PET/CT Evaluation of Cardiac Sarcoidosis

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KEYWORDS

• Cardiac sarcoidosis • Positron emission tomography • Fluorine-18 deoxyglucose

KEY POINTS

- Sarcoidosis can involve the heart at with resultant significant morbidity and mortality.
- PET/CT is the most accurate method by which to diagnose cardiac sarcoidosis.
- Patient preparation prior to the PET/CT cardiac sarcoid study is critical to ensure diagnostic images are obtained.
- PET/CT detection of both active inflammation and scar has diagnostic, prognostic, and therapeutic importance.
- Ongoing areas of research include the use of PET to quantify the extent of myocardial inflammation and the discrepancies in myocardial blood flow in the cardiac sarcoidosis population.

INTRODUCTION

The increasing implementation of advanced cardiovascular imaging in the form of cardiac PET/CT has had a significant impact on the management of cardiac sarcoidosis (CS), one that continues to evolve. Sarcoidosis is characterized histologically by the presence of noncaseating granulomas, with a predilection for the pulmonary system but with the ability to involve nearly every organ. Although the development of sarcoidosis is believed the sequelae of an exaggerated immune or inflammatory response to an inciting infectious or environmental trigger, the specific etiology of this disease remains elusive. The exact prevalence of sarcoidosis is unknown but tends to be highest in women ages 25 years to 44 years (100 in 100,000) and in African Americans.[1,2] There is also a geographic predilection for the development of sarcoidosis, with some regions within the United States reporting rates as high as 330 in 100,000 patients.[2] The course of the disease is variable, with approximately two-thirds of patients experiencing spontaneous remission and the remaining one-third developing either a stable or progressive course.[3]

The rate of cardiac involvement by sarcoidosis, otherwise termed CS, is variable and ranges from 20% to 75%.[4,5] Furthermore, CS accounts for one-fourth of sarcoid-related mortality in the United States and upward of 85% of death attributed to sarcoidosis in the Japanese population.[4,6] The high rate of involvement of the cardiovascular system by sarcoidosis coupled with the potential lethal outcomes has rendered accurate and timely diagnosis of this disease entity as imperative to patient care. Unfortunately, the prompt recognition of CS itself may be elusive, with both traditional imaging techniques as well as invasive endomyocardial biopsies often providing a low diagnostic yield.[6] Consequently, there have been focused efforts to enhance or to develop noninvasive imaging techniques that not only detect CS but also potentially provide therapeutic and prognostic information for the treating clinician. Cardiac PET/CT has emerged as a leading modality

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by which to begin to address these issues for the CS patient population.

INDICATIONS FOR CARDIAC PET/CT FOR CARDIAC SARCOIDOSIS

The limited size of investigational studies involving the CS population and the lack of available prospective data have resulted in the inability to formulate evidence-based guidelines to determine which patients warrant PET/CT imaging for the assessment of CS.[7,8] The traditional diagnostic guideline for the detection of CS, as outlined by the Japanese Ministry of Health, Labour and Welfare, did not include PET/CT imaging.[6] The more contemporary guidelines, as proposed by the Heart Rhythm Society in 2014 and the revised Japanese Society of Cardiac Sarcoidosis in 2017, did include PET/CT as a component of the diagnostic algorithm.[9,10] The surmised improved diagnostic capabilities of the Heart Rhythm Society and the revised Japanese Society of Sarcoidosis criteria due to the inclusion of PET/CT have yet to be systematically tested.

Given the absence of evidence-based guidelines, Chareonthaitawee and colleagues[8] have issued a joint expert consensus document on behalf of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the American Society of Nuclear Cardiology (ASNC), which outlines the following 4 patient scenarios for which cardiac PET/CT for the assessment of CS could be considered:

- Histologic evidence of extra CS *and* 1 or more abnormal screening results for CS (ECG demonstrating completed left and/or right bundle branch block, unexplained Q waves in 2 or more ECG leads, echocardiographic evidence of regional wall motion abnormalities and/or aneurysms, basal septal thinning or depressed left ventricular ejection fraction (<50%), ventricular tachycardia, MR imaging evidence of midmyocardial inflammation, and, lastly, unexplained palpitations or syncope)
- New-onset sustained second-degree or third-degree atrioventricular block *and* age less than 60 years old
- Idiopathic sustained ventricular tachycardia
- Serial studies to assess response to treatment

As cardiac PET/CT is further refined, standardized, and utilized and as awareness of CS expands, future evidenced-based guidelines may become available. Until that juncture, however, the aforementioned 4 patient scenarios as outlined by experts in the field provide a useful tool for clinicians in determining when to order a cardiac PET/CT for the evaluation of CS.

