

# Advanced Imaging of Cardiac Sarcoidosis

Imke Schatka and Frank M. Bengel

Department of Nuclear Medicine, Hannover Medical School, Hannover, Germany

**Learning Objectives:** On successful completion of this activity, participants should be able to describe (1) the pathophysiology, clinical appearance, and prognostic implications of cardiac sarcoidosis, (2) the practical aspects, typical image patterns, pitfalls, and clinical value of cardiac  $^{18}\text{F}$ -FDG PET in sarcoidosis; and (3) the value of  $^{18}\text{F}$ -FDG PET relative to other imaging modalities and clinical test results in cardiac sarcoidosis.

**Financial Disclosure:** The authors of this article have indicated no relevant relationships that could be perceived as a real or apparent conflict of interest.

**CME Credit:** SNMMI is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing education for physicians. SNMMI designates each *JNM* continuing education article for a maximum of 2.0 AMA PRA Category 1 Credits. Physicians should claim only credit commensurate with the extent of their participation in the activity. For CE credit, participants can access this activity through the SNMMI Web site ([http://www.snmmi.org/ce\\_online](http://www.snmmi.org/ce_online)) through January 2017.

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Cardiac involvement may occur, leading to an adverse outcome. Although early treatment to improve morbidity and mortality is desirable, sensitive and accurate detection of cardiac sarcoidosis remains a challenge. Accordingly, interest in the use of advanced imaging such as cardiac MR and PET with  $^{18}\text{F}$ -FDG is increasing in order to refine the clinical workup. Although the field is still facing challenges and uncertainties, this article presents a summary of clinical background and the current state of diagnostic modalities and treatment of cardiac sarcoidosis.

**Key Words:** cardiac sarcoidosis; inflammation; positron emission tomography; [ $^{18}\text{F}$ ]-deoxyglucose; magnetic resonance imaging

**J Nucl Med 2014; 55:99–106**

DOI: 10.2967/jnumed.112.115121

**S**arcoidosis is defined by the American Thoracic Society, European Respiratory Society, and World Association of Sarcoidosis and Other Granulomatous Disorders as “a multisystem disorder of unknown cause(s)” (1). The incidence varies according to ethnicity, sex, and region, from 3–10 per 100,000 for Caucasians to 35–80 per 100,000 for African Americans. Scandinavians have a higher incidence than other Caucasians. Women are affected more frequently, and peak incidence occurs below 40 y of age (2).

Some factors have been linked with sarcoidosis, such as environmental or occupational sources (3), infectious causes (4), and genetic predisposition (5), but the etiology remains unclear. A central role in early development and progression is attributed to the immune response and the degree of inflammation, which represent a major target for diagnosis and therapy (6).

Organ involvement is characterized histologically by noncaseating, nonnecrotic granulomas (Fig. 1) (7). Most frequently, lymph nodes and lungs are involved, but disease can affect any other

organ. The likelihood of cardiac sarcoidosis (CS) varies regionally, with a high occurrence in Japan (8,9). CS frequency is debated, with an approximate incidence of 5% based on clinical assessment (10), 27% in autopsy studies (7), and 39% in an imaging study that used cardiac MR (CMR) or PET (11). Even though CS appears to be underdiagnosed clinically, it is considered to be the second leading cause of death by sarcoidosis in the United States (12) and the leading cause in Japan (13).

## CLINICAL MANIFESTATION

The clinical manifestation of CS ranges from asymptomatic to sudden cardiac death. It is determined by localization and severity of disease. The myocardium is most frequently affected (6), but granuloma may also affect the endocardium and pericardium (14). The most frequently involved area is the ventricular septum (31.5%), followed by the inferior wall, anterior left ventricle, right ventricle, and lateral left ventricle (14). The left ventricular (LV) free wall, papillary muscles, basal septum, and atrial walls have also been reported as frequent sites of involvement at autopsy (15).

Inflammatory granulomas or postinflammatory scarring may lead to conduction abnormalities, arrhythmias, sudden cardiac death, and congestive heart failure. Involvement of the septum favors conduction abnormalities. Most frequent is a third-degree atrioventricular block, which appears in 23%–30% of cases (15). Banba et al. reported that atrioventricular block develops mainly during the inflammatory phase. Therefore, it has been speculated that early corticosteroid treatment might improve atrioventricular conduction (16). Compared with patients with idiopathic third-degree atrioventricular block, CS patients tend to be younger (17). Therefore, CS should be considered in patients younger than 55 y who present with unexplained persisting second- or third-degree atrioventricular block (18).

Ventricular tachycardia occurs in up to 23% of CS patients and represents the second most frequent clinical finding (16). Ventricular tachycardia is assumed to be reentry-related and attributable to myocardial scar tissue rather than active granuloma (16,19).

In a Japanese study, sudden cardiac death was the initial presentation in 40% of CS patients (20), underlining the need for an accurate tool for early disease detection.

In addition to arrhythmic complications, congestive heart failure is frequent, being observed in up to 73% of patients dying from CS. A variety of reasons, such as extensive myocardial infiltration, right heart failure caused by pulmonary involvement, or valve insufficiency

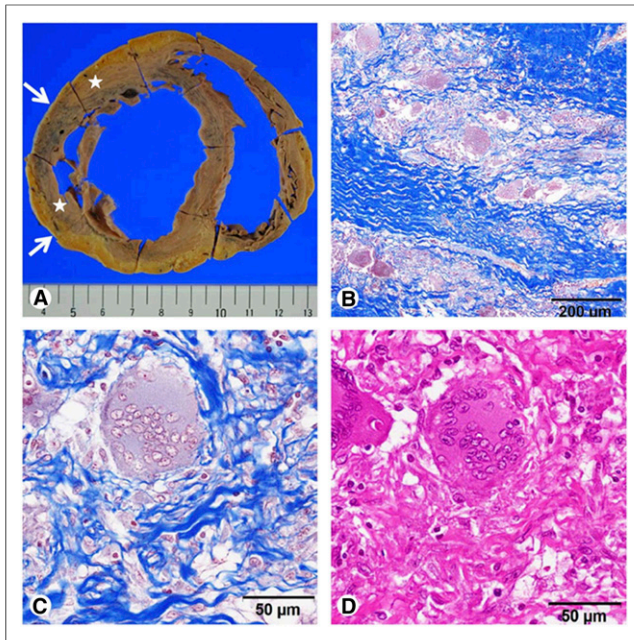
Received Jun. 27, 2013; revision accepted Sep. 3, 2013.

