as understand the

potential complementary role of hybrid approaches, particularly as different tests evaluate different pathophysiological attributes of CS.

Based on our current experience and that of others, among patients with suspected CS, cardiac MRI may serve as a useful initial testing option. The absence of any LGE can be used to exclude the presence of CS and is associated with an excellent prognosis. In patients who have a contraindication to CMR, inconclusive MRI findings, or when high probability of disease exists even after a negative MRI, the use of FDG PET may be useful. Among patients being treated for CS, cardiac PET is currently best suited for determining the response to therapy. Additional studies are needed to identify whether response to therapy based on imaging markers is associated with any improvement in clinical outcomes.

Disclosures

None.

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Evaluation of Known or Suspected Cardiac Sarcoidosis

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