PATIENT PREPARATION FOR CARDIAC PET/CT FOR CARDIAC SARCOIDOSIS

Optimal patient preparation is essential when using fluorine-18 deoxyglucose (^{18}F-FDG) PET/CT to evaluate for CS. The predilection for ^{18}F-FDG accumulation within inflamed tissues, in particular macrophages, is the pathophysiologic underpinning of ^{18}F-FDG PET/CT CS imaging. It is imperative, therefore, that physiologic myocardial uptake of ^{18}F-FDG be suppressed to identify areas of pathologic involvement in a manner tht is both accurate and reproducible.[11] Consequently, several methods have been developed to achieve suppression of physiologic ^{18}F-FDG uptake.

Cardiac myocyte metabolism is a dynamic and complex process that involves selective uses of variable fuel sources, including free fatty acids, glucose, and ketones.[12] Which substrate is preferentially used is determined by a combination of physiologic variables, including substrate availability, myocardial blood flow (MBF), and serum insulin concentration.[13] In the postprandial state, increased serum insulin levels result in glucose transporter 1 and glucose transporter 2 upregulation, resulting in increased myocyte glucose uptake.[14] One method by which to avoid physiologic myocyte uptake is instituting a prolonged fast. During the fasting state, lipids in lieu of glucose become the preferred myocyte substrate and this is particularly the case with prolonged fasting of upward of 18 hours.[15] Prior studies have demonstrated that the success rates of fasting protocols in suppressing physiologic ^{18}F-FDG range from 62% to 90% (**Fig. 1**).[16–19] Unfortunately, prolonged fasting often proves laborious, and the lack of patient compliance is a concern.[20,21] Furthermore, hypoglycemia potentially develops with the use of this technique.[16]

A potential alternative to the prolonged fast is the implementation of a diet consisting of high fat and low carbohydrates. Studies have demonstrated that this technique may be superior to fasting alone.[22] Concern again arises, however, regarding the ability of patients to adhere to such dietary recommendations due to potential religious or cultural beliefs or due to an inability to tolerate such a diet. Another potential means by which to increase serum free fatty acid levels is via the use of unfractionated heparin (typically administered dose is 50 U/kg approximately 15 minutes prior to ^{18}F-FDG administration), which stimulates lipolysis.[16,23,24] A prior investigation of healthy volunteers demonstrated that unfractionated heparin could successfully increase free fatty acid levels without prolonging the partial thromboplastin time.[25] Subsequent evaluations of the