For correspondence or reprints contact: Frank M. Bengel, Department of Nuclear Medicine, Hannover Medical School, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.

E-mail: [bengel.frank@mh-hannover.de](mailto:bengel.frank@mh-hannover.de)

Published online Nov. 14, 2013.

COPYRIGHT © 2014 by the Society of Nuclear Medicine and Molecular Imaging, Inc.



**FIGURE 1.** Histopathology of CS. (A) Macroscopic view of dilated LV wall with thinning (arrows) and scarlike white lesions (asterisks). (B–D) Microscopic view of sarcoid granuloma and interstitial fibrosis stained with Masson trichrome (B and C) and hematoxylin–eosin (D). (Reprinted with permission from (79).)

caused by involvement of papillary muscles, contribute to pump failure (21). Accordingly, it has been suggested that CS should be considered in all patients with persistent ventricular tachycardia and idiopathic dilated cardiomyopathy. Generally, cardiac involvement should be ruled out in all patients with sarcoidosis, because of the adverse outcome (18).

## THE NEED FOR RELIABLE DIAGNOSIS

Identification of cardiac involvement in sarcoidosis is difficult. A precise and early diagnosis is needed to initiate antiinflammatory therapy and to prevent an adverse outcome (11,22).

### The Missing Gold Standard

The missing gold standard is a major problem in the diagnosis of CS. Biopsies are subject to sampling error and cannot be used to rule out CS. To date, the Guidelines of the Japanese Ministry of Health and Welfare (JMHWG), as revised by the Japan Society of Sarcoidosis and Other Granulomatous Disorders in 2006, serve as a worldwide standard for clinical diagnosis of CS (Table 1) (23). But PET, in contrast to CMR or <sup>67</sup>Ga scintigraphy, is not included despite its documented sensitivity in detecting CS. There is no uniform consensus on the key aspects of diagnosis and management of CS, as underlined by a recently published Delphi study (24). A consequence of that project was the creation of a proposal for the best practice in diagnosis and management of CS (Table 2).

### Clinical Evaluation

CS should be ruled out in all patients with diagnosed extracardiac sarcoidosis and in patients younger than 55 y with unexplained persisting second- or third-degree atrioventricular block or with persistent monomorphic ventricular tachycardia and non-ischemic dilated cardiomyopathy (Table 2) (18).

The initial clinical evaluation should include medical history, physical examination, electrocardiography, 24-h Holter monitoring, and an echocardiogram. Symptoms such as chest pain, palpitations, syncope, bradycardia, peripheral edema, dyspnea, and orthopnea may occur but are nonspecific (25,26). Okura et al. showed in a CS cohort that the clinical presentation consists of atrioventricular block (50%), left-sided heart failure (40%), syncope (31%), palpitations (17%), chest pain (14%), and bradycardia (10%) (25). Like the clinical symptoms, electrocardiography

**TABLE 1**  
Revised JMHWG Criteria for Diagnosis of CS (23)

Diagnosis group	Major criteria	Minor criteria
Histologic: CS is confirmed when endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with histologic or clinical diagnosis of extracardiac sarcoidosis		
Clinical: although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies more than 2 major criteria, or 1 major criterion and 2 or more minor criteria	Advanced atrioventricular block	Abnormal electrocardiogram showing ventricular arrhythmias (multifocal or frequent premature ventricular contractions), complete right bundle branch block, axis deviation, or abnormal Q wave
	Basal thinning of interventricular septum	Abnormal echocardiography showing regional abnormal wall motion or morphologic abnormality (ventricular aneurysm, wall thickening)
	Positive cardiac <sup>67</sup> Ga uptake	<sup>201</sup> Tl or <sup>99</sup> Tc myocardial scintigraphy showing perfusion defect
	Depressed left ventricular ejection fraction (<50%)	MR imaging showing delayed gadolinium enhancement
		Endomyocardial biopsy showing interstitial fibrosis or more than moderate monocyte infiltration

**TABLE 2**  
Proposed Diagnostic and Therapeutic Strategy in CS (24)

<b>Indications for screening</b>	
Diagnosed extracardiac sarcoidosis	
Unexplained persisting second- or third-degree atrioventricular block and age < 55 y	
Unexplained monomorphic ventricular tachycardia	
Nonischemic dilated cardiomyopathy	
<b>Routine screening procedures</b>	<b>Findings leading to further work-up</b>
Clinical symptoms, physical examination 12-lead electrocardiogram	Bundle branch block, ventricular ectopy, second- or third-degree atrioventricular block (atrial arrhythmia, first-degree atrioventricular block)
Echocardiogram	Global LV dysfunction, regional wall motion abnormalities (right ventricular dysfunction)
Holter monitoring	Runs of ventricular tachycardia, nonsustained ventricular tachycardia (frequent isolated premature ventricular contractions)
<b>Further work-up</b>	<b>Findings leading to therapy</b>
CMR	Delayed hyperenhancement (LV dysfunction, perfusion defects)
PET	Patchy or focal <sup>18</sup> F-FDG uptake (patchy on diffuse uptake)
Invasive electrophysiologic study	Abnormal result
<b>Therapy</b>	<b>Triggered by</b>
Immunomodulation (prednisone [30–40 mg]; methotrexate)	Positive further work-up
Implantable cardioverter-defibrillator	Positive electrophysiologic study
<b>Response evaluation</b>	
Symptoms	
CMR (no implantable cardioverter-defibrillator)	
PET	

changes do allow for conclusions about the extent of disease or the inflammatory activity, but only persistent ventricular tachycardia predicts adverse outcome (21). Signal-averaged electrocardiography can be used to detect intramyocardial conduction delay and identifies CS with 52% sensitivity and 82% specificity using biopsy as a reference (27). Holter monitoring may be suggestive of CS, with 50% sensitivity and 97% specificity using CMR or PET as a reference (11). Freeman et al. confirmed these findings and concluded that Holter monitoring serves as a powerful screening tool to predict a positive CMR or PET scan (28).

Echocardiography abnormalities are common but nonspecific. CS may present as dilated cardiomyopathy, with valvular dysfunction, wall motion abnormalities, wall thickening due to infiltration and edema, or wall thinning, which is located mainly in the septum and associated with scarring (29,30). However, echocardiography detects later stages of CS and is not considered useful for early detection. It has been applied for monitoring of therapy (31) and may predict adverse outcome when LV dilation is present (21).

