
Role of PET/CT in Assessing Cardiac Sarcoidosis

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4.1 Introduction

Sarcoidosis is a multisystem disease of unknown origin, predominantly affecting young adults, and characterized by compact noncaseating epithelioid cell granulomas. The term *sarkoid* was first introduced in 1899 by Caesar Boeck, a Norwegian dermatologist, to describe benign cutaneous lesions that resembled sarcoma on histopathological examination [1]. With the development and progress of new imaging modalities including positron emission tomography (PET) and magnetic resonance imaging (MRI), there has been a recent increase in interest from clinicians and researchers regarding the diagnosis and treatment of cardiac sarcoidosis.

4.2 Sarcoidosis

4.2.1 Epidemiology and Pathophysiology

The incidence of sarcoidosis is estimated to be 5 per 100,000 person-years in whites, with slight female predominance, and up to 39 per 100,000 person-years in African-Americans [2–4]. However, recent data suggest even higher prevalence, reaching 3–10 and 35–80 per 100,000 person-years in whites and African-Americans, respectively [5]. Underestimation of sarcoidosis incidence is likely due in part to lack of accurate diagnostic tests, leading to under recognition and misdiagnosis of the disease [6]. Even though the exact causes of sarcoidosis are unknown, current evidence

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Table 4.1 Different agents that have been linked to increased incidence of sarcoidosis

<i>Infectious agents</i>	Herpes, Epstein-Barr, retrovirus, Coxsackie B virus, cytomegalovirus
Virus	
Bacteria	<i>Borrelia burgdorferi</i> , <i>Propionibacterium acnes</i> , <i>Mycoplasma</i>
Mycobacteria	<i>Mycobacterium tuberculosis</i>
<i>Organic compounds</i>	Clay, pine tree pollen, combustion products
<i>Inorganic compounds</i>	Aluminum, talc, titanium, zirconium

Adapted from [2]

suggests that the disease is the result of inflammation mediated by T lymphocytes and activated macrophages following exposure to specific agents in subjects with genetic predispositions [2, 6–13]. Some agents that have been linked to increased incidence of sarcoidosis are listed in Table 4.1.

4.2.2 Clinical Presentation and Treatment

Presenting symptoms of sarcoidosis typically include dyspnea and cough due to lung involvement as well as systemic symptoms including fatigue, weight loss, and fever. However, sarcoidosis can affect virtually any organ of the human body and can present with a wide variety of symptoms depending on organ involvement (Table 4.2).

Most patients with sarcoidosis present with mild symptoms and will recover spontaneously. Decision to initiate treatment should be based on risk-benefit analysis [14]. The mainstay of sarcoidosis treatment is corticosteroids. Current guidelines recommend the use of 20–40 mg of oral prednisone per day [2], and response to therapy should be assessed within 1–3 months. In case of improvement, prednisone treatment can be tapered down to dosage of 5–15 mg per day for an additional 9–12 months, whereas lack of response suggests irreversible fibrotic disease [14]. Given the nonspecific nature of sarcoidosis symptoms, it can be difficult to accurately monitor response to therapy. The use of cytotoxic medication such as methotrexate and immunomodulatory agents such as tumor necrosis factor alpha has been shown to be a viable therapeutic option in patient not responding to corticosteroids or unable to pursue corticosteroid treatment due to adverse effects [15]. Other therapeutic options include hydroxychloroquine to treat patients with skin involvement and hypercalcemia [14].

4.2.3 Diagnosis of Sarcoidosis

The diagnosis of systemic sarcoidosis is established when there is radiographic evidence of sarcoidosis with compatible clinical features and noncaseating granulomas on biopsy with other causes of granulomas ruled out. Response to corticosteroids is not enough to establish diagnosis of sarcoidosis [14]. There are no specific serum markers for sarcoidosis. C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are sensitive inflammation markers but are not specific for sarcoidosis. Serum angiotensin-converting enzyme (ACE) levels are elevated in approximately

Table 4.2 Symptoms and signs of sarcoidosis depending on organ involvement

	Clinical presentation
Constitutional	Fever Fatigue Weight loss Low-grade fever
Lungs and upper respiratory tract	Dyspnea Cough Dysphagia Chest pain
Lymphatic system	Enlarged lymph nodes
Heart	Palpitation Syncope Dizziness Chest pain
Liver	Abnormal liver function tests Hepatomegaly
Spleen	Splenomegaly
Skin	Papular sarcoidosis Erythema nodosum Lupus pernio
Eyes	Uveitis Retinal vasculitis
Central nervous system	Cranial mononeuropathies Neuroendocrine dysfunction
Musculoskeletal	Acute polyarthritis Chronic arthritis Diffuse myositis
Salivary glands	Painless swelling

60 % of patients with sarcoidosis due to production of ACE by the granulomas [14]. However, serum ACE is neither sensitive nor specific enough to screen patients with suspected sarcoidosis with its positive predictive value of 84 % and negative predictive value of 74 % [16]. Furthermore, serum ACE should not be used to diagnose sarcoidosis or guide therapy [14].

Due to lack of useful serum markers, diagnosis of sarcoidosis relies greatly on imaging. Classical features of sarcoidosis on chest radiographs include mediastinal and hilar lymphadenopathy, parenchymal opacities, and parenchymal fibrosis in more advanced cases [17]. A staging based on chest radiography has been described more than 40 years ago to monitor chest disease in patient with sarcoidosis (Fig. 4.1) [18]. Although this scale shows poor interobserver agreement, especially for advanced disease, it remains widely used due to its prognostic value [19].

Computed tomography (CT) imaging is only indicated when chest radiograph is atypical for sarcoidosis or when patients present with hemoptysis. Lymphadenopathy and parenchymal disease are more readily seen on CT. Classically, parenchymal lesions present as small pulmonary nodules in a peribronchovascular distribution or following the fissures [17]. Lymphadenopathy with coarse calcification or “icing sugar” lymphadenopathies are frequently described in sarcoidosis. In more advanced disease, lung fibrosis is seen.

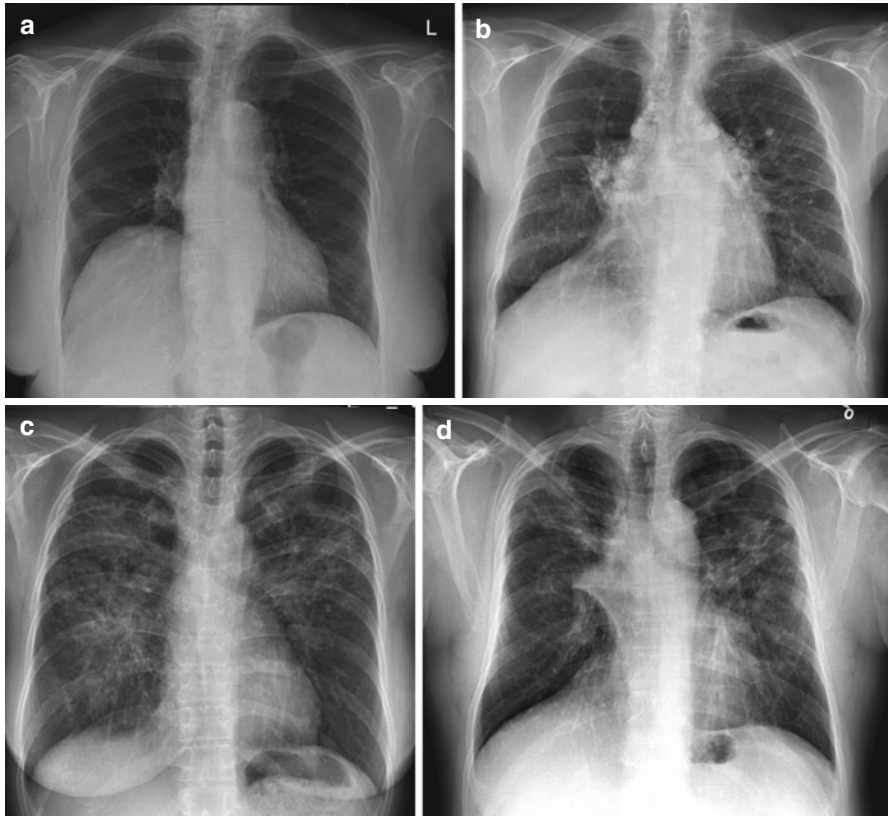


Fig. 4.1 Four stages of sarcoidosis on chest radiographs. (a) Stage I: hilar or mediastinal lymphadenopathy. (b) Stage II: lymphadenopathy and parenchymal disease. (c) Stage III: parenchymal disease alone. (d) Stage IV: pulmonary fibrosis