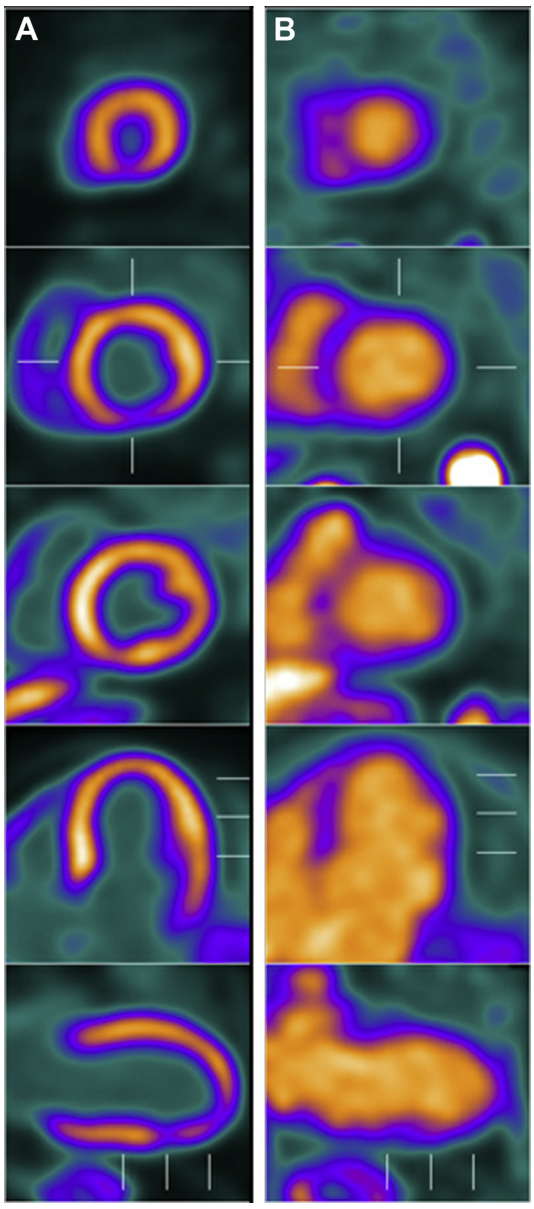

Fig. 1. ^{18}F-FDG and N-13 ammonia PET/CT for CS. No perfusion defects are present on N-13 ammonia imaging (*A*). ^{18}F-FDG is present only in the blood pool with no myocardial uptake, consistent with effective suppression of physiologic myocardial glucose and a normal study (*B*). *Panel A* is the perfusion panel as listed. From top to bottom is apex, mid, and base then horizontal and vertical long axis. *Panel B* is FDG panel as listed and from top to bottom is apex, mid, and base then horizontal and vertical long axis.

efficacy of unfractionated heparin, however, have reported conflicting results rendering its utilization uncertain.[16,17,24]

Given the myriad options for patient preparation and the potential confusion that may subsequently result, there has been a call to standardize protocols and to develop preparation guidelines.[11] As a result, both the SNMMI and the ASNC have officially recommended at least 2 high-fat (>35 g) and low-carbohydrate (<3 g) meals a day prior to the anticipated ^{18}F-FDG PET/CT followed by a fast of 4 hours to 12 hours prior to the study, with an alternative a prolonged fast of 18 hours.[26] To implement such guidelines, patient education prior to the study is imperative, with materials to facilitate such a discussion having been previously published.[27]

Regardless of the exact methodology used to prepare patients for the study, nuclear physicians should be aware of 2 specific patient populations that provide unique challenges. The first is diabetic patients for whom an optimal dietary preparation has not been identified. Insulin-dependent diabetic patients should continue basal insulin with minimization of rapid-acting insulin. If needed, a sliding scale may be implemented the day before but not the day of the study.[8] For non–insulin-dependent patients, oral hypoglycemic agents should be avoided during periods of prescribed fasting.[8]

Unfortunately, despite extensive efforts to prohibit physiologic myocardial ^{18}F-FDG uptake, approximately 30% of potential CS patients have an inconclusive scan, resulting in patient and provider frustration, nondiagnostic exposure to radiation, and financial loss (**Fig. 2**).[11,16,20,28–30] Consequently, the development of a radiotracer that does not demonstrate physiologic myocardial uptake and does not require dietary preparation would be of great potential benefit to the PET/CT assessment of the CS population. Gallium-68 (^{68}Ga) DOTATAE, a radiotracer targeted toward somatostatin receptors, is a potential alternative to ^{18}F-FDG in imaging in the CS patient. Initially developed to assess neuroendocrine tumors,[31] ^{68}Ga-DOTATAE also targets activated macrophages and multinucleated cells, which express somatostatin receptors, but does not target normal myocardial tissue, which lacks such receptors.[32] Therefore, ^{68}Ga-DOTATAE potentially obviates patient preparation protocols and could limit the incidence of uninterpretable scans. An initial feasibility study[33] followed by a small trial of 19 patients demonstrated promising results,[32] with further investigations anticipated.