Endomyocardial biopsy has less than 25% sensitivity in detecting noncaseating granuloma in CS, probably because of the patchy distribution pattern, resulting in sampling errors (7,32). Nevertheless, it is the only method that provides definitive histologic proof. To achieve a higher diagnostic yield, endomyocardial biopsy may be image-guided (33) or electroanatomic mapping-guided (34).

#### ADVANCED IMAGING

If the initial work-up for CS does not provide a safe rule-out, further testing using tomographic imaging should be performed before a therapeutic decision is made.

#### CMR

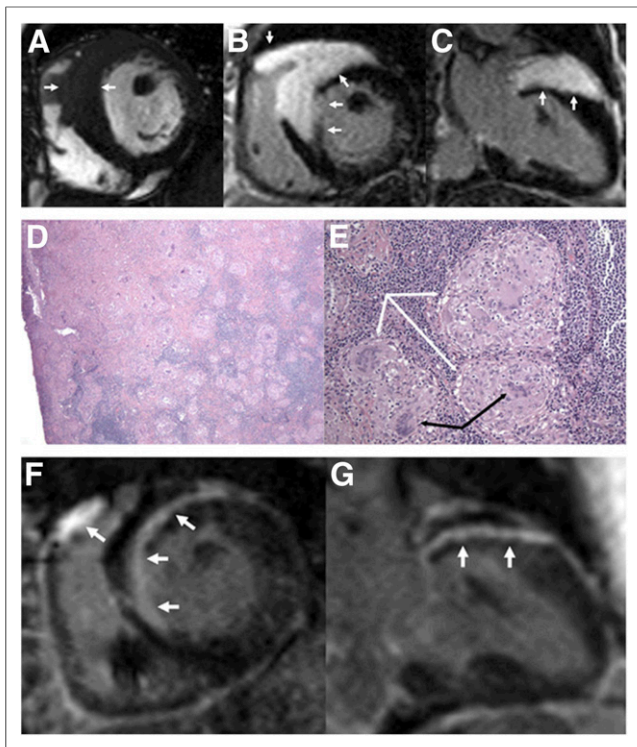
CMR provides high spatial and soft-tissue resolution. It detects the active, inflammatory phase of disease as well as the chronic

phase, in which scarring and fibrosis are predominant. The inflammatory phase is characterized by focal wall thickening due to infiltration or edema, combined with wall motion abnormalities seen on T1-weighted (cine) images, increased signal intensity on T2-weighted images, and early gadolinium enhancement (35). The chronic phase predominantly shows wall thinning and delayed gadolinium enhancement, representing myocardial damage, scarring, and fibrosis (Fig. 2) (36). Commonly, the two phases overlap. According to a Delphi study on CMR, delayed gadolinium enhancement was the strongest hallmark of CS (24). Distribution varies and usually does not adhere to coronary vascular territories (37), although it may mimic myocardial infarction (38). The basal septum (39), the basal and lateral segments of the LV (40), and the papillary muscles (6) are frequently involved. In addition to reliable detection of disease, gadolinium enhancement may also be useful to assess the response to steroid therapy (41,42). Patel et al. compared the prognostic value of late gadolinium enhancement on CMR with the criteria of the Japanese Ministry of Health and Welfare in an asymptomatic cohort of 81 patients with biopsy-proven extracardiac sarcoidosis (38). CS was detected in 26% of patients by CMR, but only 12% fulfilled JMHWG criteria. Delayed gadolinium enhancement was associated with adverse events and cardiac death. These results were confirmed by a more recent study, in which 155 patients with extracardiac sarcoidosis underwent CMR and had a follow-up of approximately 2.6 y (36).

#### PET

Increased glucose metabolism is a hallmark of inflammation, because of overexpression of glucose transporters and overproduction of glycolytic enzymes in inflammatory cells (43). Inflammation can be visualized effectively using the glucose analog <sup>18</sup>F-FDG and PET.

Under aerobic conditions, most myocardial energy consumption is extracted from oxidation of free fatty acids, followed by glucose



**FIGURE 2.** CMR imaging in case of CS. (A) Increased thickness (arrows) of mid-basal anterior and anteroseptal walls. (B and C) Transmural hyperenhancement (arrows) of mid-basal anterior, anteroseptal, and right ventricular free walls. (D and E) Excisional biopsy sample of anterior mediastinal lymph node confirming sarcoidosis (fibrosis in left upper quadrant [white arrow]; multiple noncaseating granulomas [black arrow]; no evidence of acid-fast bacilli or fungus). (F and G) Follow-up 3 mo after onset of steroids, showing significantly decreased extent of hyperenhancement (arrows). (Reprinted with permission from (80).)

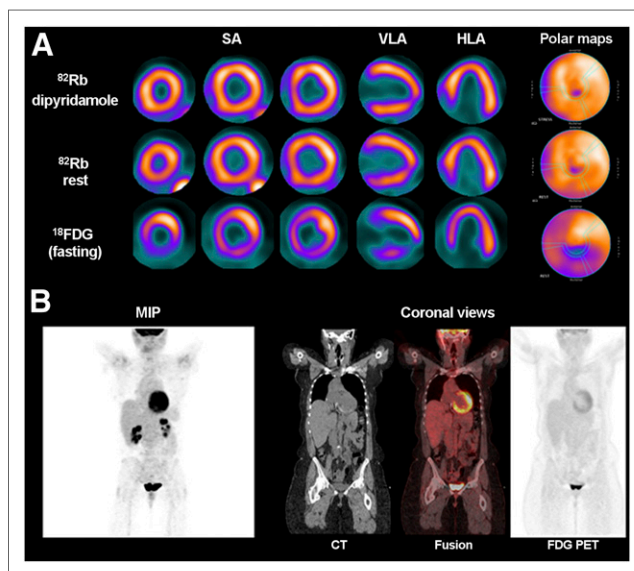
and, to a smaller part, amino acids. However, energy production and its relative contribution depend on various factors such as fasting state, neurohormonal conditions, and systemic regulation (44). The Randle cycle states that fatty acid loading suppresses glucose metabolism and vice versa.

It is essential to be aware that myocardial glucose utilization and thus  $^{18}\text{F}$ -FDG uptake may be present even under fasting conditions, during which free fatty acids are usually the preferred substrate. Studies have reported that fasting  $^{18}\text{F}$ -FDG uptake is inhomogeneous throughout the left ventricle in healthy subjects (45) and in oncologic patients (46), with a regional maximum in inferolateral and basal myocardium, probably because of local differences in substrate use (46). This uptake must not be confused with myocardial inflammation (Fig. 3) and emphasizes the need for an effective strategy to suppress myocyte uptake for a PET-based diagnostic workup of CS.

