

Review Article

Current uses and understanding of PET imaging in cardiac sarcoidosis

Alekhya Madiraju^{1*}, Abhijit Bhattaru^{1,2*}, Truongan Pham¹, Anish Pundyavana¹, Krishna Vamsi Rojulpote^{1,2}, William Y Raynor¹, Thomas J Werner¹, Abass Alavi¹

¹Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA; ²Division of Cardiology, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA. *Co-first authors.

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Abstract: Sarcoidosis is a systemic disease with unclear etiology characterized by the accumulation of noncaseating, immune granulomas in affected tissues. In cardiac sarcoidosis (CS), white blood cells build up within the heart muscles, causing cardiac abnormalities. Accurate and early diagnosis of CS proves challenging. However, usage of positron emission tomography (PET) imaging, namely ¹⁸F-FDG-PET, has proven successful in diagnosing inflammatory cardiomyopathy. This review seeks to examine the role of PET in managing ventricular tachycardia in cardiac sarcoidosis. PET, in conjunction with cardiac magnetic resonance imaging (CMR) is also endorsed as the premier method for diagnosis and management of arrhythmias associated with CS by The Heart Rhythm Society. After a CS diagnosis, risk stratification of ventricular arrhythmias is a necessity given the potential for sudden cardiac death. ¹⁸F-FDG-PET has been successful in monitoring disease advancement and treatment responses in CS patients. Early stages of CS are often treated with immunosuppression drugs if there are additional signs of VT. Currently, corticosteroid and anti-arrhythmia compounds: methotrexate, cyclophosphamide, infliximab, amiodarone, and azathioprine are used to suppress inflammation. ¹⁸F-FDG-PET has certainly proven to be an incredibly useful and accurate diagnostic tool of CS. While late gadolinium enhancement by CMR is efficient in detecting myocardial necrosis and/or advanced fibrosis scarring, ¹⁸F-FDG portrays the increased uptake level of glucose metabolism. In combination PET/MRI has proven to be more successful in improving the efficacy of both scans, addressing their drawbacks, and highlighting their advantages. Managing CS patients is highly involved in detecting inflammatory regions of the heart. Early recognition prevents cardiac abnormality, mainly VT and VF in CS patients, and extends lifespan.

Keywords: ¹⁸F-FDG, PET, LGE, cardiac sarcoidosis

Introduction

Sarcoidosis is a systemic disease with unclear etiology. It is characterized by the accumulation of noncaseating immune granulomas in affected tissues [1]. Sarcoidosis is predominantly found in the lungs and lymph nodes, but can also affect the bones, liver, and heart [2]. In cardiac sarcoidosis (CS), white blood cells build up within the heart muscles, causing cardiac abnormalities. Despite frequent findings in the myocardium, CS also occurs, in descending order of relevance, in the posterior, anterior, and lateral sides of the left ventricle, the interventricular septum, the right ventricle, and the pericardium [3, 4]. Post inflammatory tissue scarring can potentially result in irregular myocardial electrical conduction, ventricular arrhythmia, and death [2]. Accurate and early diagnosis of CS proves challenging. However, usage of positron emission tomography (PET) imaging, namely ¹⁸F-FDG-PET, has proven successful in diagnosing inflammatory cardiomyopathy. This review seeks to examine the role of PET in managing ventricular tachycardia in cardiac sarcoidosis.

Sarcoidosis has an incidence of 16.5 per 100,000 men and 19 per 100,000 individuals in women [1]. Of all cases pertaining to sarcoidosis, 5-7% of patients are diagnosed

with cardiac involvement [5, 6]. However, sarcoidosis involved with the heart varies across populations in different regions of the world. In general, CS has poor prognosis, and often leads to a high mortality rate [7, 8]. In the United States, CS accounts for roughly 10-25% of all sarcoidosis death [9]. The number of CS cases was also shown to grow exponentially in northern Europe between 1988 and 2012 [10]. CS is the leading cause of death in Japan, ranging between 50-85% from sarcoidosis alone [9, 11, 12]. Between ethnic groups, an autopsy study reported 21% black, 14% white, and 68% Japanese patients, who developed myocardial granuloma accumulation [12]. Systemic sarcoidosis appears to show higher occurrence in females, with the exception of sarcoidosis of the heart, where occurrence is indistinguishable between males and females [13, 14]. Regardless, CS can be fatal, especially if not detected early.

Diagnosis of cardiac sarcoidosis

Diagnosis of CS remains a challenge. The Japanese Ministry of Health and Welfare diagnostic guidelines listed four major and five minor methods for CS detection [15]. However, these methods have limitations. One method by which CS can be diagnosed is with endomyocardial biopsy (EMB). EMB is not only invasive in nature, but its

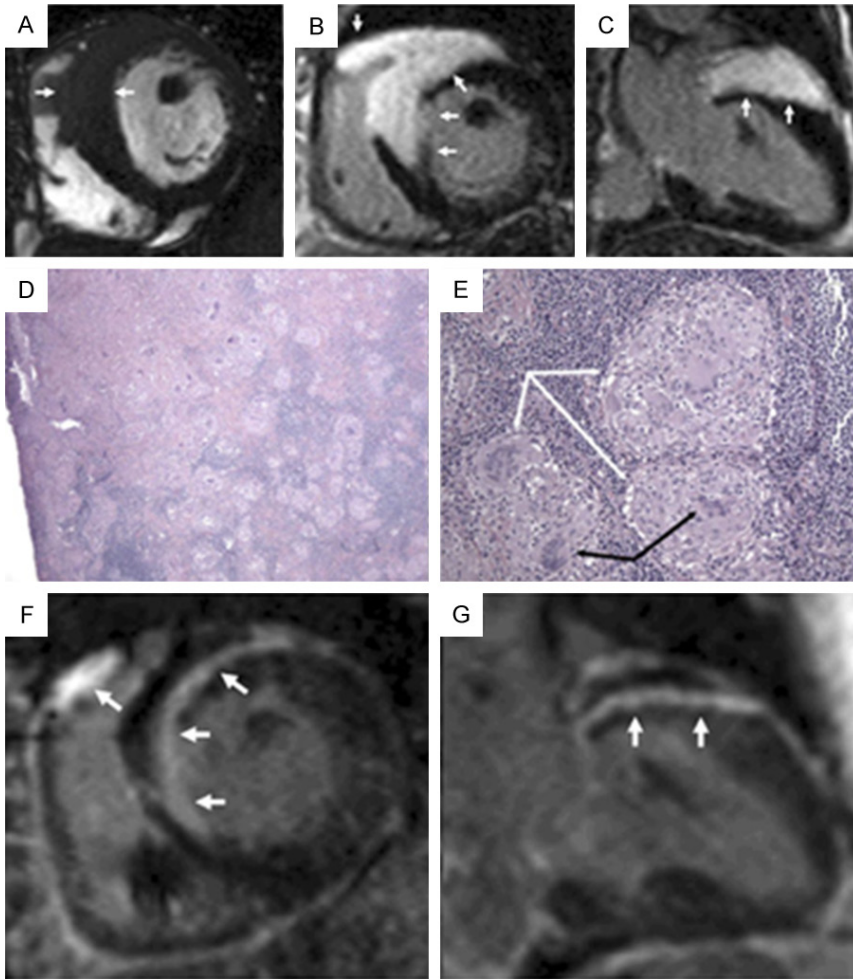


Figure 1. CMR imaging in case of CS. A. Increased thickness (arrows) of mid-basal anterior and anteroseptal walls. B and C. Transmural hyperenhancement (arrows) of mid-basal anterior, anteroseptal, and right ventricular free walls. D and E. Excisional biopsy sample of anterior mediastinal lymph node 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 [29]).