PERFORMANCE OF PET/CT FOR ASSESSMENT OF CARDIAC SARCOIDOSIS

PET/CT assessment of CS is composed of 2 resting images—one to assess myocardial perfusion and the second to assess myocardial

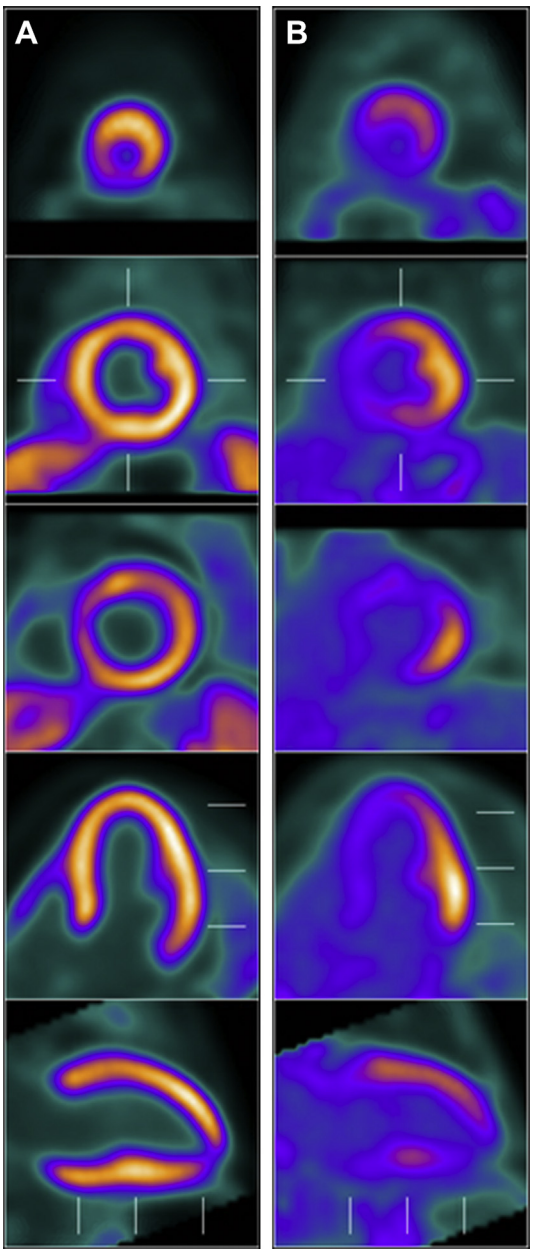

Fig. 2. ^{18}F-FDG and N-13 ammonia PET/CT for CS. No perfusion defects are present on N-13 ammonia imaging (*A*). ^{18}F-FDG images demonstrated diffuse uptake throughout the entire myocardium with areas of focal on diffuse uptake. These findings are nonspecific and are likely secondary to ineffective suppression of physiologic myocardial glucose uptake (*B*). *Panel A* is the perfusion panel as listed. From top to bottom is apex, mid, and base then horizontal and vertical long axis. *Panel B* is FDG panel as listed and from top to bottom is apex, mid, and base then horizontal and vertical long axis.

inflammation. A gated perfusion study is performed first utilizing either N-13 ammonia or rubidium-82. Gating is critical because it allows for assessment of left ventricular ejection fraction as well as regional wall motion abnormalities. Atter the perfusion study, the inflammatory assessment scan is performed, with ^{18}F-FDG the most common radiotracer used. Approximately a 60-minute to 90-minute uptake period for ^{18}F-FDG is required, followed by a 10-minute to 30-minute nongated acquisition.[34] The field of view for the inflammation acquisition scan may be focused on the heart alone or may be extended to include base of the skill to the upper thigh. The latter is typically recommended if clinical suspicion of extracardiac sarcoid exists or a recent whole-body investigation has not been completed, because the detection of extracardiac disease may have diagnostic and prognostic implications as well as potentially providing targets for subsequent biopsy attempts (**Fig. 3**).[8]