Gallium-67 citrate has been used for the diagnosis, staging, and treatment follow-up of patients with sarcoidosis. Classical findings include the so-called lambda sign, arising from uptake in the mediastinal and hilar lymphadenopathy, and the panda sign, from abnormal parotid and lacrimal gland uptake (Fig. 4.2). However, accuracy of gallium scintigraphy varies greatly from one study to another with reported sensitivity ranging from 60 to 90 % and suboptimal interobserver variability [20–25].

4.2.4 Role of PET/CT in Sarcoidosis

^{18}F -fluorodeoxyglucose (FDG) is a diagnostic PET radiopharmaceutical with half-life of 109.7 min. FDG is a glucose analog that is transported from the blood into the cells by glucose transporters GLUT 1 and GLUT 4. Once intracellular, FDG is then phosphorylated by hexokinase to form FDG-6-phosphate [26]. Unlike glucose, FDG-6-phosphate is not further metabolized, which leads to trapping of the

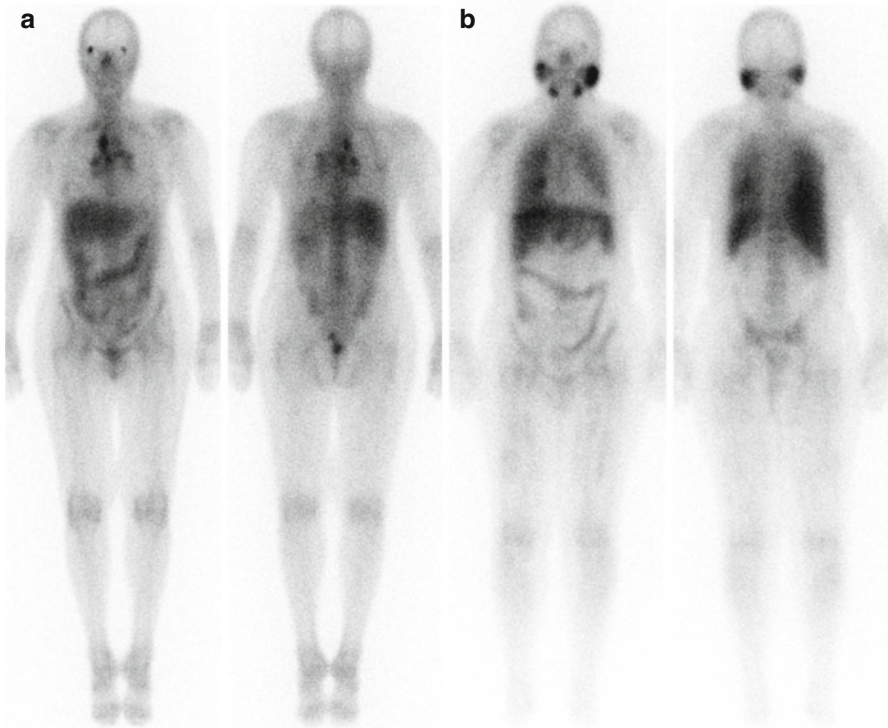


Fig. 4.2 Gallium-67 scintigraphy of two different patients with sarcoidosis. (a) Increased activity in the mediastinal and hilar lymph nodes gives the characteristic lambda sign. (b) Uptake in the parotid and submandibular salivary glands as well as diffuse lung uptake due to sarcoidosis

radiopharmaceutical into the cells (Fig. 4.3). Uptake of FDG is proportional to glucose metabolism, and therefore, increased FDG uptake is seen in several conditions including infection, inflammation, and malignancies.

FDG-PET has several practical and technical advantages over ^{67}Ga , including favorable tracer kinetics, lower radiation exposure, and better quality images [27]. FDG-PET is more accurate and allows better evaluation of extrapulmonary involvement compared to ^{67}Ga [25, 28].

4.2.4.1 Evaluation of Disease Extent

FDG-PET imaging permits whole-body assessment in a single-step examination. A large proportion of patients with suspected pulmonary sarcoidosis have extrapulmonary involvement visualized on FDG-PET [29]. Frequent extrapulmonary sites include the bone, spleen, liver, and abdominal lymph nodes [30]. Accurate determination of the spread of active disease with FDG-PET provides an explanation for persistent disabling symptoms and has been shown to influence patient management [29, 31]. Moreover, identification of sites of extrapulmonary sarcoidosis can identify potential biopsy sites (Fig. 4.4) [29].

Fig. 4.3 Mechanism of uptake and trapping of FDG

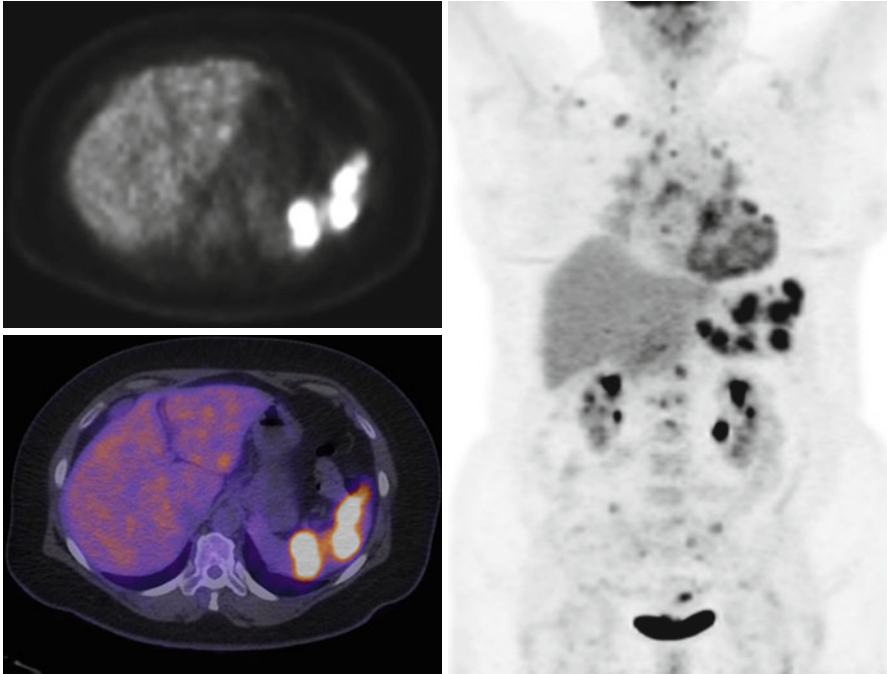
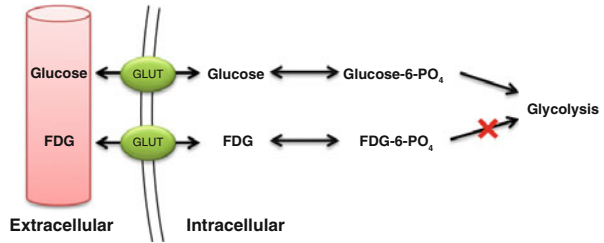