sensitivity for CS is only about 19-30% [16, 17]. Additionally, diagnosing CS through EMB requires a history of known extracardiac sarcoidosis, or previous detection of histologically noncaseating granulomas built up in different organs to achieve an accurate prediction [18]. A study conducted by Kandolin et al demonstrated that repeated EMB or mediastinal lymph node biopsy can also increase detection rate of CS. However, EMB still proves to be an inefficient strategy in clinical diagnosis of isolated CS due to possible false negative results [19-21]. Non-invasive imaging modalities like echocardiography may also be employed in the detection of structural abnormalities relating to CS. However, findings from echocardiography tend to be non-specific anatomic changes that cannot provide a definitive diagnosis. Isolated CS can result in acute cardiac issues without proper detection from an X-ray, a blood test, or a histology presence sample [10]. Guidelines and criteria for isolated myocardial sarcoidosis

are still under investigation. Given the reported mortality rate, precaution and treatment are still recommended in isolated CS with the absence of histological confirmation [22].

Non-invasive techniques involving radioactive tracers such as thallium-201 (^{201}Tl) and gallium-67 (^{67}Ga) scintigraphy in combination with SPECT can be integrated into the diagnosis of CS [23]. For years, gallium-67 has been used in predicting the effects of steroid therapy in CS, but its poor resolution and high false-positive rates prompted the necessity for other imaging techniques [24]. The current imaging technique preferences are cardiovascular MRI (CMR) and ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET). CMR is known to provide high spatial resolution. Delayed gadolinium enhancement and T1 mapping of CMR allow identification of scarring and fibrosis after CS manifestation (Figure 1) [2]. ^{18}F -FDG, a glucose analogue, accumulates at regions where high metabolic activity is present. Since glucose is highly concentrated at inflammatory sites, ^{18}F -FDG acts as a marker, visualized through PET imaging (Figure 2) [25]. It is recommended by Hulten et al that long fasting period (≥ 4 hours) combined with a low carbohydrate diet would allow for superior visualization of myocardial pathology by decreasing physiologic uptake [15]. However, there is ongoing literature about optimal imaging protocols for sarcoidosis using ^{18}F -FDG [104, 105]. Several studies confirm that ^{18}F -FDG

uptakes reveal accurate activity of active inflammatory regions in the heart, as confirmed by EMB and after autopsy [26, 27]. PET scans expose patients to less radiation, exhibit higher sensitivity (71-100%) and better resolution (summarized by Orie et al) [28]. Both CMR and ^{18}F -FDG-PET are the main modalities that are widely used in diagnosing CS.

Arrhythmias in CS

Ventricular arrhythmias act as the emblem of CS with ventricular tachycardia (VT) and ventricular fibrillation (VF) being the most common types of arrhythmias seen in CS patients [30]. It is responsible for 25-65% of sudden deaths caused by CS, which is why VT has also been established as the first indication of a potential CS diagnosis [30, 31]. In addition to known instances of VT, CS is also speculated to be the root cause of 28% of monomorphic VT cases, which are supposedly inexplicable [32].