INTERPRETATION OF PET/CT CARDIAC SARCOIDOSIS STUDIES

As recommended with traditional PET/CT perfusion imaging, a systematic approach to image interpretation is considered optimal practice. Image interpretation begins with quality-control assessment, including determination of proper coregistration between the transmission (CT) and emission (PET) scans.[34] Misalignment between the 2 scans can occur for multiple reasons, including voluntary and involuntary patient movement.[35] Prior studies have reported that upward of 40% of cardiac PET/CT scans demonstrate false-positive perfusion defects secondary to misregistration.[36] Careful attention should be made for anterior and lateral myocardial perfusion defects because these territories are most prone to misalignment artifacts between the transmission and emission images. Another critical step in the quality-control process is to ensure that there is adequate suppression of physiologic myocardial ^{18}F-FDG uptake. Adequate suppression is considered to be no visible uptake or at least uptake lower than the blood pool.[26]

After determination of the quality of the study, the authors' typical practice is to assess left ventricular size and ejection fraction. Subsequently, a simultaneous qualitative assessment is performed of both the myocardial perfusion and the inflammatory images.[37,38] A resting myocardial perfusion defect could be attributed to microvascular compression from inflammation or may be due to scar. If concurrent ^{18}F-FDG is noted in the same territory, then the perfusion defect is likely secondary to inflammation (**Fig. 4**). If ^{18}F-FDG uptake is lacking in this territory and if a regional wall motion abnormality exits, then scar is favored (**Fig. 5**). Myocardial inflammation secondary to

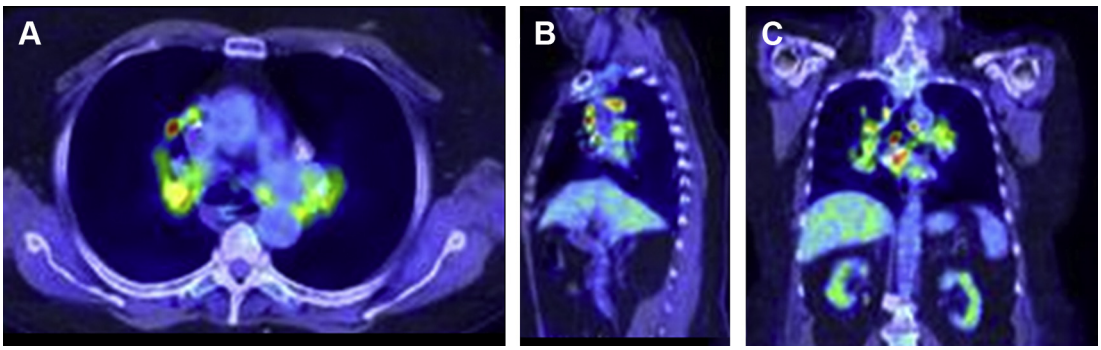

Fig. 3. ^{18}F-FDG PET/CT for CS axial (*A*), sagittal (*B*), and coronal (*C*) chest images, demonstrating extracardiac manifesting as 18F-FDG-avid hilar lymphadenopathy.

CS manifests as patchy or focal on diffuse ^{18}F-FDG uptake, which may or may not have correspondent myocardial perfusion abnormalities. Care should be taken to not misinterpret focal ^{18}F-FDG surrounding implantable cardiac leads as pathologic[39] or isolated lateral ^{18}F-FDG uptake, which may be a nonspecific finding.[8] Quantitative assessment of myocardial inflammation by determination of ^{18}F-FDG standard uptake value (SUV) is an area of active research interest. Initial studies have demonstrated the determination of SUV may improve ^{18}F-FDG PET/CT specificity for the detection of CS without compromising sensitivity.[30,40] Currently, however, there is no specific SUV threshold that can be used to delineate inflamed from normal myocardial tissue.

After assessment of the myocardial perfusion and inflammatory images, extracardiac structures should be evaluated for both areas of sarcoid involvement and for incident findings. With the advent of CT as the transmission source for PET imaging, it has been reported that as many as half of all cardiac studies contain an extracardiac incidental finding worth including in the final report.[41–43] Finally, if available, prior PET/CT CS studies should be compared for any change because this may have implications for subsequent clinical decision making.