Fig. 4.4 Whole-body FDG-PET scan with selected axial slice in a patient with known thoracic sarcoidosis demonstrating abnormal uptake corresponding to sarcoidosis involvement of the spleen, thoracolumbar spine, and heart as well as in pelvic lymph nodes

4.2.4.2 FDG-PET as a Marker of Disease Activity and in Assessment of Therapy Response

The goal of treatment in sarcoidosis is to treat reversible granulomatous inflammation. Still, there is currently no gold standard method for monitoring inflammatory activity in patients with sarcoidosis. Because of the serious side effects associated with sarcoidosis therapy, it is important to differentiate active and treatable inflammation from quiescent fibrosis. Sarcoidosis often presents with nonspecific systemic symptoms such as fatigue. Monitoring of these nonspecific symptoms does not allow to assess disease progression or response to therapy [32]. Besides, some

patients are completely asymptomatic. Serum ACE is also used to monitor response to treatment but does not accurately reflect inflammatory activity [33]. Changes on conventional anatomical imaging, including x-ray and high-resolution CT, are not reliable markers of active inflammation, as they can remain positive even without active disease [34]. On the contrary, PET was shown to provide additional value to assess inflammatory activity in patients with pulmonary fibrosis [35]. Bronchoalveolar lavage (BAL) is an important tool in diagnosis of pulmonary sarcoidosis, but is not recommended for assessment of treatment response [36]. The prognostic value of BAL depends on the number of T lymphocytes, neutrophils, and mast cells [37–39]. Although gallium-67 has been used to detect active granulomas, it lacks correlation with BAL lymphocyte counts [23, 40]. Because FDG accumulates in inflammatory cells and allows imaging of active inflammation, FDG-PET could be used to monitor response to therapy (Figs. 4.4 and 4.5) [41]. FDG-PET has been shown to be a useful adjunct to other diagnostic methods for detecting active inflammation, especially in patients with persistent symptoms and normal ACE levels [31]. FDG-PET is also used to monitor response to therapy. So far, only few studies, most retrospective and with a small sample size, have looked at FDG-PET before and after corticosteroid therapy [20, 42–45] and TNF- α inhibitor therapy [46, 47]. FDG-PET post therapy was shown to correlate with symptoms [44, 46] as well as corticosteroid dosage [42]. It also correlates with endoscopic findings in patients with sinonasal sarcoidosis [45]. On the other hand, FDG-PET does not correlate with serum ACE, serum IL-2R, or pulmonary function tests (PFT) [20, 44, 46, 47]. These findings suggest that FDG-PET could provide useful information to assess response to treatment and adjust steroid dosage.

4.3 Cardiac Sarcoidosis

4.3.1 Epidemiology

In the United States, myocardial involvement is recognized in approximately 25 % of patients with sarcoidosis [48]. In the Japanese population, the prevalence of cardiac involvement in patients with sarcoidosis is significantly greater, reaching 58 % [49–51]. Cardiac sarcoidosis is characterized by noncaseating granulomas in the myocardium surrounded by lymphocytes [52]. The left ventricular free wall and septum are the most frequently affected myocardial regions [49, 52].

4.3.2 Clinical Presentation and Treatment

Patients with cardiac sarcoidosis may have different presentations depending on the extension and location of the disease [14]. They can present with conduction abnormalities due to direct infiltration of inflammatory cell and/or scar formation. These can also manifest as atrioventricular block or bundle branch block [49]. Atrioventricular block affects approximately 25 % of patients with cardiac sarcoidosis and is caused by

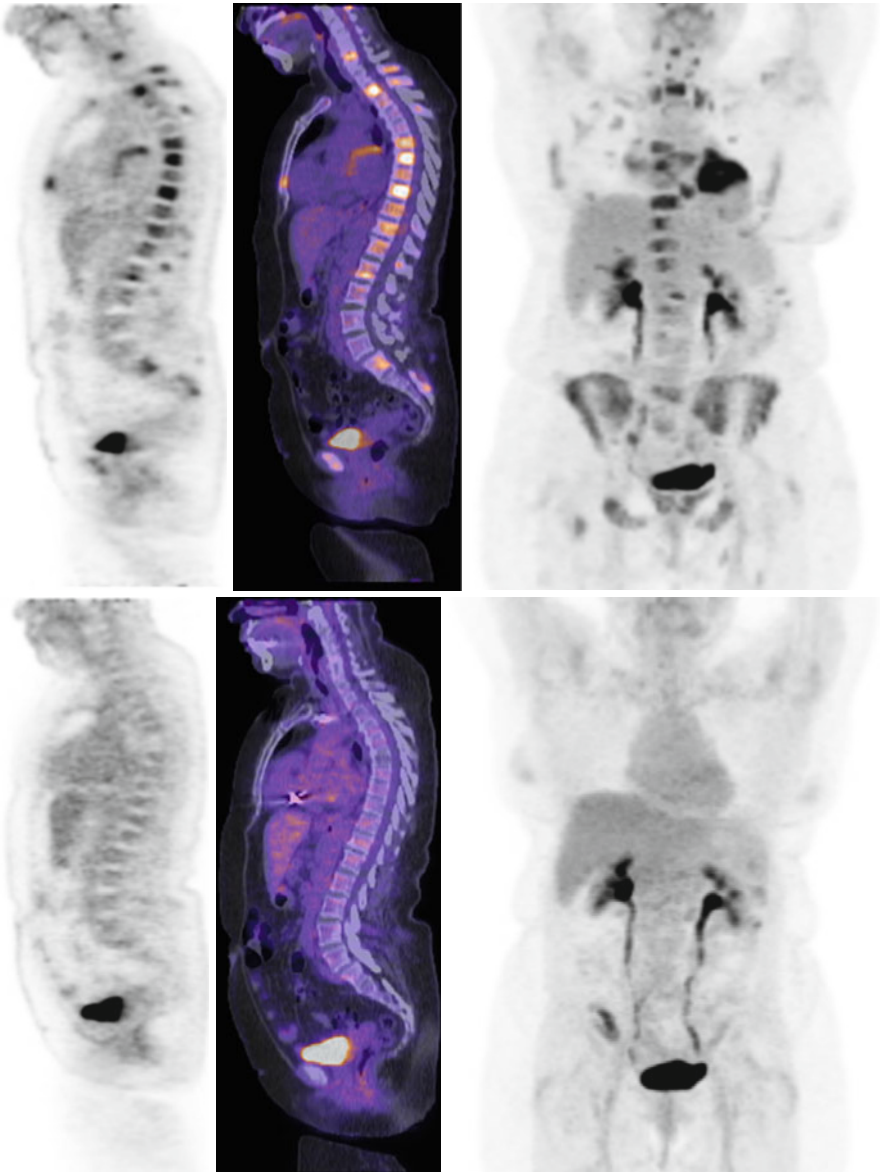


Fig. 4.5 Whole-body FDG-PET scan with selected sagittal slice and maximum intensity projection (MIP) of a patient with extensive sarcoidosis in the heart and bone. Follow-up scan after corticosteroid therapy demonstrates normal biodistribution of FDG, consistent with response to treatment

inflammation or scar in the basal septum [53, 54]. Diagnosis of cardiac sarcoidosis should be considered in young patients with atrioventricular heart block of unknown etiology [54, 55]. Patients with cardiac sarcoidosis can also present with congestive heart failure due to extensive infiltration of the myocardium by granulomas [49, 56].