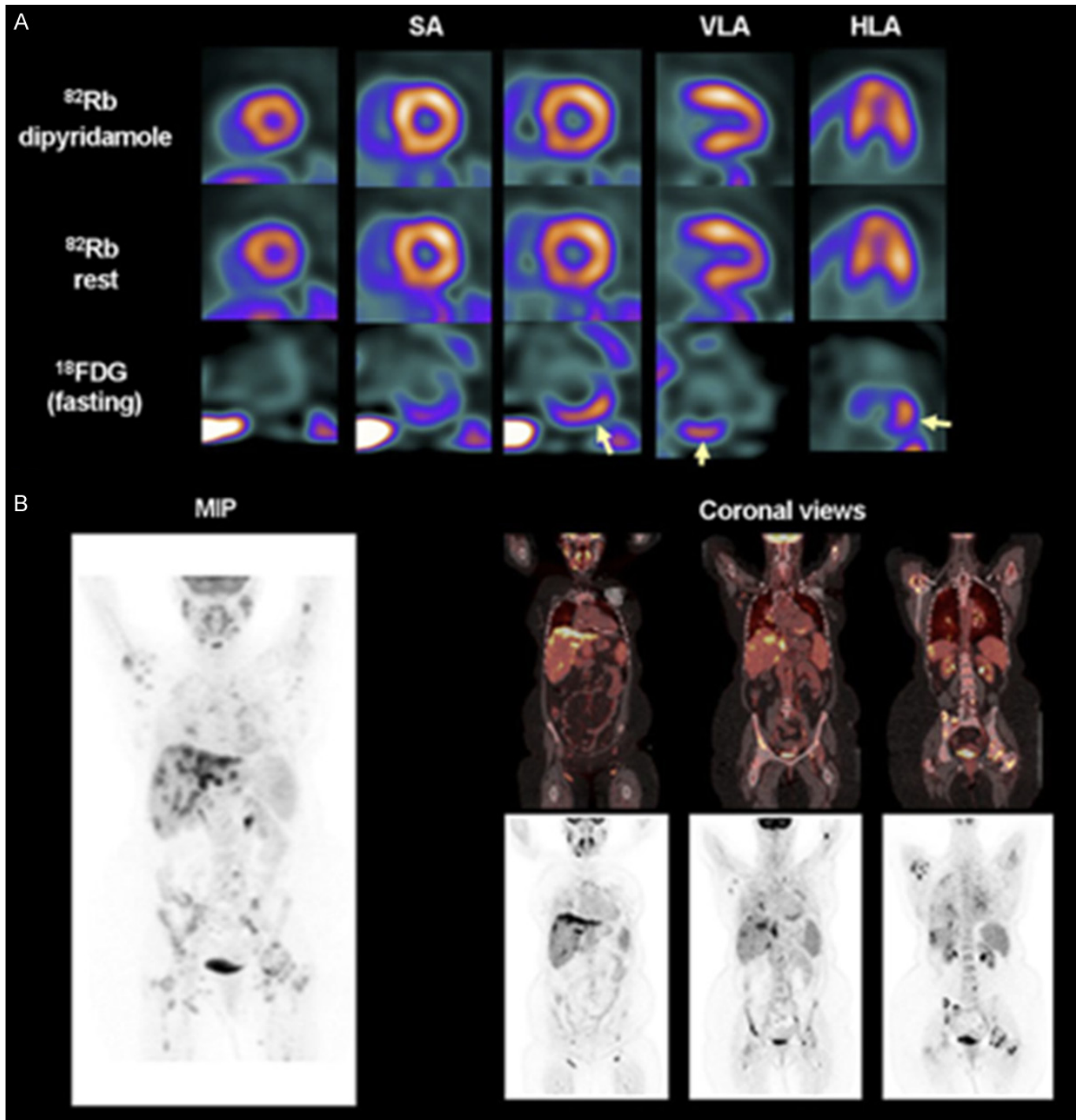


Figure 2. PET/CT study in subjects with CS and extracardiac sarcoidosis. A. Re-angled images of stress (⁸²Rb dipyridamole) and rest (⁸²Rb rest) perfusion rule out ischemic heart disease. Fasting glucose uptake (¹⁸F-FDG) is focally increased in the basal inferior wall, consistent with active CS, and is suppressed in other LV walls (arrows). B. Whole-body study shows multiple extracardiac foci of ¹⁸F-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 (Reprinted with *permission* from [2]).

There have also been some reported instances of supraventricular arrhythmias like atrial fibrillation, atrial flutter, and atrial tachycardias [33]. In a retrospective study interested in examining the prevalence of supraventricular arrhythmias, 18% of biopsy specimens showed signs of atrial fibrillation, followed by 7% showing signs of atrial tachycardias, and finally 5% showing signs of atrial flutter

[34]. Another common conduction abnormality seen in CS patients is atrioventricular block, also known as heart block. Complete heart block has been reported to be found in 23-30% of CS patients [33].

The mechanism for ventricular arrhythmias has been reported to be reentry. One study reports that 68% of

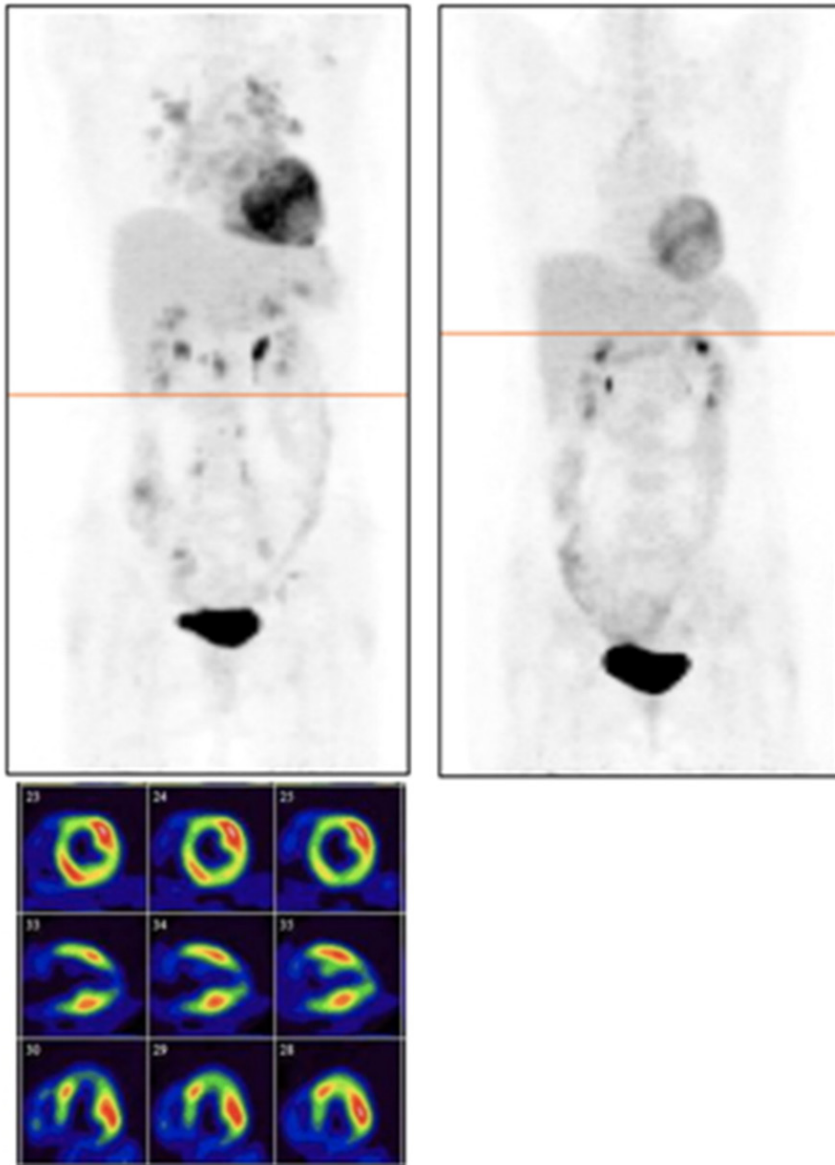


Figure 3. A 52-year-old woman who presented with atrial tachycardia and New York Heart Association class III congestive heart failure. High-resolution chest CT revealed pulmonary sarcoidosis. (Left) Extensive multifocal increased cardiac ^{18}F -FDG is seen on short-, horizontal-, and vertical-axis views (bottom) and on whole-body fasting ^{18}F -FDG PET (top), with increased pulmonary and hilar lymph nodes uptake. Findings were interpreted as positive for cardiac sarcoidosis (Patient was considered positive according to MHLW guidelines). (Right) Two months after treatment with prednisone (30 mg/d), marked improvement is seen in cardiac and pulmonary ^{18}F -FDG uptake (Reprinted with permission from [37]).

observed VTs followed this mechanism [35]. Reentrant VTs are formed in both the active and inactive states of CS, originating from active granulomatous foci and healed or scarred granulomas [33]. However the challenge with CS is the discernibility between the active and inactive phases within the electrophysiologic study, since the inducibility of VTs are different between these two states. This makes treatment for CS via catheter ablation, corticosteroids, and antiarrhythmic agents especially challenging [35]. A study in support of the reentry mechanism demonstrates observation of the electrophysiological

characteristics of 98 patients with VT, concluding that the EPS mapping was consistent with the reentry mechanism [36]. Atrial arrhythmias on the other hand are usually the result of atrial dilatation, pulmonary involvement, or inflammatory atrial foci [30, 33].

Detection of cardiac sarcoid arrhythmias

^{18}F -FDG-PET scans have been used extensively in the diagnosis of CS, and there is much research to suggest that clinicians should consider using ^{18}F -FDG-PET as a diagnostic tool in patients presenting with ventricular arrhythmias (Figure 3). PET, in conjunction with cardiac magnetic resonance imaging (CMR) is also endorsed as the premiere method for diagnosis and management of arrhythmias associated with CS by The Heart Rhythm Society [18].

In a study exploring the prevalence of CS in patients with monomorphic VT, ^{18}F -FDG-PET was used successfully in identifying abnormal myocardial inflammation. Of the 14 patients presenting with MMVT, six had PET scans with increased myocardial inflammation, and four of those six, after extracardiac or endomyocardial biopsy, were found to have had CS as the primary condition for their arrhythmias [31].