CLINICAL RELEVANCE OF THE PET/CT CARDIAC SARCOIDOSIS STUDY

The results of the PET/CT examination have diagnostic, prognostic, and therapeutic ramifications. In regard to diagnosis, PET/CT has the highest diagnostic accuracy among both invasive and noninvasive techniques, with a meta-analysis of 7 studies involving 164 patients with systemic sarcoidosis reporting a sensitivity of 89% and a specificity of 78%.[44] In terms of prognosis, the combination of both a perfusion and ^{18}F-FDG abnormality portends a worse outcome ,with a reported 4-fold increase in the annual rate of malignant arrhythmias and mortality compared with patients with normal images.[45] This finding remains significant even after adjusting for left ventricular ejection fraction and clinical variables. Furthermore, abnormal right ventricular ^{18}F-FDG uptake also demonstrated a significant negative influence on patient outcomes.[45] Using PET/CT to assess therapeutic response is also of great interest. A study of 95 patients demonstrated initiation of immunosuppressive therapy prior to deterioration in cardiac systolic function resulted in excellent clinical outcomes.[46] Additional investigations demonstrated that reduction of ^{18}F-FDG after initiation of therapy, as noted on PET/CT imaging, correlated with improvement in left ventricular ejection fraction as well as a decrease in major associated cardiovascular events.[47,48] Furthermore, Muser and colleagues[49] have demonstrated the utility of PET/CT imaging in assessing the CS patient prior to electrophysiologic anatomic mapping and potential ablation therapy, noting that abnormal electrograms were more likely in areas of a lower degree of inflammation as determined by PET and that a positive PET/CT for CS at baseline or lack of improvement on serial PET/CT imaging portended worse arrhythmia-free survivals in patients undergoing catheter ablation therapy.[50] Standard methodology for determining changes from one PET/CT study to another for the CS patient is lacking. Attempts have been made to implement quantitative techniques in the form of comparing SUV maximum as well as the total volume of myocardium demonstrating abnormal ^{18}F-FDG uptake between serial examinations.[25,47,51] What constitutes a meaningful change in SUV, however, is uncertain, with some investigators proposing that at least a 20% difference should be seen before declaring a difference between studies.[25] Further investigations are required to help clarify what constitutes a therapeutic response or failure.

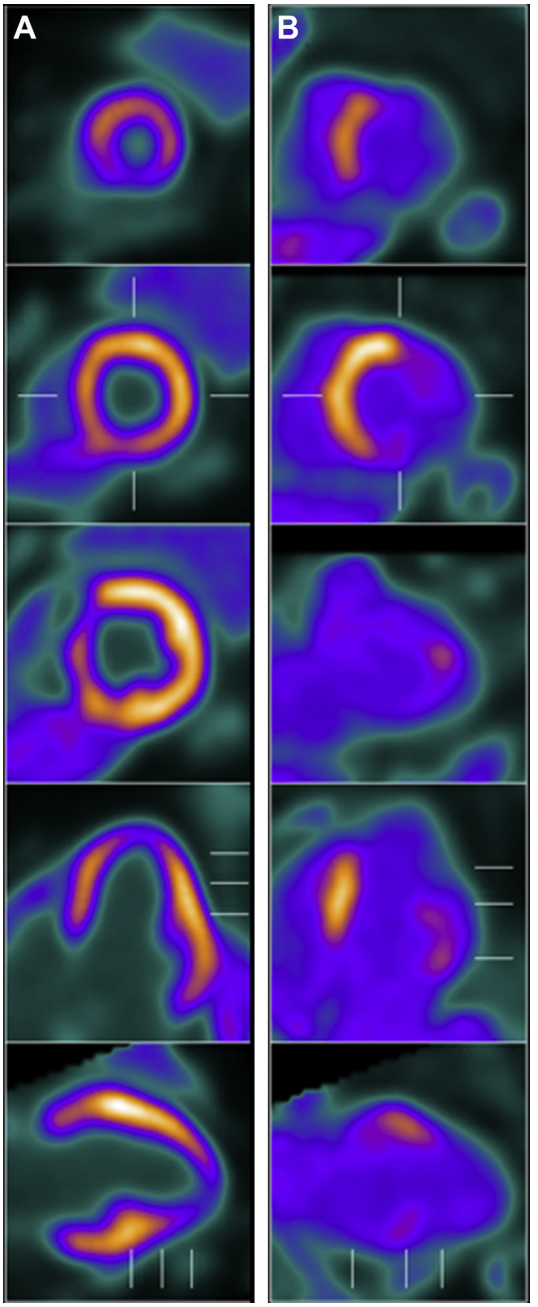

Fig. 4. ^{18}F-FDG and N-13 ammonia PET/CT for CS. A myocardial perfusion defect is present in the septum on N-13 ammonia imaging (*A*) with corresponding ^{18}F-FDG uptake in the same territory (*B*) consistent with active CS.