As with pulmonary sarcoidosis, cardiac inflammation from sarcoidosis is typically treated with corticosteroids. Several uncontrolled series and small sample retrospective studies suggest that steroids may be valuable to treat cardiac sarcoidosis [53, 54, 57–59]. Thus far, there are no randomized controlled trials available to confirm these results and treatment of cardiac sarcoidosis with corticosteroids remains controversial [60]. Initiation of corticosteroid therapy, even with antiarrhythmic drugs, does not prevent arrhythmic event [61]. Pacemakers and ICD are often required when there is extensive involvement of the conduction system or when there is significant heart failure [60]. A systematic review of corticosteroid therapy in cardiac sarcoidosis revealed a wide range of steroid regimens, with prednisone dosage of 20–60 mg daily or 50–60 mg on alternate day [62]. In small single-center retrospective studies, corticosteroid therapy was associated with maintenance of LV function in patients with normal function at diagnosis and improvement of ejection fraction in patients with mild to moderate LV dysfunction [58, 59, 63]. However, no improvement was observed in patients with severe LV dysfunction. As regards to ventricular arrhythmias, some studies showed benefits of immunosuppression therapy [59, 64, 65], whereas others showed no benefit or worsening [61, 66]. As for LV dysfunction, immunosuppressive therapy appears more beneficial in early phase of disease [58, 59]. There is, however, currently not enough data to establish mortality benefit from steroid therapy [62].

4.3.3 PET Imaging

4.3.3.1 Patient Preparation

The myocardium can metabolize different substrates, including free fatty acids, glucose, pyruvate, and ketone bodies. Under physiological conditions, the heart metabolizes mainly free fatty acids and glucose, with free fatty acids accounting for 60–90 % of the energy substrates [67–69]. The source of energy used by the myocardium depends mainly on free fatty acids and glucose plasma concentration and insulin levels [70]. In order to obtain diagnostic FDG-PET images for assessing active cardiac sarcoidosis, pretest preparation is required to suppress physiological uptake in the normal myocardium. Adequate suppression of physiological myocardial FDG uptake is crucial to maximize diagnostic accuracy (Fig. 4.6).

Fasting

When fasting, the myocardial metabolism is shifted and 90 % of its energy comes from metabolism of free fatty acids [71]. For this reason, prolonged fasting is routinely used to suppress physiological myocardial glucose uptake. Several protocols have been described using different fasting time to suppress physiological myocardial FDG uptake, typically between 5 and 18 h [72–75]. To maximize specificity of myocardial FDG uptake, current guidelines recommend fasting for at least 12 h [76].

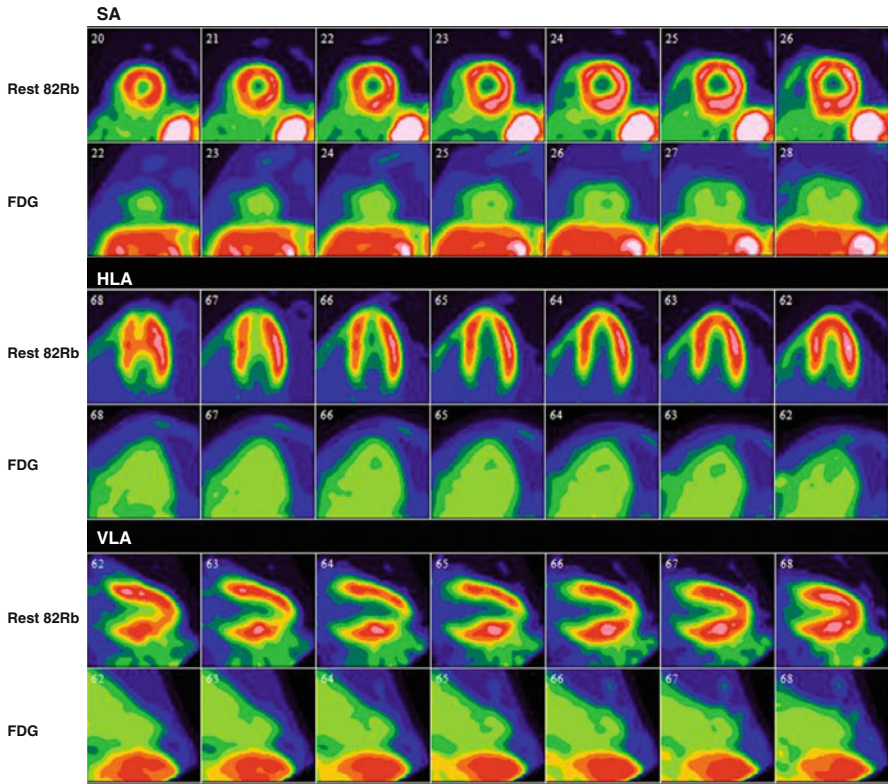


Fig. 4.6 Rest rubidium-82 and FDG-PET scan of a patient with suspected cardiac sarcoidosis. After adequate suppression of physiological myocardial uptake, there is no significant FDG uptake in the myocardium with only blood pool activity, representing a negative study for cardiac sarcoidosis

Diet

Twelve-hour fasting alone can lead to variable myocardial FDG uptake and additional measures are important to consider to minimize physiological uptake [76]. Changing diet prior to imaging has been shown to be at least as effective as fasting to suppress physiological myocardial uptake [72]. Indeed, the fatty acid-glucose cycle, known as the Randle cycle, indicates that glucose loading suppresses fatty acid utilization and that fatty acid loading suppresses glucose utilization by the myocardium [77]. Different low-carbohydrate diets and low-carbohydrate high-fat (LCHF) diets have been used to minimize myocardial FDG uptake (Table 4.3). In a small randomized study, Cheng et al. showed that a simple low-carbohydrate diet in combination with prolonged fasting of 6 h provided adequate myocardial suppression of FDG uptake, while addition of fatty acid loading did not, suggesting that low carbohydrate might be preferable [78]. Others suggested that high-fat meal 3–6 h or 1 h prior to imaging provided adequate myocardial suppression [79]. Harisankar et al. demonstrated that LCHF diet is superior to prolonged fasting of 12 h to

Table 4.3 Review of different patient preparation to minimize physiological myocardial uptake of FDG

Authors	Year	N	Patients	Fasting	Diet	Fat	Carbohydrates
Lum et al. [82]	2002	69	Cancer staging	Overnight	Low carbohydrate	N/A	N/A
Williams and Kolodny [79]	2008	161	Cancer staging	3–6 h	Very high fat, low carbohydrate, protein permitted	N/A	N/A
Cheng et al. [78]	2010	63	Cancer staging	6 h	Low carbohydrate	N/A	<5 g
Wykrzykowska et al. [83]	2009	32	Cancer staging with suspected CAD	Overnight	Very high fat, low carbohydrate, protein permitted	N/A	<5 g
Harisankar et al. [80]	2011	120	Coronary artery disease	12 h	Low carbohydrate, high fat, protein permitted	20.8 g	1.2 g
Coulden et al. [84]	2012	120	Cancer staging	Overnight	Low carbohydrate	N/A	<3 g
Kobayashi et al. [85]	2013	14	Healthy volunteers	6 h	24 h low-carbohydrate diet with high-fat meal	9 g	1 g
Soussan et al. [81]	2013	58	Cardiac sarcoidosis	4 h	Low-carbohydrate high-fat meal 4 h	N/A	N/A

Table 4.4 Example of the LCHF recommendations provided to the patients prior to FDG imaging at the University of Ottawa Heart Institute