Currently used strategies for myocardial suppression include prolonged fasting (47), dietary modifications (48,49), and a heparin load before imaging (50). Williams and Kolodny were able to show that a very high-fat, low-carbohydrate, protein-permitted diet suppresses myocardial  $^{18}\text{F}$ -FDG uptake more effectively than overnight or 4-h fasting in an oncologic cohort (49). Harisankar et al. compared the effectiveness of myocardial  $^{18}\text{F}$ -FDG suppression due to a low-carbohydrate, high-fat, protein-permitted diet with prolonged fasting over 12 h. In that oncologic cohort, dietary restriction better suppressed cardiac uptake than did prolonged

fasting (48). Heparin, on the other hand, increases plasma free fatty acid levels and thereby suppresses glucose metabolism. In a Japanese CS study cohort after a fasting period of at least 6 h, 50 units of nonfractionated heparin per kilogram of body weight were injected 15 min before application of  $^{18}\text{F}$ -FDG (50). The result was robust suppression of cardiac  $^{18}\text{F}$ -FDG uptake. However, a more recent study compared heparin with prolonged fasting of more than 17.5 h and reported that cardiac uptake was more severely inhibited by extended fasting (51). Although there is currently no consensus on the best protocol for suppressing cardiac  $^{18}\text{F}$ -FDG uptake, a recently proposed protocol that combines fasting, a fatty meal, and heparin appears to be an attractive solution (52).

If patient preparation is performed correctly,  $^{18}\text{F}$ -FDG PET is accurate in the diagnosis of CS.  $^{18}\text{F}$ -FDG PET provides functional imaging of inflammatory disease activity and is therefore considered to be beneficial not only for early disease detection but also for therapy monitoring and image-guided biopsy (52). A patchy, focal uptake pattern is most suggestive of CS (Fig. 4). If there is a more diffuse uptake, the physiologic myocardial suppression may have been insufficient and other pitfalls should be considered. These include insufficient myocardial uptake suppression leading to heterogeneous  $^{18}\text{F}$ -FDG uptake (maximum in basal and lateral walls); other nonischemic cardiomyopathy or other inflammatory diseases of the heart leading to a substrate shift toward glucose, resulting in (heterogeneous) myocardial  $^{18}\text{F}$ -FDG uptake; and myocardial ischemia resulting in sustained regionally increased myocardial  $^{18}\text{F}$ -FDG uptake. Diffuse or focally increased uptake of the lateral wall is commonly seen as a normal variant and should not be mistaken for inflammation (53). Maurer et al. were able to show that suppression of total cardiac activity was present in only 9% of an oncologic patient cohort despite adequate fasting (46). Additionally,



**FIGURE 3.** PET/CT study in subject with idiopathic dilated cardiomyopathy and insufficient suppression of physiologic  $^{18}\text{F}$ -FDG uptake. (A) Reangulated images and polar maps of stress ( $^{82}\text{Rb}$  dipyridamole) and rest ( $^{82}\text{Rb}$  rest) perfusion show dilated ventricle with inhomogeneous perfusion but no evidence of regional ischemia. Fasting glucose uptake ( $^{18}\text{F}$ -FDG) maximizes in basal lateral wall and is otherwise diffuse and mild. (B) Whole-body study shows no extracardiac foci of  $^{18}\text{F}$ -FDG uptake. HLA = horizontal long axis; MIP = maximum intensity projection; SA = short axis; VLA = vertical long axis.

Israel et al. pointed out that cardiac  $^{18}\text{F}$ -FDG uptake was significantly higher in male patients, patients younger than 30 y, patients who had fasted for less than 5 h, patients with heart failure, and patients receiving benzodiazepines (54).

$^{18}\text{F}$ -FDG PET is often combined with a perfusion scan and electrocardiographic gating to rule out coronary artery disease or identify resting perfusion defects suggestive of inflammation-induced tissue damage (52). Normal perfusion and increased focal  $^{18}\text{F}$ -FDG uptake represent early CS, whereas abnormal perfusion and increased  $^{18}\text{F}$ -FDG uptake more likely represent advanced disease with tissue damage. Scarring, a potential end stage of disease, may result in abnormal perfusion without  $^{18}\text{F}$ -FDG uptake (55). After steroid therapy, a small study in 17 biopsy-proven CS patients showed a significant decrease in  $^{18}\text{F}$ -FDG uptake whereas perfusion defects remained stable (56).

Also, cardiac assessment can be combined with whole-body imaging to determine the presence and activity of extracardiac sarcoidosis lesions (Fig. 5). Cardiac involvement cannot be predicted by the extent of pulmonary disease (11). Rarely, CS may appear without extracardiac lesions (57). A proposed comprehensive protocol for PET imaging of CS is presented in Table 3.

In a recent prospective study on 28 patients with biopsy-proven sarcoidosis,  $^{18}\text{F}$ -FDG PET/CT influenced clinical management in 63% (47). In a current metaanalysis of 7 studies (164 patients), Youssef et al. reported 89% sensitivity and 78% specificity for CS detection with  $^{18}\text{F}$ -FDG PET, compared with JMHWG (53). But like all other diagnostic studies on CS, larger prospective studies are desirable to better define the clinical role of  $^{18}\text{F}$ -FDG PET and to determine its value for predicting outcome.