PET/CT COMPARED WITH ALTERNATIVE IMAGING MODALITIES FOR THE DETECTION OF CARDIAC SARCOIDOSIS

Alternatives to PET/CT imaging for the assessment of CS include single-photon emission CT (SPECT), echocardiography, and MR imaging. In regard to SPECT techniques, both technetium Tc 99m (^{99m}Tc) and thallium-201 (^{201}Tl) may demonstrate perfusion defects due to either scar or arteriole constriction secondary to inflammation. If inflammation is present, myocardial perfusion defects may improve or resolve on vasodilator stress imaging (reverse redistribution) due to dilation of the microvasculature that is constricted by inflamed tissue.[52] One study suggested that the finding of reverse redistribution could predict a positive response to immunosuppressive therapy.[53] ^{18}F-FDG PET/CT has a greater sensitivity for the detection of CS than either SPECT ^{99m}Tc-labeled perfusion tracers or SPECT ^{201}Tl and allows for direct detection of inflamed tissues rendering it the preferred modality for this patient population.

Gallium-67 (^{67}Ga) is another SPECT technique that has demonstrated the capability to detect CS. ^{67}Ga is taken up by activated macrophages in inflamed tissue[54] and correlates with both clinical and histologic evidence of CS.[54–56] Furthermore, the presence of ^{67}Ga has therapeutic implications because it is an indicator of steroid responsiveness.[57] Unfortunately, extracardiac uptake of ^{67}Ga may obscure cardiac uptake and thereby limit test sensitivity to less than 40%.[58] Modest improvements to sensitivity have been demonstrated with the concurrent use of ^{99m}Tc-labeled perfusion tracers to delineate the heart; however, sensitivity reaches only 68% with this technique, which unfortunately also entails higher patient radiation exposure.[58,59]

Echocardiography and MR imaging are among the non-nuclear imaging modalities that have been used to assess CS. Cited echocardiographic characteristics of CS include thinning of the basal interventricular septal and regional wall motion abnormalities with or without aneurysm in territories not consistent with a coronary distribution.[5,6] These findings are often not seen until the late stages of CS, however, and have a very low reported sensitivity of 25%.[60] T1-weighted and T2-weighted cardiac MR imaging sequences can be used to detect myocardial inflammation and scar, with sensitivity and specificity of 75% for CS.[61] MR imaging findings also have prognostic and therapeutic importance, as evident in a study demonstrating a 20-fold increase in mortality in patients with abnormal delayed enhancement[61] whereas others have also noted a correlation between decreased delayed enhancement and a positive response to immunosuppressive therapy.[62,63] A particular benefit of MR imaging compared with PET/CT imaging is that it does