Do eat	Do not eat
<p><i>Beverages:</i> Mineral water, seltzer, water, clear liquids without milk or sugar, coffee, tea, and herbal tea (without milk or sugar)</p> <p><i>Eggs:</i> Fried, scrambled prepared without milk, omelet prepared without milk or vegetables</p> <p><i>Condiments and seasonings:</i> Anything that does not contain sugar</p> <p><i>Fats/oils:</i> Animal fats that are part of the meat you eat, butter, margarine</p> <p><i>Sweeteners:</i> Aspartame, NutraSweet, Sweet'N Low, Equal</p> <p><i>Fish:</i> any fish</p> <p>Fatty unsweetened fish (fried or broiled but not grilled)</p> <p><i>Meats:</i> Fatty unsweetened (fried or broiled but not grilled) red meat, bacon, meat only sausages, bacon, ham</p> <p><i>Poultry:</i> Fatty unsweetened chicken and turkey (fried or broiled but not grilled)</p> <p><i>Shellfish:</i> Any non-processed shellfish</p> <p><i>Low-carbohydrate vegetables:</i> Cucumber, broccoli, lettuce, celery, mushroom, radish, asparagus, green pepper, cabbage, spinach</p> <p><i>Sweeteners:</i> Aspartame, NutraSweet, Sweet'N Low, Equal</p>	<p><i>No sugar:</i> Sugar in any form is strictly forbidden (including natural sugars in fruit)</p> <p><i>No starches:</i> Pasta, breads, bagels, cereals, crackers, cookies, muffins, rice, potatoes</p> <p><i>No candy:</i> Candy, chewing gum, mints, cough drops</p> <p><i>No processed products:</i> Processed foods such as deli meats. These products often contain hidden sugars</p> <p><i>No Splenda substitutes</i></p> <p><i>No milk or milk products</i></p> <p><i>No cheese or cheese products</i></p> <p><i>No peanut butter or nuts</i></p> <p><i>No alcohol</i></p> <p><i>No fruit</i></p> <p><i>No vegetables with higher carbohydrate content</i></p>

suppress myocardial FDG uptake [80]. More recently, Soussan et al. demonstrated that a LCHF diet for the dinner and breakfast preceding imaging followed by 4 h fasting provided sufficient myocardial suppression of uptake for the diagnosis of cardiac sarcoidosis [81]. There is currently no evidence that clearly established usefulness of LCHF diet over low carbohydrate alone. Furthermore, there is no data on improvement of diagnosis of cardiac sarcoidosis using such diets. Nevertheless, because diet modification is an easily applicable measure, it is routine to follow a diet with less than 5 g of carbohydrate, with or without high-fat meal prior to imaging. Table 4.4 shows an example of the LCHF recommendations provided to the patients prior to FDG imaging.

Heparin

Nuutila et al. showed that increased free fatty acid serum levels induced by heparin infusion were associated with decreased myocardial FDG uptake in healthy volunteers [86]. The protocol used in their study consisted of two 200 IU boluses

Table 4.5 Oral diabetic medication that should be continued or held on the day of PET scan based on the University of Ottawa Heart Institute protocol

Oral medication that should be continued on the day of the PET scan	Oral medication that should be held on the day of the PET scan
Exenatide (Byetta)	Acarbose (Glucobay)
Linagliptin (Trajenta)	Gliclazide (Diamicon)
Liraglutide (Victoza)	Gliclazide MR (Diamicon MR)
Metformin (Glucophage or Glumetza)	Glimepiride (Amaryl)
Pioglitazone (Actos)	Glyburide (Diabeta)
Rosiglitazone (Avandia)	Repaglinide (Gluconorm)
Saxagliptin (Onglyza)	
Sitagliptin (Januvia)	

of unfractionated heparin, injected intravenously, 90 min before FDG injection and at time of injection, with continuous infusion of 15 IU/min starting 90 min prior to FDG injection. The increased in FFA levels is mediated via activation of the lipoprotein and hepatic lipase [87]. Heparin injection is now routinely done to suppress myocardial FDG uptake, and typical dosage is 50 IU/kg divided in one or two intravenous bolus injections [25, 74, 88, 89], without reports of increased bleeding risk [25, 89]. However, using heparin infusion alone to suppress myocardial uptake is not sufficient since approximately half of the patients still present diffuse myocardial FDG uptake following heparin injection and 6 h fasting [89, 90]. Administration of unfractionated heparin prior to injection of FDG has not been shown to improve detection of cardiac sarcoidosis yet. Nevertheless, many centers have implemented heparin injection in their imaging protocol to maximize diagnostic accuracy.

Diabetic Patients

While many studies on patient preparation prior for FDG imaging exclude patients with diabetes [80, 82, 83, 85], others include only very small number of patients with diabetes [78]. In the small number of studies that do include patients with diabetes, there are discrepancies between the protocols with some suggesting to continue diabetic medication [79], while others are prescribing to hold diabetic medication on the day of the scan [81]. Currently, there are no data addressing specifically the optimal pretest preparation of patients with diabetes prior to FDG-PET in the context of cardiac sarcoidosis.

Different centers have different protocols to image diabetic patients. At the University of Ottawa Heart Institute, diabetic patients are scheduled as the first case of the day, following 12 h fasting and low-carbohydrate high-fat diet, to minimize patient discomfort and glycemic issues. It is recommended that diabetic patients monitor their blood sugar levels following their usual routine with one measurement obtained the morning of the PET scan. If the glycemia falls to less than 4 mmol/L, patients are instructed to drink juice or take glucose to raise their sugar level to higher than 4 mmol/L. Some oral medications should be held on the morning of the scan, while others should be continued (Table 4.5).

In many cases, usual doses of long-acting and intermediate-acting insulin can be continued the night before the PET scan. Short-acting insulin dosage and premixed insulin may need to be reduced the evening before the scan given the low-carbohydrate diet. Since the patients will be fasting on the day of the test, the usual breakfast dose of short-acting insulin should not be taken. Finally, for patients with type 1 diabetes using an insulin pump, basal insulin should be continued on the day of the test.

4.3.4 Imaging Protocol

Imaging protocol includes three components: (1) cardiac rest perfusion scan, (2) whole-body FDG scan, and (3) dedicated cardiac FDG scan. The imaging protocol used at the University of Ottawa Heart Institute (UOHI) is illustrated in Fig. 4.7.

Cardiac rest perfusion scan is typically performed using PET perfusion tracers such as rubidium-82 or ammonia-N13 and follows regular procedure guidelines for rest myocardial perfusion [91]. With Rb-82, dosages of 10–20 MBq/kg up to 2,200 MBq are used and ECG-gated images are acquired over 4–8 min after injection. Ammonia-N13 rest images are acquired over 15–30 min approximately 5 min after intravenous injection of 5–10 MBq/kg (up to 750 MBq). Images are reconstructed using CT-based attenuation correction and displayed in the usual short and long axes.