A case series with patients diagnosed with CS using ^{18}F -FDG-PET scans identifies a patient with heart failure and VT. This patient underwent an endomyocardial biopsy, which showed no inflammatory infiltrates. However, upon further examination with a cardiac ^{18}F -FDG-PET scan, it was discovered that the patient experienced “decreased perfusion at the anteroapical, mid-anterior, anterolateral, and mid-inferolateral walls, with increased ^{18}F -FDG uptake at the anteroapical, mid-anterior, apical lateral, and mid-lateral walls”. These trends are all consistent with CS, and PET played an essential role in its identification. Another patient in this series was treated for VT via ablation. ^{18}F -FDG-PET scans revealed areas with multinucleated giant cells and lymphocytic infiltration, characteristic specific to sarcoidosis, that were targeted for the VT ablation [38].

^{18}F -FDG-PET uptake has also been documented to change from negative to positive within the short period of 9

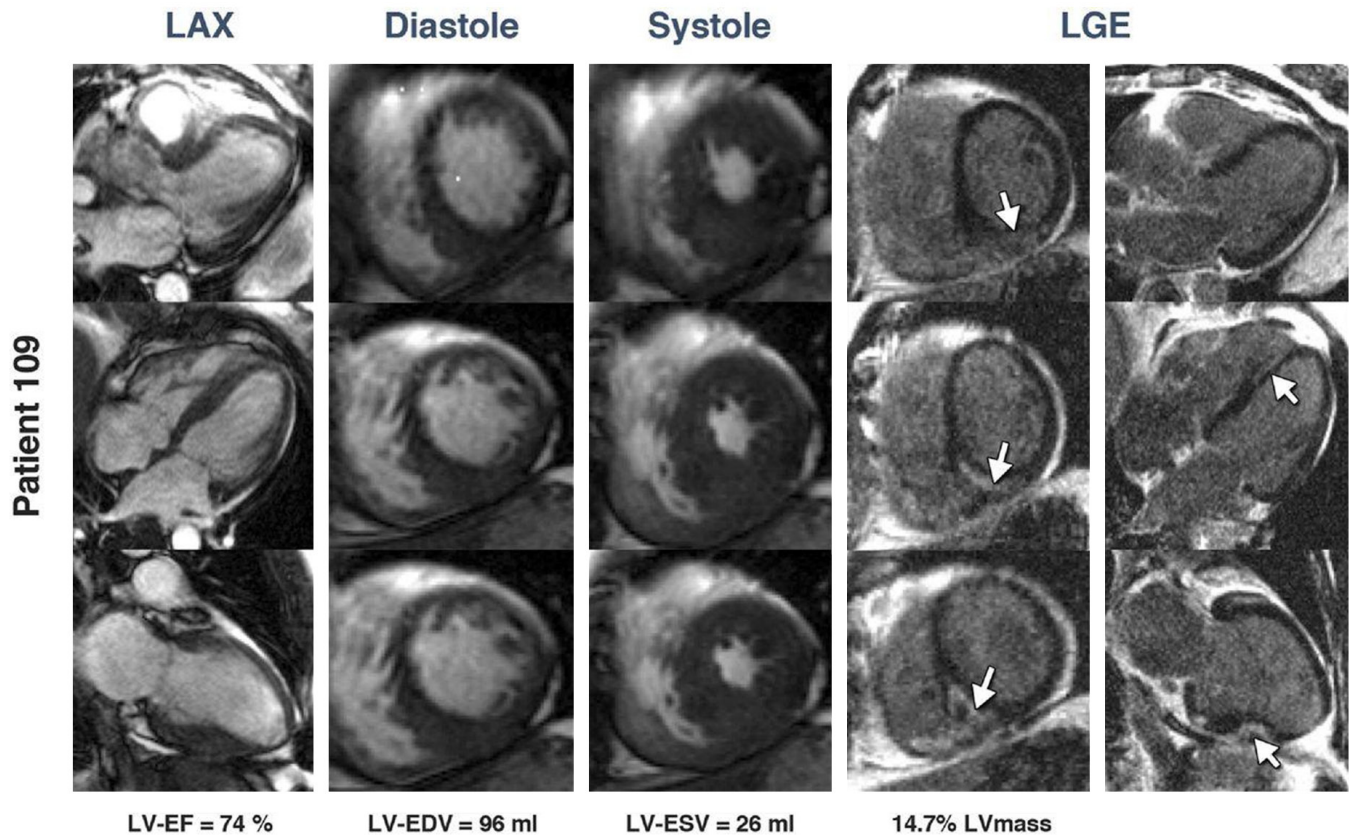


Figure 4. Typical CMR results in the setting of cardiac sarcoidosis. Cardiac magnetic resonance (CMR) of a 48-year-old woman presenting with shortness of breath and new onset of third-degree atrioventricular block. Cine images reveal a normal left ventricle (LV) with preserved left ventricular ejection fraction (LVEF). Late gadolinium enhancement (LGE) is present in multiple locations (white arrows) adding up to 14.7% of LV mass. Endomyocardial biopsy confirmed cardiac sarcoidosis in the LV and right ventricle. This patient received an implantable cardioverter-defibrillator due to recurrent sustained ventricular tachycardia, which discharged appropriately several times during follow-up despite amiodarone and high-dose beta-blockers. LAX = long axis; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume (Reprinted with permission from [42]).

months as a consequence of rapid decrease in left ventricular systolic function, paired with ventricular tachycardia, to effectively diagnose the patient with isolated CS, without preceding diagnosis of extracardiac disease [39]. Finnish patients that were suspected of having CS participated in ¹⁸F-FDG-PET scans and showed increased uptake in the right ventricle which was associated with VT as well as atrial fibrillation (P < 0.05) [40]. Right ventricle uptake has also been associated with positive EMB in CS patients. As a result, right ventricular uptake has the potential to increase the rate of a positive endomyocardial biopsy by up to 42% in CS patients [41].

A meta-analysis investigating the efficacy of ¹⁸F-FDG-PET in the diagnosis of CS yielded a sensitivity of 89% (95% confidence interval) and a specificity of 78% (95% confidence interval) [37]. This analysis provides evidence of high diagnostic accuracy for ¹⁸F-FDG-PET in this circumstance.

Another imaging method that has proven to be successful in the diagnosis of CS is CMR. CMR has been successful in identifying the presence of late gadolinium enhancement, which is an indicator of severe effects including VT,

and even impending death [15, 42]. CMR can also be used as a diagnostic tool with accurate prognosis. CMR has been found to have a higher specificity than ¹⁸F-FDG-PET, but a lower sensitivity (**Figure 4**). However, the disadvantage of CRM is that it cannot be used to study patients with defibrillators, a significant drawback considering the number of CS patients with defibrillator implantations [2].