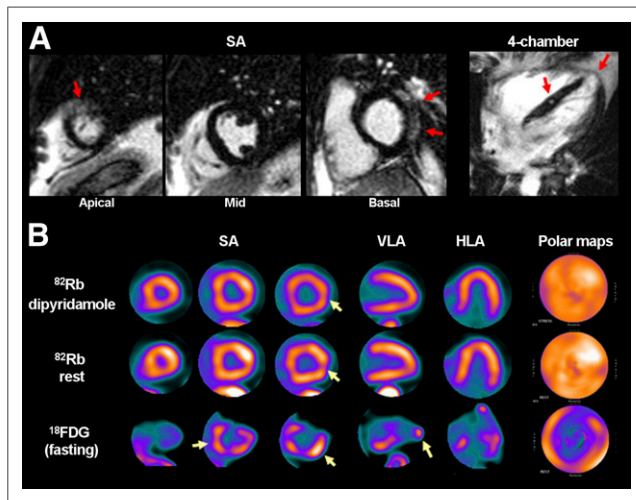
#### Comparing PET and CMR

Several studies compared late enhancement in CMR and  $^{18}\text{F}$ -FDG uptake in PET. While delayed enhancement represents car-

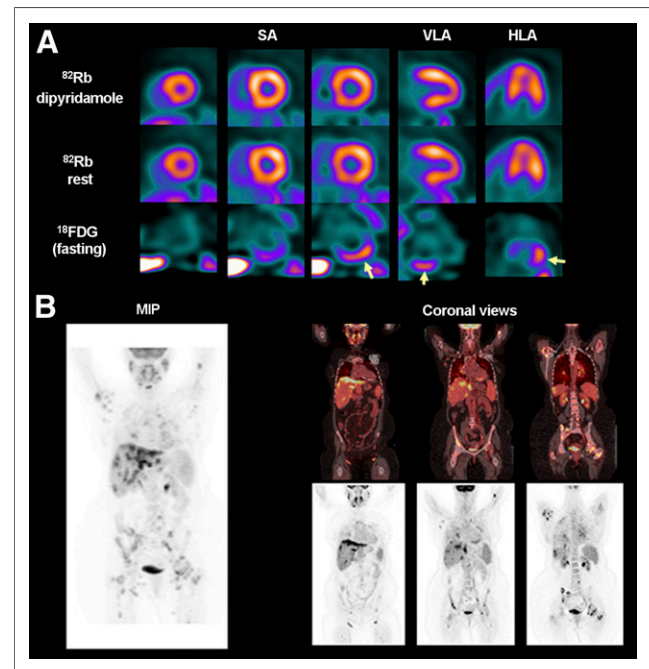
diac damage and scarring,  $^{18}\text{F}$ -FDG uptake represents active inflammation. Consequently, the mild to moderate correlation between CMR and PET is not surprising (58–60). When CMR and  $^{18}\text{F}$ -FDG PET were compared with the JMHWG, CMR had a higher specificity but a lower sensitivity (24,58).

In a study of 57 patients undergoing both CMR and  $^{18}\text{F}$ -FDG PET, CMR had a better negative predictive value, indicating it might be superior for ruling out CS (60). The main disadvantage of CMR, however, is the inability to study patients with defibrillators, which are increasingly implanted in CS patients. Another limitation is the inability to use gadolinium to image patients with renal impairment.

Advantages of  $^{18}\text{F}$ -FDG PET include the biologic nature of the imaging signal, the potential to identify cardiac and extracardiac sarcoidosis involvement (52), and the feasibility of imaging patients with electrical devices. Another advantage for therapy response or risk stratification may be quantification. According to European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging guidelines for  $^{18}\text{F}$ -FDG in inflammation, standardized uptake value should be used with caution in this setting (61). But McArdle et al. found higher quantitative  $^{18}\text{F}$ -FDG uptake in CS patients with ventricular tachycardia than in those with atrioventricular block and asymptomatic controls (62). And Blankstein et al. concluded in a group of 125 patients that abnormal cardiac PET findings are associated with a higher risk of death or ventricular tachycardia, whereas JMHWG criteria or the ejection fraction are not (63). Nevertheless, therapy monitoring and risk stratifications are areas for which prospective clinical studies are needed to determine the value of imaging.



**FIGURE 4.** CMR and PET/CT studies in subject with active CS. (A) CMR images, obtained at initial diagnosis, show foci of delayed gadolinium enhancement in basal lateral wall, septum, and apex (arrows). (B) Reanulated PET/CT images and polar maps obtained after cardioverter-defibrillator implantation and steroid therapy show multiple foci of increased fasting glucose uptake ( $^{18}\text{F}$ -FDG) in basal lateral wall, septum, and apex, suggesting persistent active CS (arrows). Stress ( $^{82}\text{Rb}$  dipyrindamole) and rest ( $^{82}\text{Rb}$  rest) perfusion images rule out ischemic heart disease and show fixed perfusion deficit in area of active sarcoid in basal lateral wall, consistent with regional tissue damage (arrows). HLA = horizontal long axis; SA = short axis; VLA = vertical long axis.



**FIGURE 5.** PET/CT study in subject with CS and extracardiac sarcoidosis. (A) Reanulated images of stress ( $^{82}\text{Rb}$  dipyrindamole) and rest ( $^{82}\text{Rb}$  rest) perfusion rule out ischemic heart disease. Fasting glucose uptake ( $^{18}\text{F}$ -FDG) is focally increased in basal inferior wall, consistent with active CS, and is suppressed in other LV walls (arrows). (B) Whole-body study shows multiple extracardiac foci of  $^{18}\text{F}$ -FDG uptake in chest, liver, bone, and lymph nodes, consistent with active extensive systemic sarcoidosis. HLA = horizontal long axis; MIP = maximum intensity projection; SA = short axis; VLA = vertical long axis.

**TABLE 3**  
Protocol for <sup>18</sup>F-FDG PET to Detect CS

Procedure	Goal
Preparation	Suppress myocardial glucose utilization
Long-term fasting (>12 h), and/or	
High-fat, low-carbohydrate meal, and/or	
Intravenous nonfractionated heparin (50 units/kg, 15 min before <sup>18</sup> F-FDG)	
Prolonged uptake period (>90 min) after <sup>18</sup> F-FDG injection	
Imaging	
Stress perfusion imaging (only if needed)	Rule out ischemic heart disease
Rest perfusion imaging	Identify myocardial contours to localize <sup>18</sup> F-FDG hot spots; detect regional tissue damage
Electrocardiographic gating of perfusion study	Identify LV dysfunction
Cardiac <sup>18</sup> F-FDG imaging	Identify or localize inflammatory hot spots
Whole-body <sup>18</sup> F-FDG imaging	Identify extracardiac inflammatory lesions

Disadvantages of <sup>18</sup>F-FDG PET include the radiation exposure, the potential pitfalls of inadequately suppressed physiologic cardiac uptake, and the inability to detect smaller regions of myocardial damage. Also, a potential source of error in patients with an implantable cardioverter-defibrillator may be hot-spot artifacts at the lead insertion site on attenuation-corrected images. Although some studies suggested a significant overestimation of SUV (64), others suggested that images in the presence of metallic leads could be interpreted without correction for metal artifacts (65). Evaluation of images without attenuation may be used as an adjunct in case of suspected lead insertion artifacts.