Approximately 1 h after intravenous injection of 5 MBq/kg (up to 550 MBq) of ^{18}F -FDG, whole-body PET scan is acquired. The patient is positioned supine with his or her arms up above his head. A low-dose CT for attenuation correction and localization is first acquired. Then, whole-body FDG-PET images are acquired from the base of the skull to mid thighs, 3 min per bed position. Following

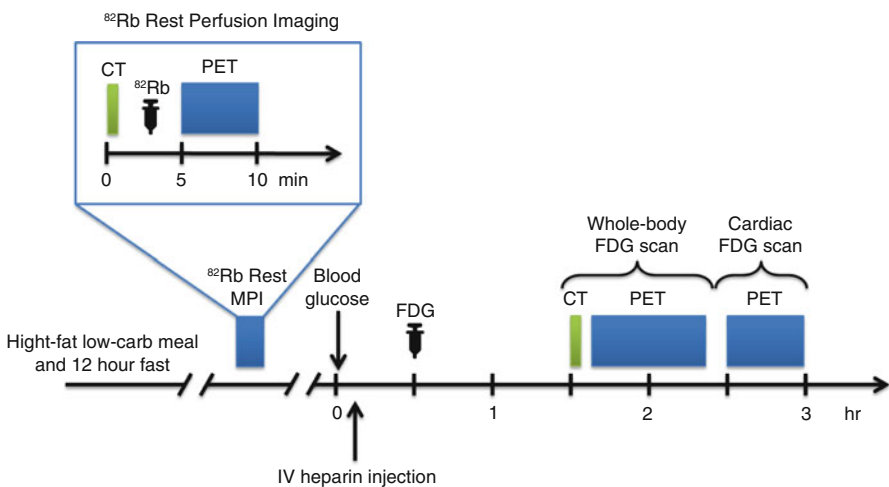


Fig. 4.7 Typical imaging protocol combining rest Rb-82 perfusion imaging and whole-body and dedicated cardiac FDG-PET scan

whole-body imaging, dedicated cardiac PET scan is performed. This acquisition includes a static and, if available, ECG-gated acquisitions. Images are reconstructed by OSEM with attenuation correction and displayed along the perfusion images in the usual short and long axes (Fig. 4.6).

4.3.5 Image Interpretation

Cardiac FDG interpretation must ensure adequate patient preparation. Indeed, poor patient preparation can result in equivocal study due to physiological myocardial FDG uptake. For interpretation, cardiac FDG-PET images are displayed along with rest perfusion images with conventional cardiac display software in the usual short and long axes. Ishimaru et al. described four patterns of FDG uptake: none, focal, focal on diffuse, and diffuse (Fig. 4.8) [89]. This classification has been adopted by other studies and is now frequently used [88, 92]. Focal and focal on diffuse uptake patterns are considered suspicious for cardiac sarcoidosis, whereas diffuse or absence of uptake are considered negative. In order to increase specificity of the diagnostic test, correlation with clinical history is crucial in the interpretation of FDG-PET scan. The interventricular septum is known to be frequently affected in patients with CS and is associated with second- and third-degree atrioventricular block [53, 54]. Therefore, uptake in that region in a patient presenting with atrioventricular block is highly suspicious for sarcoidosis (Fig. 4.9) [93].

Similarly, if the onset site of VT demonstrates focal FDG uptake on FDG-PET, the likelihood that the uptake represents active cardiac sarcoidosis is increased [76]. Although not routinely used, quantification of heterogeneity of uptake can be used to increased specificity. Quantification of heterogeneity of uptake using SUV

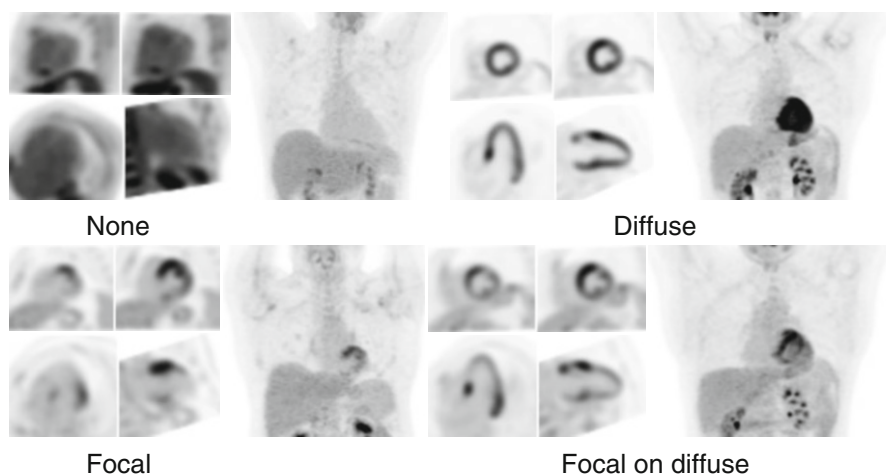


Fig. 4.8 Four different patterns of myocardial FDG uptake: none, diffuse, focal, and focal on diffuse

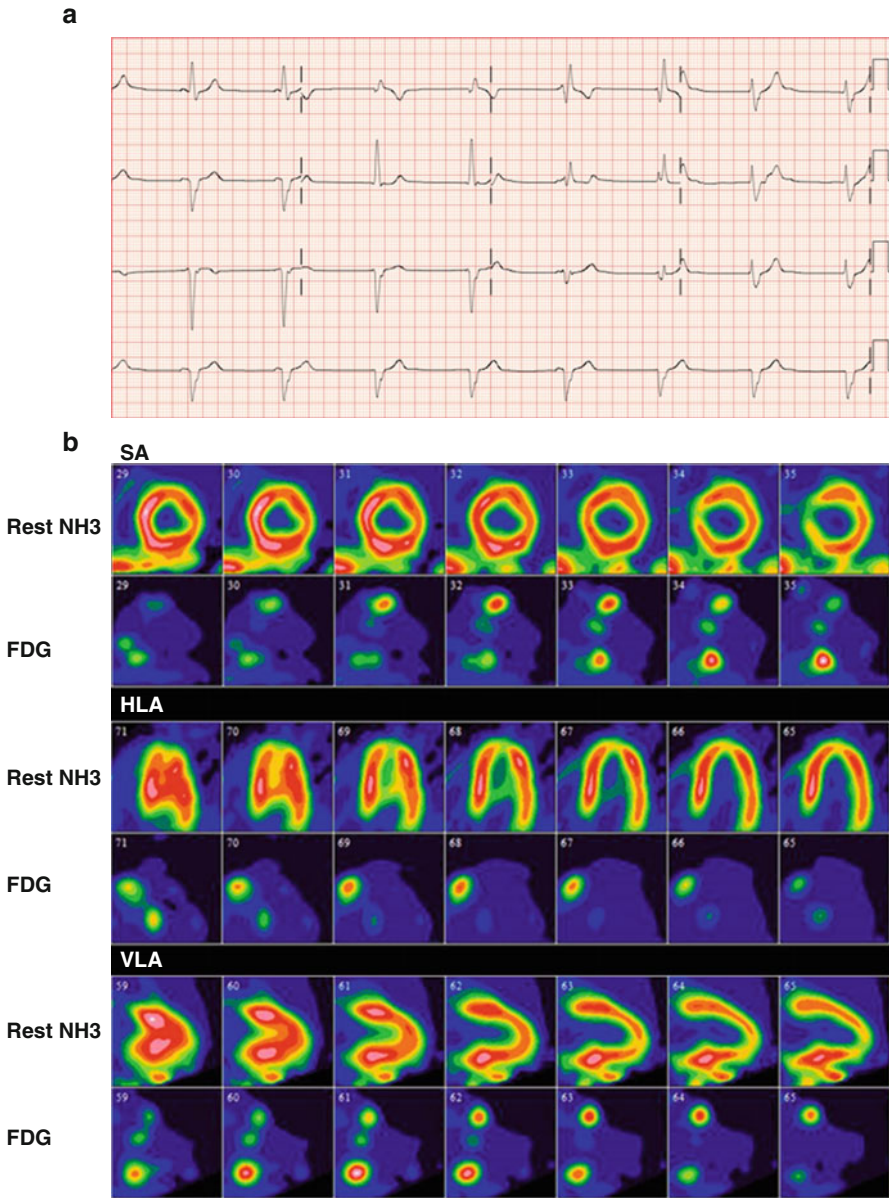


Fig. 4.9 (a) ECG of a patient without known history of sarcoidosis presenting with complete atrioventricular block and junctional escape beat with right bundle branch block. (b) Subsequent FDG-PET/CT with ammonia-N13 rest imaging shows focal increased uptake in the basal septal wall, right ventricular insertion, as well as right ventricular free wall

coefficient of variation has been shown to be significantly higher in patients with CS compared to normal healthy subjects and in patients with DCM [92].