The use of ¹⁸F-FDG-PET in CS patients

The role of ¹⁸F-FDG-PET in clinical practices has increased significantly within the past decade [43]. One study reported PET imaging has the highest efficiency at early stages of CS [44]. Metabolic cardiac activity is increased with the inflammatory cell accumulation in the early stage, allowing higher ¹⁸F-FDG uptake for detection. Presence of some perfusion abnormalities, through myocardial perfusion imaging (MPI), as well as high ¹⁸F-FDG concentration uptake through PET scan, might act as potential markers for patients at risk of contracting VT [45, 46]. During the late stages of CS, ¹⁸F-FDG uptake decreases, indicating non-caseating granulomas retrieval with fibrosis formation [44, 47]. Another study looked at active inflammation cells in the extracardiac organ with the absence of CS

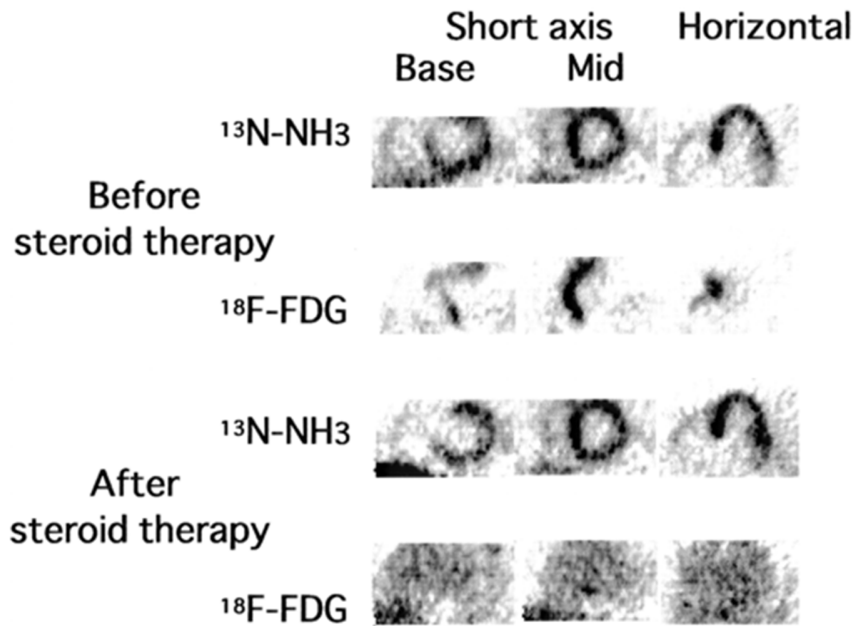


Figure 5. $^{13}\text{N-NH}_3$ and $^{18}\text{F-FDG}$ PET images before and after steroid therapy in patient 15. Cardiac $^{13}\text{N-NH}_3$ PET revealed moderate defects in basal ventricular septum, and $^{18}\text{F-FDG}$ PET revealed increased $^{18}\text{F-FDG}$ uptake in basal and mid-antero-septal wall of LV and free wall of right ventricle. After 1 mo of steroid therapy (prednisolone, 30 mg/d), increased $^{18}\text{F-FDG}$ uptake in basal and mid-antero-septal wall of LV and free wall of right ventricle disappeared completely, whereas $^{13}\text{N-NH}_3$ defects exhibited no significant change. $^{18}\text{F-FDG}$ uptake indices of mid-septum before and after steroid therapy were 3.0 and 1.2, respectively. Base = basal level of LV; Mid = middle level of LV (Reprinted with permission from [50]).

[48]. Most of the patients (88%) with high $^{18}\text{F-FDG}$ uptake overall were subjected to electrophysiologic programmed electrical stimulation (EPS) for VT risk stratification. However, after a 1.8-year (mean) follow-up, no patients suffered or died due to VT. With the presumption that CS is common amongst sarcoidosis patients, it was concluded $^{18}\text{F-FDG}$ -PET failed to predict the presence of arrhythmia with sarcoidosis lesion or with preserved LVEF [25, 48]. Serial PET imaging can help monitor the status of inflammation and improve outcomes for CS patients. Moreover, PET/MR integration can help monitor inflammation status and scar status.

However, this conclusion is not reflected across the literature. A study exploring the correlation of $^{18}\text{F-FDG}$ uptake in the active inflammatory region demonstrated that increased uptake is present in inflammatory regions, thus showing that $^{18}\text{F-FDG}$ -PET acted as a prognostic tool for VT/VF in the 45 patients observed [49]. Another study corroborated these findings and reported that abnormality in PET uptake findings or an involvement of RV increased the cardiac risks by 3 fold. Blankstein et al reported in his study that patients with abnormal PET uptake in their heart is a good indication for VT occurrence. Out of 118 patients scanned for CS initially for the study, and with a 1.5 years median follow-up, 27 (23%) develop VT and 8 (7%) death [45]. Further prognostic tools and guidelines still need to be developed as it is important and beneficial to patients who might need early monitoring such as ICD

implantation or treatment such as immunosuppressive drugs.

After a CS diagnosis, risk stratification of ventricular arrhythmias is a necessity given the potential for sudden cardiac death. $^{18}\text{F-FDG}$ -PET has been successful in monitoring disease advancement and treatment responses in CS patients (Figure 5) [25]. A Japanese study in which patients underwent corticosteroid therapy, follow up $^{18}\text{F-FDG}$ -PET scans showed significantly lowered levels of uptake. The lowered uptake levels correlated with reduced frequency, and sometimes disappearance of VT [50]. In another study, 125 patients underwent an $^{18}\text{F-FDG}$ -PET scan, and were later monitored for VT and death. It was found that abnormal $^{18}\text{F-FDG}$ uptake was associated with increased risk of major cardiac events [45].

Global $^{18}\text{F-FDG}$ uptake for disease monitoring

An emerging methodology to quantify sarcoid disease burden is a global assessment of disease burden. Current standards of assessing CS or suspected

CS in PET scans involves leveraging continuous changes in SUVmax [51]. There is no question that serial assessment of SUVmax across PET scans is a highly important measure of assessing disease burden and evolution/resolution: studies have leveraged serial pet SUVmax to study treatment response, cardiac complications, and timing of treatment (Figure 6) [52, 106]. However, pure SUVmax misses valuable information about total inflammatory response; global assessment can serve as a valuable alternative to be used in conjunction with SUVmax [53]. While SUVmax can be manipulated by noise and scanner variability, average SUVmean (aSUVmean) presents as an easily reproducible, highly specific alternative to assessing global disease burden (Figure 7) [54-56]. Current studies have extensively explored aSUVmean for inflammatory measures both in $^{18}\text{F-FDG}$ and other radiotracers [57-62, 107-109]. There is growing research in this area, and it will be important for a greater understanding of CS disease progression.