Ultimately, given that cardiac involvement in sarcoidosis is underdiagnosed and associated with an adverse outcome, and given the different strengths and weaknesses and the different biologic signals of PET and CMR, a combination of the two may be beneficial (59,60) and there may be a future role for integrated PET/MR (66).

#### Other Radionuclide Imaging Tests

Before the advent of clinical PET, myocardial perfusion studies with <sup>201</sup>Tl or <sup>99m</sup>Tc-sestamibi, and <sup>67</sup>Ga scintigraphy, were commonly performed to detect and monitor cardiac involvement in sarcoidosis (67). Because of the higher accuracy of PET/CT and CMR, these newer techniques have mostly replaced other radionuclide imaging.

Myocardial perfusion imaging may show patterns of reverse distribution, in which perfusion defects at rest decrease under stress conditions (68). It is believed that reverse redistribution in CS is caused by focal reversible microvascular constriction in coronary arterioles around the granulomas (69). According to the results of a few studies, <sup>99m</sup>Tc-sestamibi seems to be superior to <sup>201</sup>Tl in detecting reverse distribution (67,70).

<sup>67</sup>Ga scintigraphy detects CS during its inflammatory phase, because of accumulation in inflamed areas. <sup>67</sup>Ga scintigraphy can also be used in systemic sarcoidosis. Studies reported a high specificity of almost 100%, whereas sensitivity varied from 0% to 36%, using JMWG as a reference (56). A weak signal from the long-lived isotope with high-energy photon emission explains the low sensitivity.

#### THERAPEUTIC OPTIONS AND PROGNOSIS

Imaging-test-driven evidence of active CS is an indication for treatment, because of the poor prognosis and increased risk of

sudden death. Even though there are no published clinical consensus guidelines, management aims at controlling inflammation and fibrosis. Basic medical treatment is similar to that for dilated cardiomyopathy, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, and  $\beta$ -blocking agents (71). According to Milburn et al. (72), corticosteroids attenuate inflammation by reestablishing balance between type 1 and 2 T-helper cell cytokines, which are altered in sarcoidosis.

Beneficial effects of early corticosteroid therapy on LV function have been reported in several studies (16,73). Corticosteroid use has been associated with maintenance of LV function in patients having normal function at diagnosis and with improvement in patients having moderate LV dysfunction. In contrast, LV function in patients who have severe LV dysfunction is unlikely to improve (74). This benefit of early therapy initiation emphasizes the need for early diagnosis. Although corticosteroids remain the mainstay of treatment, there is still uncertainty about optimal initiation, dosage, or duration of therapy and about effects on the clinical course of CS, as they have not been studied in any randomized, prospective trials.

CS may cause reentrant arrhythmias and therefore increase the risk of sudden cardiac death. Hence, there is a trend toward early implantation of prophylactic defibrillators in patients with biopsy-proven systemic sarcoidosis and positive cardiac imaging (71). Even though there are few clinical data, CS is regarded as a class IIa recommendation for an implantable cardioverter-defibrillator (75).

In addition to device implantation, antiarrhythmic agents are often required in patients with CS to eliminate or reduce recurrent ventricular tachyarrhythmia (76). Analogous to medical therapy and cardiac devices, the indication for antiarrhythmic agents is similar to that in nonsarcoidosis patients.

Ultimately, especially in young patients with severe heart failure refractory to medical therapy, heart transplantation needs to be considered carefully (77). Because of the uncommon nature of CS and concomitant disease in other organs, the number of patients undergoing heart transplantation is small (71). But notably, outcomes have been reported to be identical or even superior to those in nonsarcoidosis patients (78).

#### SUMMARY

The importance of early recognition of cardiac involvement by sarcoidosis is increasingly recognized because of its implications for adverse outcome. <sup>18</sup>F-FDG PET/CT and delayed-enhancement CMR are powerful imaging techniques for accurate detection and

therapy monitoring. Although protocols for imaging are increasingly well defined for these modalities, the clinical evidence for their accuracy, their relative value compared with each other and with alternative strategies, and the most useful indications is still limited to small-scale observational studies. To address the existing uncertainties and to standardize clinical practice, larger prospective trials including high-end imaging are necessary in CS. It is expected that such trials will better define the value of imaging, and, ultimately, improve outcome through test-driven personalized treatment.

## ACKNOWLEDGMENT

The images shown in Figures 3–5 were obtained during the tenure of Dr. Bengel at Johns Hopkins University, Baltimore, MD.