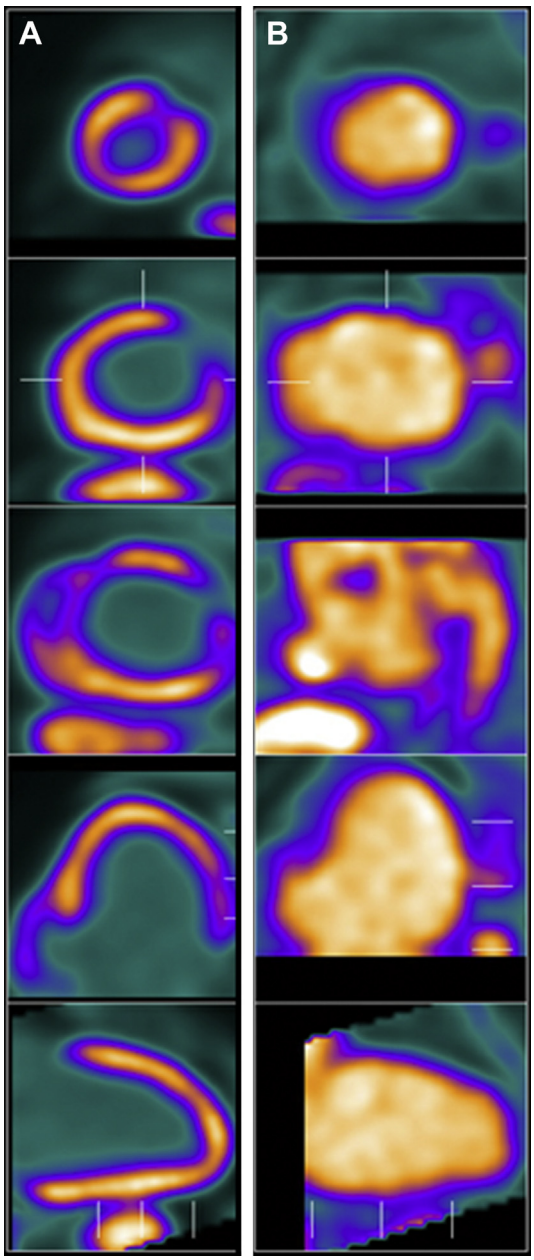

Fig. 5. ^{18}F-FDG and N-13 ammonia PET/CT for CS. A myocardial perfusion defect is present in the apical and anterolateral wall at the mid and base on N-13 ammonia imaging (*A*) without corresponding pathologic ^{18}F-FDG uptake consistent with scar from prior disease (*B*).

not expose patients to ionizing radiation. Limitations of MR imaging, however, include incompatibility with some intracardiac devices, contraindication in severe renal failure, limited accessibility, and difficulty in performing the test for patients who suffer from claustrophobia.

DEVELOPING ADVANCES IN PET IMAGING OF CARDIAC SARCOIDOSIS

Several advances in PET imaging of CS, including the potential use of alternative inflammatory radiotracers in the form of ^{68}Ga-DOTATATE[32,33] as well as the ongoing attempts to quantify inflammatory burden through calculation of SUV,[30,40] have been addressed previously.[30,32,33,40] Additional developing areas of interest include MBF quantification and the coupling of PET with MR imaging to perform hybrid PET/MR imaging of CS.

Recent technological advances in myocardial PET imaging have allowed for more routine quantification of MBF (mL/g/min) and myocardial flow reserve (MBF at stress/MBF at rest). In patients with known or suspected coronary artery disease, MBF has proved both reproducible and accurate while also adding incremental diagnostic and prognostic value.[64,65] Studying a small CS population of 32 patients, Kruse and colleagues[66] demonstrated that MFR was decreased in myocardial segments afflicted by active CS disease and that global MFR was decreased in patients who did not responded to immunosuppressive therapy compared with those who did. Further investigations are needed to validate these findings and to assess the potential role of MBF and MFR in the CS population.

Advancements in semiconductor technology have allowed for the creation of hybrid PET/MR imaging.[67] In the CS population, the hope is that the coregistration of the metabolic imaging capabilities of PET with the morphologic, functional, and tissue imaging of MR imaging may improve diagnostic accuracy and potentially provide further prognostic and therapeutic insights.[68] Initial feasibility studies using the hybrid PET/MR imaging technique have been promising (see **Fig. 5**).[30] Potential challenges for the implementation of hybrid PET/MR imaging are both technical, including the need to refine MR imaging attenuation methods[69] and optimizing acquisition protocols, and practical, including demonstrating that such a hybrid technique provides incremental benefits to the care of the CS patient beyond traditional imaging techniques.

SUMMARY

Accurate diagnosis of CS is critical for diagnostic, therapeutic, and prognostic purposes. Cardiac PET/CT has emerged as the leading modality by which to detect CS. Effective performance of PET/CT for CS entails knowledge of appropriate indications, patient preparation,

study performance, and interpretation and its ultimate bearing on clinical care. Further advances in the technique, including alternative metabolic radiotracers, quantification of MBF, and inflammation and potential hybridization are actively being explored and could further enhance the capabilities of PET imaging.

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