Management and treatment of ventricular arrhythmias in CS

Recurrent VT in CS is common, but difficult to manage. Several different treatment strategies were implemented, but none are successful in completely preventing all arrhythmia [36]. In either ischemic or nonischemic VT, activation of VT is due to scarring, mainly in the intramural space and RV regions [63, 64]. Arrhythmias that are

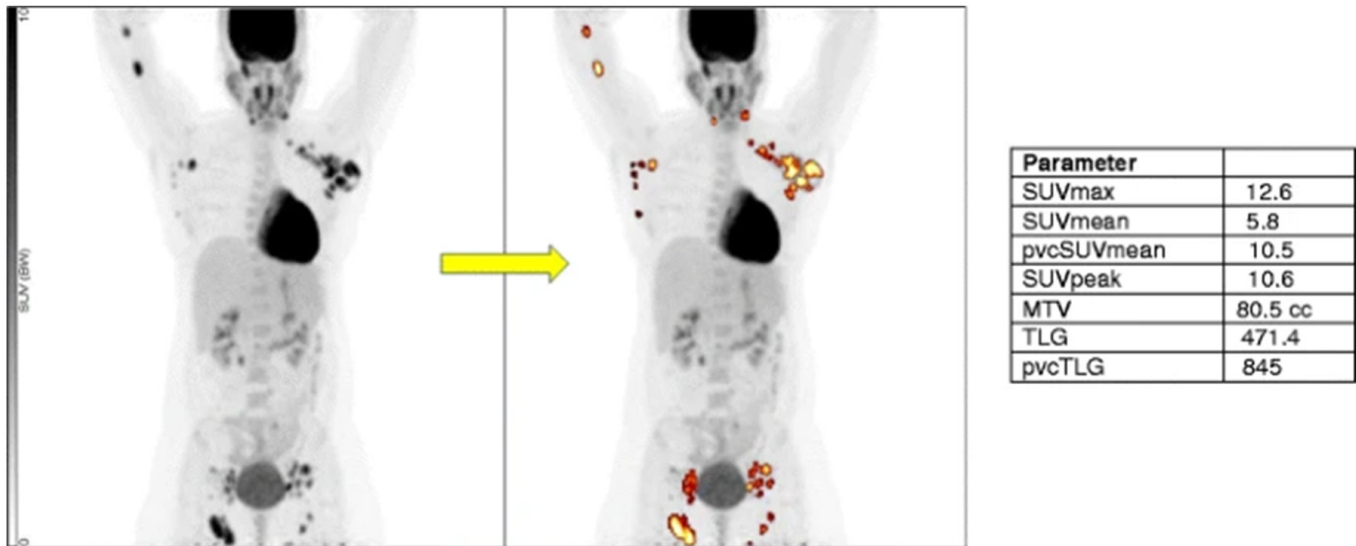


Figure 6. Representative image analysis results in identifying disease sites, and the corresponding quantitative measures provided by this analysis scheme in a patient with Non-Hodgkin Lymphoma. SUVmax, SUVmean, SUVpeak, MTV (Metabolic Tumor Volume), TLG (Total Lesional Glycolysis = MTV*SUVmean), pvcSUVmean (partial volume effect corrected SUVmean), pvcTLG (partial volume effect corrected TLG = MTV*pvcSUVmean) (Reprinted with permission from [51]).

caused by CS are oftentimes spread throughout the myocardium, epicardium, and deep intramural circuits [3, 36]. Due to the many locations of VT in CS patients, it is important and beneficial to determine the reentry point of the VT substrate. This will allow accurate observation using methods like endocardial mapping.

Catheter ablation, often guided with endocardial mapping, is the preferred method in dealing with patients who develop VT from CS. Both unipolar and bipolar voltage mapping are used to identify the distribution of scarring regions during electroanatomical mapping. Generally, unipolar has a wider “field-of-view” than bipolar mapping [65]. The usage of unipolar voltage mapping to guide bipolar electrogram mapping is also common [66]. Endocardial voltage mapping (at 5.5 mV) is able to identify a more extensive area of epicardial bipolar abnormality in ARVC/D patients with VT [67]. Endocardial substrate is usually the main ablation strategy, while epicardial substrate is used in the presence of acute ablation failure or limited endocardial substrates. The usage of endocardial ablation technique alone yields a 96% success rate (80% completed and 16% partial) [68].

Numerous studies have shown that ablation, in the long term, proves to be unsuccessful due to recurrent VT [69, 70]. One study shows that only 25-57% of Patients who underwent ablation treatment were arrhythmia-free, with the longest follow-up being 33 months post treatment [71]. This is consistent with data previously reported in other studies which demonstrate a recurrence rate of 50% [36, 72]. Despite partial elimination of inducible VT, catheter ablation is adequate to palliate granulomas accumulation. With catheter ablation, it is found that there is a significant reduction in arrhythmic burden (VA), with or without recurrent VT, in 88.4% and 90% of the

cases [71, 73]. Another study reported no recurrence of VT in 70% of patients within the first year of catheter ablation [74].

Early stages of CS are often treated with immunosuppression drugs if there are additional signs of VT. Currently, corticosteroid and anti-arrhythmia compounds: methotrexate, cyclophosphamide, infliximab, amiodaron, and azathioprine are used to suppress inflammation [73, 75]. A comprehensive study reviewed by Kron et al shows that patients with isolated CS are also more likely to be prescribed with antiarrhythmic medication. Isolated CS patients (61.5%) were also medicated with amiodarone compared to patients with extracardiac sarcoidosis (16.7%, P = 0.0006) [76]. Usage of steroid therapy yielded better outcomes in the early and middle stages of CS compared to advanced stages [47, 77].

Mainly, corticosteroids are used to improve patients with LV dysfunction and to reduce the chance of recurrent VT [77, 78]. Corticosteroids work to balance the difference of type 1 and type 2 helper T-cells cytokines [79]. It is recommended that patients who are diagnosed with CS should be prescribed about 30-40 mg of corticosteroid daily for the first three months after diagnosis and reduce dosage to 5-15 mg for one year [75]. A different group of research recommended ingestion of 15 mg daily of prednisolone or 6 mg of methotrexate per week [80]. When a patient with CS was subject to high dosage corticosteroid treatment, and was screened with ¹⁸F-FDG months later, it was also shown that the scans revealed decreased level of uptake in the inflammatory region [47]. In another study, corticosteroids with other antiarrhythmic medication suppressed VT in 33/42 (79%) patients [18]. Despite reducing inflammatory effects, immunosuppressive therapies can only be used in the managmange of CS and VT in the short