## REFERENCES

- Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med.* 1999;160:736–755.
- Rybicki BA, Iannuzzi MC. Epidemiology of sarcoidosis: recent advances and future prospects. *Semin Respir Crit Care Med.* 2007;28:22–35.
- Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis environmental and occupational risk factors. *Am J Respir Crit Care Med.* 2004;170:1324–1330.
- du Bois RM, Goh N, McGrath D, Cullinan P. Is there a role for microorganisms in the pathogenesis of sarcoidosis? *J Intern Med.* 2003;253:4–17.
- Rybicki BA, Iannuzzi MC, Frederick MM, et al. Familial aggregation of sarcoidosis: a case-control etiologic study of sarcoidosis (ACCESS). *Am J Respir Crit Care Med.* 2001;164:2085–2091.
- Doughan AR, Williams BR. Cardiac sarcoidosis. *Heart.* 2006;92:282–288.
- Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation.* 1978;58:1204–1211.
- Design of a case control etiologic study of sarcoidosis (ACCESS). *J Clin Epidemiol.* 1999;52:1173–1186.
- Matsui Y, Iwai K, Tachibana T, et al. Clinicopathological study of fatal myocardial sarcoidosis. *Ann N Y Acad Sci.* 1976;278:455–469.
- Sharma OP, Maheshwari A, Thaker K. Myocardial sarcoidosis. *Chest.* 1993;103:253–258.
- Mehta D, Lubitz SA, Frankel Z, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest.* 2008;133:1426–1435.
- Gideon NM, Mannino DM. Sarcoidosis mortality in the United States, 1979–1991: an analysis of multiple-cause mortality data. *Am J Med.* 1996;100:423–427.
- Tachibana T, Iwai K, Takemura T. Study on cause of death in the patients with sarcoidosis in Japan. *Vasc Diffuse Lung Dis.* 1992;9:307.
- Tavora F, Cresswell N, Li L, Ripple M, Solomon C, Burke A. Comparison of necropsy findings in patients with sarcoidosis dying suddenly from cardiac sarcoidosis versus dying suddenly from other causes. *Am J Cardiol.* 2009;104:571–577.
- Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart: a clinicopathologic study of 35 necropsy patients (group I) and review of 78 previously described necropsy patients (group II). *Am J Med.* 1977;63:86–108.
- Banba K, Kusano KF, Nakamura K, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. *Heart Rhythm.* 2007;4:1292–1299.
- Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. *Circ Arrhythm Electrophysiol.* 2011;4:303–309.
- Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. *Heart.* 2011;97:2078–2087.
- Furushima H, Chinushi M, Sugiura H, Kasai H, Washizuka T, Aizawa Y. Ventricular tachyarrhythmia associated with cardiac sarcoidosis: its mechanisms and outcome. *Clin Cardiol.* 2004;27:217–222.
- Sekiguchi M, Numao Y, Imai M, Furue T, Mikami R. Clinical and histopathological profile of sarcoidosis of the heart and acute idiopathic myocarditis: concepts through a study employing endomyocardial biopsy. I. Sarcoidosis. *Jpn Circ J.* 1980;44:249–263.
- Yazaki Y, Isobe M, Hiroe M, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol.* 2001;88:1006–1010.
- Sekhri V, Sanal S, Delorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. *Arch Med Sci.* 2011;7:546–554.
- Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. *J Cardiovasc Electrophysiol.* 2009;20:578–583.
- Hamzeh NY, Wamboldt FS, Weinberger HD. Management of cardiac sarcoidosis in the United States: a Delphi study. *Chest.* 2012;141:154–162.
- Okura Y, Dec GW, Hare JM, et al. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. *J Am Coll Cardiol.* 2003;41:322–329.
- Kim JS, Judson MA, Donnino R, et al. Cardiac sarcoidosis. *Am Heart J.* 2009;157:9–21.
- Schuller JL, Lowery CM, Zipse M, et al. Diagnostic utility of signal-averaged electrocardiography for detection of cardiac sarcoidosis. *Ann Noninvasive Electrocardiol.* 2011;16:70–76.
- Freeman AM, Curran-Everett D, Weinberger HD, et al. Predictors of cardiac sarcoidosis using commonly available cardiac studies. *Am J Cardiol.* 2013;112:280–285.
- Uemura A, Morimoto S, Kato Y, et al. Relationship between basal thinning of the interventricular septum and atrioventricular block in patients with cardiac sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2005;22:63–65.
- Smedema JP. Tissue Doppler imaging in cardiac sarcoidosis. *Eur J Echocardiogr.* 2008;9:579–580.
- Chapelon-Abrie C, de Zuttere D, Duhaut P, et al. Cardiac sarcoidosis: a retrospective study of 41 cases. *Medicine (Baltimore).* 2004;83:315–334.
- Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation.* 2007;116:2216–2233.
- Kandolin R, Lehtonen J, Graner M, et al. Diagnosing isolated cardiac sarcoidosis. *J Intern Med.* 2011;270:461–468.
- Nery PB, Keren A, Healey J, Leug E, Beanlands RS, Birnie DH. Isolated cardiac sarcoidosis: establishing the diagnosis with electroanatomic mapping-guided endomyocardial biopsy. *Can J Cardiol.* 2013;29:1015.e1-3.
- Tadamura E, Yamamuro M, Kubo S, et al. Effectiveness of delayed enhanced MRI for identification of cardiac sarcoidosis: comparison with radionuclide imaging. *AJR.* 2005;185:110–115.
- Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. *JACC Cardiovasc Imaging.* 2013;6:501–511.
- Cummings KW, Bhalla S, Javidan-Nejad C, Bierhals AJ, Gutierrez FR, Woodard PK. A pattern-based approach to assessment of delayed enhancement in nonischemic cardiomyopathy at MR imaging. *Radiographics.* 2009;29:89–103.
- Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation.* 2009;120:1969–1977.
- Ichinose A, Otani H, Oikawa M, et al. MRI of cardiac sarcoidosis: basal and subepicardial localization of myocardial lesions and their effect on left ventricular function. *AJR.* 2008;191:862–869.
- Smedema JP, Snoep G, van Kroonenburgh MP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol.* 2005;45:1683–1690.
- Vignaux O, Dhote R, Duboc D, et al. Clinical significance of myocardial magnetic resonance abnormalities in patients with sarcoidosis: a 1-year follow-up study. *Chest.* 2002;122:1895–1901.
- Shimada T, Shimada K, Sakane T, et al. Diagnosis of cardiac sarcoidosis and evaluation of the effects of steroid therapy by gadolinium-DTPA-enhanced magnetic resonance imaging. *Am J Med.* 2001;110:520–527.
- Meller J, Sahlmann C-O, Scheel AK. <sup>18</sup>F-FDG PET and PET/CT in fever of unknown origin. *J Nucl Med.* 2007;48:35–45.
- Abel ED. Glucose transport in the heart. *Front Biosci.* 2004;9:201–215.
- Iozzo P, Chareonthaitawee P, Di Terlizzi M, Betteridge DJ, Ferrannini E, Camici PG. Regional myocardial blood flow and glucose utilization during fasting and physiological hyperinsulinemia in humans. *Am J Physiol Endocrinol Metab.* 2002;282:E1163–E1171.
- Maurer AH, Burshteyn M, Adler LP, Gaughan JP, Steiner RM. Variable cardiac <sup>18</sup>F-FDG patterns seen in oncologic positron emission tomography computed tomography: importance for differentiating normal physiology from cardiac and paracardiac disease. *J Thorac Imaging.* 2012;27:263–268.
- Ambrosini V, Zompatori M, Fasano L, et al. <sup>18</sup>F-FDG PET/CT for the assessment of disease extension and activity in patients with sarcoidosis: results of a preliminary prospective study. *Clin Nucl Med.* 2013;38:e171–e177.