Image interpretation should include comparison with perfusion images. This allows detection of myocardial scar and assessment of active sarcoidosis in these

Table 4.6 Interpretation criteria combining rest perfusion imaging and FDG findings

Rest perfusion	FDG	Interpretation
Normal	No uptake	Negative for CS
Normal	Diffuse	Diffuse FDG most likely due to suboptimal patient preparation
Normal	Focal	Could represent early disease
Defect	No uptake	Perfusion defect represents scar from sarcoidosis or other etiology
Defect	Focal in area of perfusion defect	Active inflammation with scar in the same location
Defect	Focal on diffuse with focal in area of perfusion defect	Active inflammation with scar in the same location with either diffuse inflammation or suboptimal preparation
Defect	Focal in area of normal perfusion	Presence of both scar and inflammation in different segments of the myocardium

Adapted from Blankstein et al. [95]

areas [94]. Interpretation criteria including perfusion images are summarized in Table 4.6 [95]. Finally, whole-body FDG-PET scan should be reviewed to assess for extracardiac sarcoidosis and other incidental findings. Detection of extrathoracic sarcoidosis can facilitate and accelerate the diagnosis of sarcoidosis by identifying potential biopsy sites [29]. It must be noted that imaging represents one of the criteria used for the diagnosis of cardiac sarcoidosis and diagnosis cannot be established solely on the base of a positive FDG-PET scan.

4.3.6 Role of FDG-PET in Cardiac Sarcoidosis

4.3.6.1 Diagnosis of Cardiac Sarcoidosis

Revision of the original Japanese Ministry of Health and Welfare (JMHW) guidelines for the diagnosis of cardiac sarcoidosis was presented by the joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Japanese College of Cardiology in 2006 (Table 4.7) [96]. These new guidelines, simply referred as the JMHW guidelines, are currently used in many studies as a gold standard for cardiac sarcoidosis. Although FDG-PET is not explicitly included in these criteria, gallium-67 scintigraphy is often substituted by FDG-PET. According to these criteria, diagnosis of CS requires histopathological or clinical diagnosis of extracardiac sarcoidosis. Endomyocardial biopsy has limited sensitivity due to sampling method and heterogeneous myocardial involvement [97]. Unlike amyloidosis, cardiac involvement with sarcoidosis is typically patchy; therefore, even in the cases of negative endomyocardial biopsy, the diagnosis of cardiac sarcoidosis can still be established in the appropriate clinical setting [76]. Because of poor correlation between imaging findings and JMHW diagnosis of CS, some authors have suggested that JMHW has limited sensitivity for detection of CS [88, 95, 98].

More recently, the Heart Rhythm Society (HRS), in collaboration with many organisms including the World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG), published an expert consensus recommendation on criteria

Table 4.7 2006 revised JMHW guidelines for the diagnosis of cardiac sarcoidosis presented by the joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Japanese College of Cardiology [96]

1. Histological diagnosis

Cardiac sarcoidosis is confirmed when cardiac biopsy specimens demonstrate noncaseating epithelioid cell granuloma with histological or clinical diagnosis of extracardiac sarcoidosis

2. Clinical diagnosis group

Cardiac sarcoidosis is diagnosed without endomyocardial biopsy or in the absence of typical granulomas on cardiac biopsy when histological or clinical diagnosis of extracardiac sarcoidosis is established and a combination of major or minor diagnostic criteria has been satisfied as follows:

(a) ≥ 2 of the 4 following major criteria are satisfied

- Advanced atrioventricular block
- Basal thinning of the ventricular septum
- Positive cardiac gallium uptake*
- Left ventricular ejection fraction $< 50\%$

or

(b) 1 of the 4 major criteria and ≥ 2 of the following minor criteria are satisfied:

- Abnormal electrocardiogram findings including ventricular tachycardia, multifocal frequent premature ventricular contractions, complete right bundle branch block, abnormal Q waves, or abnormal axis deviation
- Abnormal echocardiogram demonstrating regional wall motion abnormalities, ventricular aneurysm, or unexplained increase in wall thickness
- Perfusion defects detected by myocardial scintigraphy
- Delayed gadolinium enhancement of the myocardium on cardiac MRI scanning
- Interstitial fibrosis or monocyte infiltration greater than moderate grade by endomyocardial biopsy

Table 4.8 Expert consensus recommendation from the Heart Rhythm Society on criteria for the diagnosis of cardiac sarcoidosis [99]

1. Histological diagnosis from myocardial tissue

CS is diagnosed in the presence of noncaseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable)

2. Clinical diagnosis from invasive and noninvasive studies:

It is probable that there is CS if:

(a) There is a histological diagnosis of extracardiac sarcoidosis

and

(b) One or more of the following is present:

- Steroid +/- immunosuppressant responsive cardiomyopathy or atrioventricular block
- Unexplained reduced LVEF ($\leq 40\%$)
- Unexplained sustained (spontaneous or induced) VT
- Mobitz type II second-degree heart block or third-degree heart block
- Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
- Late gadolinium enhancement on cardiac MRI (in a pattern consistent with CS)
- Positive gallium uptake (in a pattern consistent with CS)

and

(c) Other causes for the cardiac manifestation(s) have been reasonably excluded

for the diagnosis of cardiac sarcoidosis (Table 4.8) [99]. Imaging modalities recommended in these guidelines include FDG-PET, Ga-67 scintigraphy, and cardiac MRI. Furthermore, these criteria are more stringent, requiring histological diagnosis of cardiac or extracardiac sarcoidosis.

4.3.6.2 Diagnostic Accuracy

Establishing diagnostic accuracy for cardiac sarcoidosis (CS) of any imaging modality is challenging because of lack of a proper gold standard. Ideally, diagnostic accuracy studies would use myocardial biopsy on all subjects. However, this gold standard is invasive and has a poor sensitivity below 25 % due to the heterogeneity of myocardial involvement [100, 101]. Because of this, studies tend to have small sample size and/or rely on JMWH criteria as their gold standard. A meta-analysis reviewing seven studies with a total of 164 patients reported sensitivity of FDG-PET scan for cardiac sarcoidosis ranging from 79 to 100 % with pooled sensitivity of 89 % [74]. They reported a wide range of specificity values from 38 to 100 % with pooled specificity of 78 %. It was hypothesized that this wide range of specificity is due to physiological myocardial uptake leading to false-positive studies and low sensitivity of the use of JMWH criteria as gold standard [74].

FDG-PET vs Gallium 67

As for other sites of extrapulmonary sarcoidosis, sensitivity of Ga-67 to detect cardiac sarcoidosis is very low, ranging from 15 to 40 % [25, 75, 102]. In a retrospective study including 76 patients with suspected cardiac sarcoidosis using the 1993 JMWH criteria as their gold standard, fasting FDG-PET sensitivity and specificity were 85 % and 90 %, respectively, compared to 15 % and 80 % for Ga-67 scintigraphy [75]. These results reinforce the importance of revising JMWH diagnostic criteria to incorporate FDG-PET instead of Ga-67.