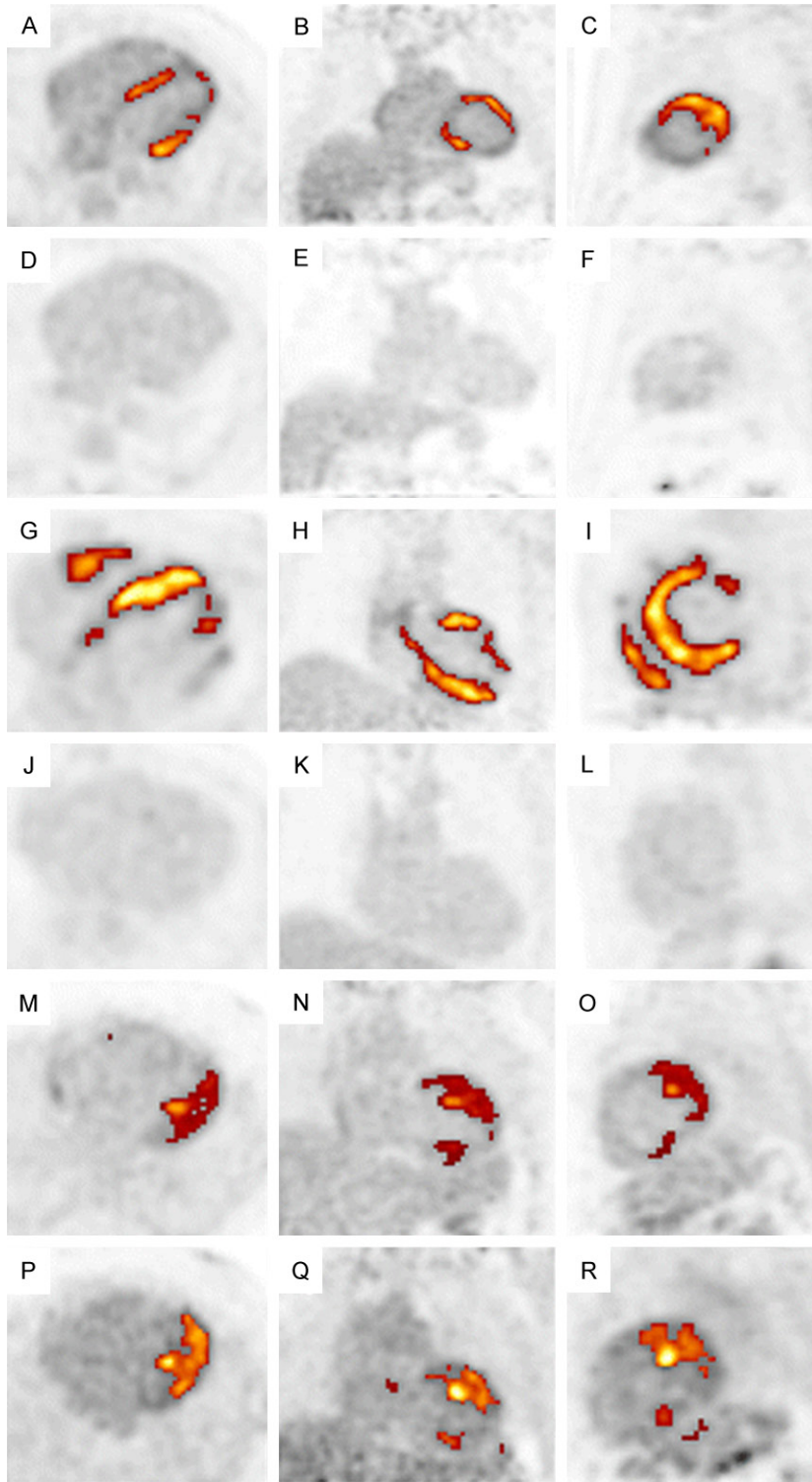


Figure 7. Examples of serial PET scans among patients with cardiac sarcoidosis (CS) responding (A-L) or not (M-R) to immunosuppressive treatment. Each row shows a single scan in three projections (transverse, coronal and sagittal). Baseline PET scan in a patient with CS involving the mid-basal septum, mid-basal anterior and basal inferior wall of the left ventricle (A-C) that demonstrate complete normalization after 6 months of immunosuppressive therapy (D-F). Baseline PET scan in a patient with CS involving the free wall of the right ventricle, all the septum and the basal anterior and inferior wall of the left ventricle (G-I). Same patient at 6-month control (J-L) no longer showing active inflammation of the myocardium. Patient with CS involving the lateral and anterior wall of the left ventricle as well as the anterolateral papillary muscle at baseline (M-O) and persistent inflammation of the same areas regardless of 6 months of immunosuppressive treatment (P-R) (Reprinted with permission from [71]).

term. On a long-term scale, there is conflicting data about corticosteroid efficacy and increased chance of recurrent VT [77, 79, 81]. It has been reported that after corticosteroid treatment for CS, 54% of patients showed improvement, 40% remained in status quo, and 6% were worse than before [82].

Severe and late stage cases of CS often involve an implantable cardioverter defibrillator (ICD). ICD is used to assess the risk of sudden cardiac death (SCD) in both primary and secondary prevention [83]. Primary prevention ICD targets individuals who are at risk for SCD due to underlying medical conditions, while secondary prevention ICD are offered to patients who have a history of sustained ventricular arrhythmia [84]. Isolated CS patients have usually ICD implantations for secondary prevention purposes [76]. The primary prevention role of an ICD involving CS patients remains unclear. Some medical centers offer to implant ICDs in all CS patients, while other centers implant ICDs only in patients who have LVEF $\leq 35\%$ [85, 86]. Appropriate ICD therapies deliver either anti-tachycardia pacing (ATP) or ICD shocks to VT or VF [87]. It is shown that patients with CS who received either ICD/PPM have a lower mortality rate from SCD compared to those without ICD/PPM [88]. ICD is deemed necessary and recommended for those who are asymptomatic to CS or recurrent VT in order to monitor cardiac activity [89, 90].

Intensive inflammation of CS will likely lead to the formation of fibrosis in the myocardium, which can also lead to heart failure. At late CS stages, heart transplantation might be the only option. There have been reported cases of recurrent CS even after allograft, as early as 6 months post operation [91, 92]. However, studies have also shown that patients with heart transplantations due to CS have a higher percentage of no rejection reports within the first year compared to patients who underwent heart transplantation for other causes (57.1% vs 49.4%) [93].

¹⁸F-FDG-PET/MRI in CS diagnosis

¹⁸F-FDG-PET has certainly proven to be an incredibly useful and accurate diagnostic tool of CS. While late gadolinium enhancement by CMR is efficient in detecting myo-

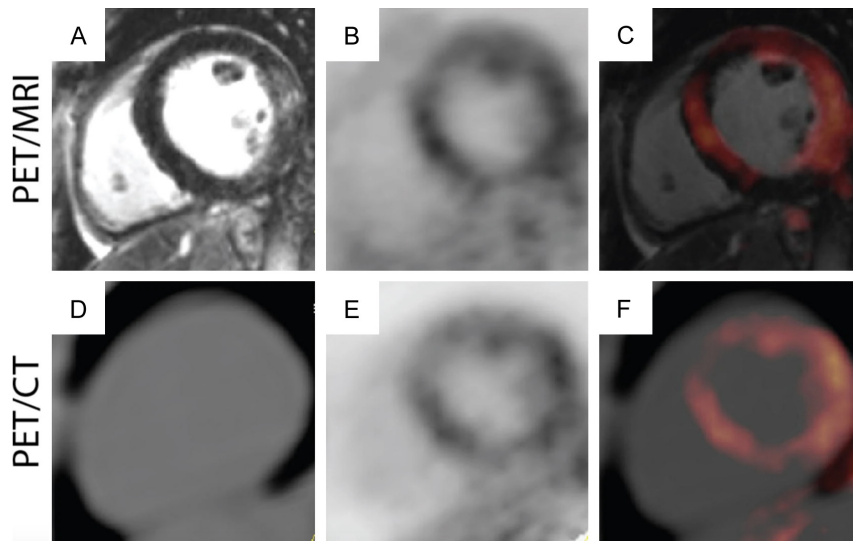


Figure 8. Images presented from Patient 1 with PET/MR (A-C) and PET/CT (D-F). In this patient, note the enhanced signal seen on the delayed enhancement MR images in the lateral wall (A), and the enhanced ^{18}F -FDG uptake in the septal, anterior, and lateral regions on both the PET/CT and PET/MR images (C, F). Although this extensive uptake of ^{18}F -FDG could be interpreted as poor suppression, an increase in ^{18}F -FDG in the hilum and great vessels (not shown in these images) is supportive of this interpretation. This patient had an ejection fraction of 49% with mild global hypokinesis. There were no regional wall motion abnormalities (Reprinted with permission from [99]).