48. Harisankar CN, Mittal BR, Agrawal KL, Abrar ML, Bhattacharya A. Utility of high fat and low carbohydrate diet in suppressing myocardial FDG uptake. *J Nucl Cardiol*. 2011;18:926–936.
49. Williams G, Kolodny GM. Suppression of myocardial <sup>18</sup>F-FDG uptake by preparing patients with a high-fat, low-carbohydrate diet. *AJR*. 2008;190:W151–W156.
50. Ishimaru S, Tsujino I, Takei T, et al. Focal uptake on <sup>18</sup>F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. *Eur Heart J*. 2005;26:1538–1543.
51. Morooka M, Moroi M, Ito K, Minamimoto R. Heparin vs. long fasting method: which inhibits the FDG myocardial physiological uptake more strongly? [abstract]. *J Nucl Med*. 2013;54(suppl):406P.
52. McArdle BA, Leung E, Ohira H, et al. The role of F(18)-fluorodeoxyglucose positron emission tomography in guiding diagnosis and management in patients with known or suspected cardiac sarcoidosis. *J Nucl Cardiol*. 2013;20:297–306.
53. Youssef G, Leung E, Mylonas I, et al. The use of <sup>18</sup>F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med*. 2012;53:241–248.
54. Israel O, Weiler-Sagie M, Rispler S, et al. PET/CT quantitation of the effect of patient-related factors on cardiac <sup>18</sup>F-FDG uptake. *J Nucl Med*. 2007;48:234–239.
55. Okumura W, Iwasaki T, Toyama T, et al. Usefulness of fasting <sup>18</sup>F-FDG PET in identification of cardiac sarcoidosis. *J Nucl Med*. 2004;45:1989–1998.
56. Yamagishi H, Shirai N, Takagi M, et al. Identification of cardiac sarcoidosis with <sup>13</sup>N-NH<sub>3</sub>/<sup>18</sup>F-FDG PET. *J Nucl Med*. 2003;44:1030–1036.
57. Nelson JE, Kirschner PA, Teirstein AS. Sarcoidosis presenting as heart disease. *Sarcoidosis Vasc Diffuse Lung Dis*. 1996;13:178–182.
58. Ohira H, Tsujino I, Ishimaru S, et al. Myocardial imaging with <sup>18</sup>F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. *Eur J Nucl Med Mol Imaging*. 2008;35:933–941.
59. Soussan M, Brillet PY, Nunes H, et al. Clinical value of a high-fat and low-carbohydrate diet before FDG-PET/CT for evaluation of patients with suspected cardiac sarcoidosis. *J Nucl Cardiol*. 2013;20:120–127.
60. Campbell P, Stewart GC, Padera RF, et al. Evaluation for cardiac sarcoidosis: uncertainty despite contemporary multi-modality imaging [abstract]. *J Card Fail*. 2010;16(suppl):S107.
61. Jamar F, Buscombe J, Chiti A, et al. EANM/SNMMI guideline for <sup>18</sup>F-FDG use in inflammation and infection. *J Nucl Med*. 2013;54:647–658.
62. McArdle BA, Birnie DH, Klein R, et al. Is there an association between clinical presentation and the location and extent of myocardial involvement of cardiac sarcoidosis as assessed by <sup>18</sup>F-fluorodeoxyglucose positron emission tomography? *Circ Cardiovasc Imaging*. 2013;6:617–626.
63. Blankstein R, Naya M, Osborne M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoid. *J Am Coll Cardiol*. October 1, 2013 [Epub ahead of print].
64. DiFilippo FP, Brunken RC. Do implanted pacemaker leads and ICD leads cause metal-related artifact in cardiac PET/CT? *J Nucl Med*. 2005;46:436–443.
65. Ghafarian P, Aghamiri SM, Ay MR, et al. Is metal artefact reduction mandatory in cardiac PET/CT imaging in the presence of pacemaker and implantable cardioverter defibrillator leads? *Eur J Nucl Med Mol Imaging*. 2011;38:252–262.
66. Schneider S, Batrice A, Rischpler C, Eiber M, Ibrahim T, Nekolla SG. Utility of multimodal cardiac imaging with PET/MRI in cardiac sarcoidosis: implications for diagnosis, monitoring and treatment. *Eur Heart J*. 2013 Aug 23, 2013 [Epub ahead of print].
67. Le Guludec D, Menad F, Faraggi M, Weinmann P, Battesti JP, Valeyre D. Myocardial sarcoidosis: clinical value of technetium-99m sestamibi tomoscintigraphy. *Chest*. 1994;106:1675–1682.
68. Okayama K, Kurata C, Tawarahara K, Wakabayashi Y, Chida K, Sato A. Diagnostic and prognostic value of myocardial scintigraphy with thallium-201 and gallium-67 in cardiac sarcoidosis. *Chest*. 1995;107:330–334.
69. Hirose Y, Ishida Y, Hayashida K, et al. Myocardial involvement in patients with sarcoidosis: an analysis of 75 patients. *Clin Nucl Med*. 1994;19:522–526.
70. Eguchi M, Tsuchihashi K, Hotta D, et al. Technetium-99m sestamibi/tetrofosmin myocardial perfusion scanning in cardiac and noncardiac sarcoidosis. *Cardiology*. 2000;94:193–199.
71. Dubrey SW, Falk RH. Diagnosis and management of cardiac sarcoidosis. *Prog Cardiovasc Dis*. 2010;52:336–346.
72. Milburn HJ, Poulter LW, Dilmecc A, Cochrane GM, Kemeny DM. Corticosteroids restore the balance between locally produced Th1 and Th2 cytokines and immunoglobulin isotypes to normal in sarcoid lung. *Clin Exp Immunol*. 1997;108:105–113.
73. Chiu CZ, Nakatani S, Zhang G, et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. *Am J Cardiol*. 2005;95:143–146.
74. Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. *Can J Cardiol*. 2013;29:1034–1041.
75. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2013;61:e6–e75.
76. Bussinguer M, Danielian A, Sharma OP. Cardiac sarcoidosis: diagnosis and management. *Curr Treat Options Cardiovasc Med*. 2012;14:652–664.
77. Akashi H, Kato TS, Takayama H, et al. Outcome of patients with cardiac sarcoidosis undergoing cardiac transplantation: single-center retrospective analysis. *J Cardiol*. 2012;60:407–410.
78. Zaidi AR, Zaidi A, Vaitkus PT. Outcome of heart transplantation in patients with sarcoid cardiomyopathy. *J Heart Lung Transplant*. 2007;26:714–717.
79. Terasaki F, Tsuji M, Kizawa S, et al. Sarcoidosis does not belong to or overlap with immunoglobulin G4-related diseases based on an assessment of serum immunoglobulin G4 levels in cardiac and noncardiac sarcoidosis. *Hum Pathol*. 2012;43:818–825.
80. Kadosh B, Steele J, Gulkarov I, Mamkin I. Cardiac sarcoidosis. *J Am Coll Cardiol*. 2013;61:1548.