cardiac necrosis and/or advanced fibrosis scarring, ^{18}F -FDG portrays the increased uptake level of glucose metabolism. In combination PET/MRI has proven to be more successful in improving the efficacy of both scans, addressing their drawbacks, and highlighting their advantages [94]. ^{18}F -FDG-PET is known to have better sensitivity, while CMR is known to have better specificity when compared to one another; by combining the two, PET/MRI are both more sensitive and more specific than either one alone [95]. For example, one study showed that the sensitivity for individual PET and MRI in detecting CS is about 85% and 82% respectively, while hybrid PET/MRI yields up to 94% [96]. Studies have shown that PET/MRI is a fantastic diagnostic tool that has the ability to show both the disease activity and nature of the injury within a single scan (**Figure 8**) [97]. Specifically, the usage of PET/MRI has higher potential clinical involvement in detecting CS, ischemic heart diseases and cardiomyopathy as compared to acute coronary syndromes [98]. In a comparison between PET/CT scans and PET/MRI scans, and a sample size of ten patients with suspected CS, it was shown that both showed similar diagnostic results, however, the PET/MRI was able to provide deeper characterization of the disease process [99].

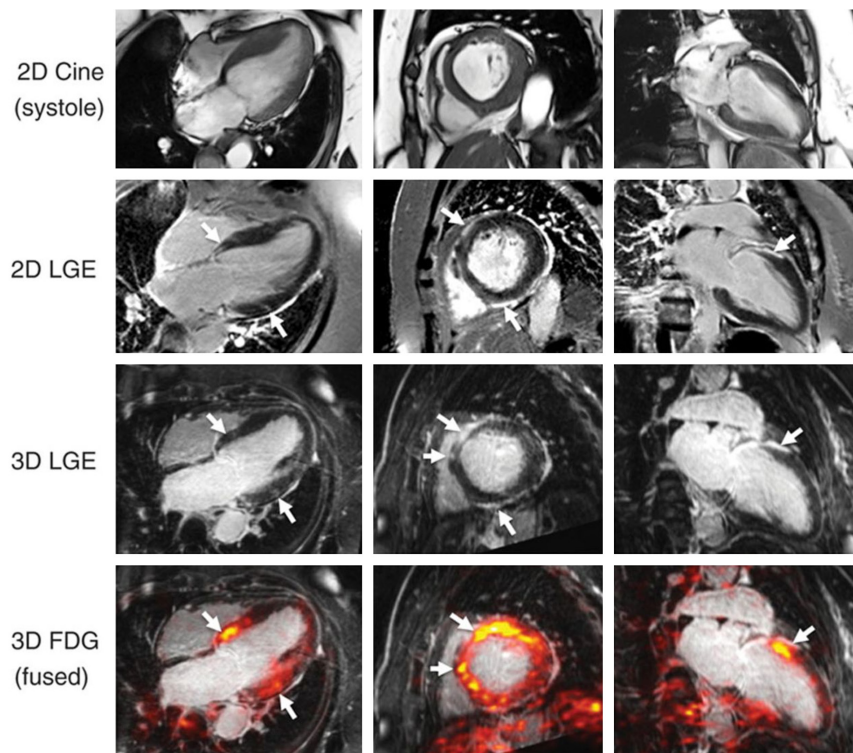


Figure 9. Cardiac magnetic resonance images for respective 4-chamber, short-axis, and 2-chamber orientations showing systolic frame cine imaging and corresponding 2-dimensional (2D) late gadolinium enhancement (LGE) and 3-dimensional (3D) LGE scar imaging. White arrows indicate regions of abnormal LGE, consistent with mature scar. Bottom row shows 3D LGE images with fusion of ^{18}F -labeled fluoro-2-deoxyglucose (^{18}F -FDG) positron emission tomography signal suggestive of active inflammation surrounding regions of established scar (Reprinted with permission from [102]).

Finally, a case study shows that a PET/MRI scan was able to identify active myocardial inflammation within a scarred area [100, 101]. A 72 years old woman showed normal coronary arteries but with a noncaseating granulomas via biopsy and an ejection fraction of 36%, which subjected the patient with CS considerations. MRI showed severe inferoseptal hypokinesis by cine and both 2D and 3D LGE showed subepicardial signaling of anteroseptal and inferoseptal wall. Fusion of ^{18}F -FDG-PET with either 2D/3D LGE enhanced accuracy as uptake is seen around the fibrosis regions (**Figure 9**). It is important to note that the T2-weighted MRI sequences were not able to pinpoint the regions of inflammation where ^{18}F -FDG showed increased uptake [102]. This study describes one of the first examples of PET/MRI being used in a clinical setting, in

which it has effectively differentiated between active and chronic cardiac sarcoidosis within a single scan and addressing the importance of using integrated PET-MR.

Conclusion

CS is a complex inflammatory disease that requires non-invasive imaging for effective management. Early recognition prevents cardiac abnormality, mainly VT and VF in CS patients, and extends lifespan. ^{18}F -FDG-PET is useful for accurate diagnosis, tissue characterization, and alerts for therapeutic treatment. Patients with positive screen tests such as ECG abnormality and abnormal Holter Monitor should first be subjected to CMR. Cardiac MRI is usually preferred due to its high specificity; however, ^{18}F -FDG-PET is a better option in diagnosing patients who have a contradiction to CMR [28]. Integrated ^{18}F -FDG-PET with MRI is still in its early stages for the widespread application for cardiovascular diseases, however preliminary results seem to be exceptional. Despite a few issues that arise, such as attenuation correction in bone segmentation, PET/MRI has shown fruitful results in its ability to reduce radioactive exposure (50%) as compared to PET/CT and multiparametric pathology assessment [28, 98, 103]. This fusion method will certainly prove to be promising in the future. Overall, the role of PET in ^{18}F -FDG-PET scan alone or in PET/MRI has shown to be instrumental in the management of CS patients with relation to VT and VT, and offers a better medical understanding in patient treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Abass Alavi, Department of Radiology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA. Tel: 215-662-3069; Fax: 215-573-4107; E-mail: abass.alavi@pennmedicine.upenn.edu

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