Pitfalls

The wide range of reported specificity of FDG-PET to detect cardiac sarcoidosis has been attributed in part to a suboptimal gold standard [74]. Additionally, other conditions can render false-positive results. One of the major causes of false-positive study is related to poor patient preparation. Without preparation, uptake in the myocardium is usually diffuse but can be focal or focal on diffuse [103]. Respect of protocol can be optimized by good communication with patients and an interview to ensure adequate preparation prior to imaging. Nevertheless, even after proper fasting, normal myocardium can demonstrate uptake with regional disparities, with the lateral and inferior wall containing more activity compared to the septum and anterior wall [104]. Indeed, lateral wall uptake in a normal heart following adequate preparation was reported and is thought to represent a normal variation [74, 88, 89], possibly related to regional substrate availability (Fig. 4.10) [92].

Dilated cardiomyopathy (DCM) can also present as focal on diffuse FDG uptake, possibly due to myocardial cell loss or regional fibrosis. Consequently, in the appropriate clinical context, DCM should be included in the differential diagnosis of a positive FDG-PET study [92]. Other causes of myocarditis, cardiac amyloidosis, infection, and myocardial metastases can also demonstrate abnormal myocardial uptake. Finally, patients with pulmonary hypertension can demonstrate increased right ventricular FDG [105, 106], mimicking RV involvement.

FDG-PET is a sensitive examination to detect CS, and therefore, there are few circumstances under which FDG-PET will be falsely negative [74]. Patient receiving

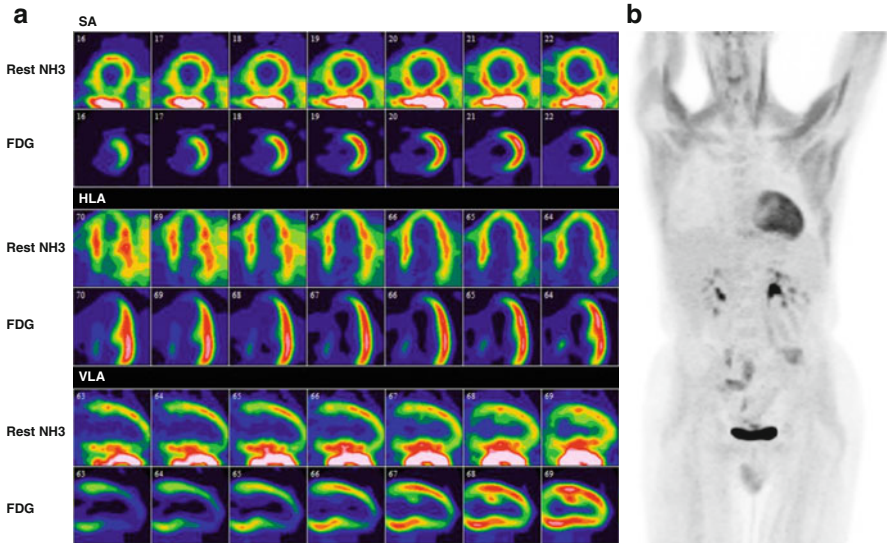


Fig. 4.10 (a) Rest ammonia-N13 and FDG-PET scan of a patient with suspected cardiac sarcoidosis. After following fasting and HCLF diet to suppress physiological myocardial uptake, there is FDG uptake in the lateral wall of the left ventricle, representing a normal variant. (b) Anterior projection of maximal intensity projection showing no evidence of extracardiac sarcoidosis. Note the diffuse uptake in muscle of the upper extremities, in keeping with recent strenuous activity

corticosteroids or with “burned-out” sarcoidosis can have a negative FDG-PET scan [107]. In the case of burned-out sarcoidosis, rest perfusion scan will demonstrate a perfusion defect in the area of granulomatous scar [95]. Finally, another potential cause of false negative is related to the size of the area of inflammation. Although spatial resolution of FDG-PET is significantly greater than [67] Ga scintigraphy, it remains lower than MRI and very small foci of inflammation could be missed.

4.3.6.3 Prognostic Value of PET/CT

Cardiac involvement in sarcoidosis can lead to congestive heart failure due to progressive infiltration of the myocardium by granulomas [49, 56]. In a survey conducted in the United Kingdom, the 5-year survival rate of patients with sarcoidosis and suspected cardiac involvement was 40 %, with most of these patients receiving steroid treatments [108]. In a more recent study by Yazaki et al., the 5-year survival rate of patients treated for cardiac sarcoidosis and systolic impairment was 75 %, while the 5-year survival rate reached 90 % in patients treated for cardiac sarcoidosis with normal systolic function [56]. These results suggest that identification and treatment of patients with active cardiac sarcoidosis before the occurrence of systolic dysfunction is fundamental in the prevention of adverse outcomes. Unfortunately, approximately half of the patients with cardiac sarcoidosis are asymptomatic [109]. Furthermore, the severity of pulmonary involvement assessed either by imaging or PFTs does not correlate with the presence of CS [109, 110]. Therefore, identification of patients with CS before occurrence of systolic dysfunction can be challenging. For this reason, it is

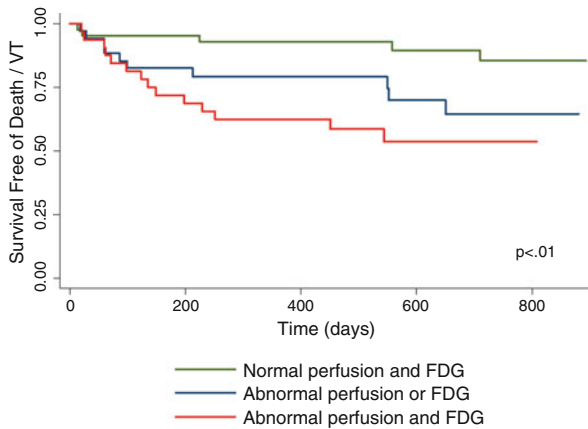


Fig. 4.11 Survival free of death or ventricular tachycardia stratified by perfusion and FDG-PET results, demonstrating that combination of perfusion abnormality and abnormal FDG-PET uptake is associated with increased risk of death and ventricular tachycardia (Reprinted from Blankstein et al. [95] with permission from the author and Elsevier)

thought that imaging could play a central role in the identification of patients with CS and could lead to prevention of adverse outcome.

Other complications of patients with cardiac sarcoidosis are ventricular arrhythmias and sudden death [49]. Patients with cardiac sarcoidosis diagnosed based on the JMHW presenting with unsustained VT display significantly higher FDG uptake when compared with those with AV blocks and asymptomatic controls [111]. Conversely, patients demonstrating both perfusion abnormality and inflammation on FDG-PET have threefold increased rate of event rate (VT or sudden death) [95]. Blankstein et al. demonstrated, using a multivariable model including left ventricular ejection fraction (LVEF), JMHW criteria, and pattern of abnormality on PET scan, that the presence of both abnormal FDG uptake and perfusion abnormalities had the strongest link to death or VT (Fig. 4.11) [95]. Furthermore, they showed that risk was greater when there was RV involved [95]. There is likely a relationship between arrhythmias and FDG findings, but there is currently only sparse data on prognostic value of FDG-PET in CS, and therefore, current guidelines on ICD implantation in patients with CS do not rely specifically on FDG-PET [99].

FDG-Pet allows detection of CS before functional and structural changes are detectable, allowing early diagnosis and appropriate management. Furthermore, close monitoring of patients with myocardial inflammation demonstrated on FDG-PET is warranted and may prevent progressive cardiac disease [109].

4.3.6.4 Assessment of Response to Therapy

Another potential role of FDG-PET in CS is the assessment of response to therapy. Because FDG accumulates in active inflammation and not fibrosis [41], it could be used to evaluate response to therapy on serial studies. Several studies showed that following steroid therapy, there is a decrease in FDG uptake in both extracardiac

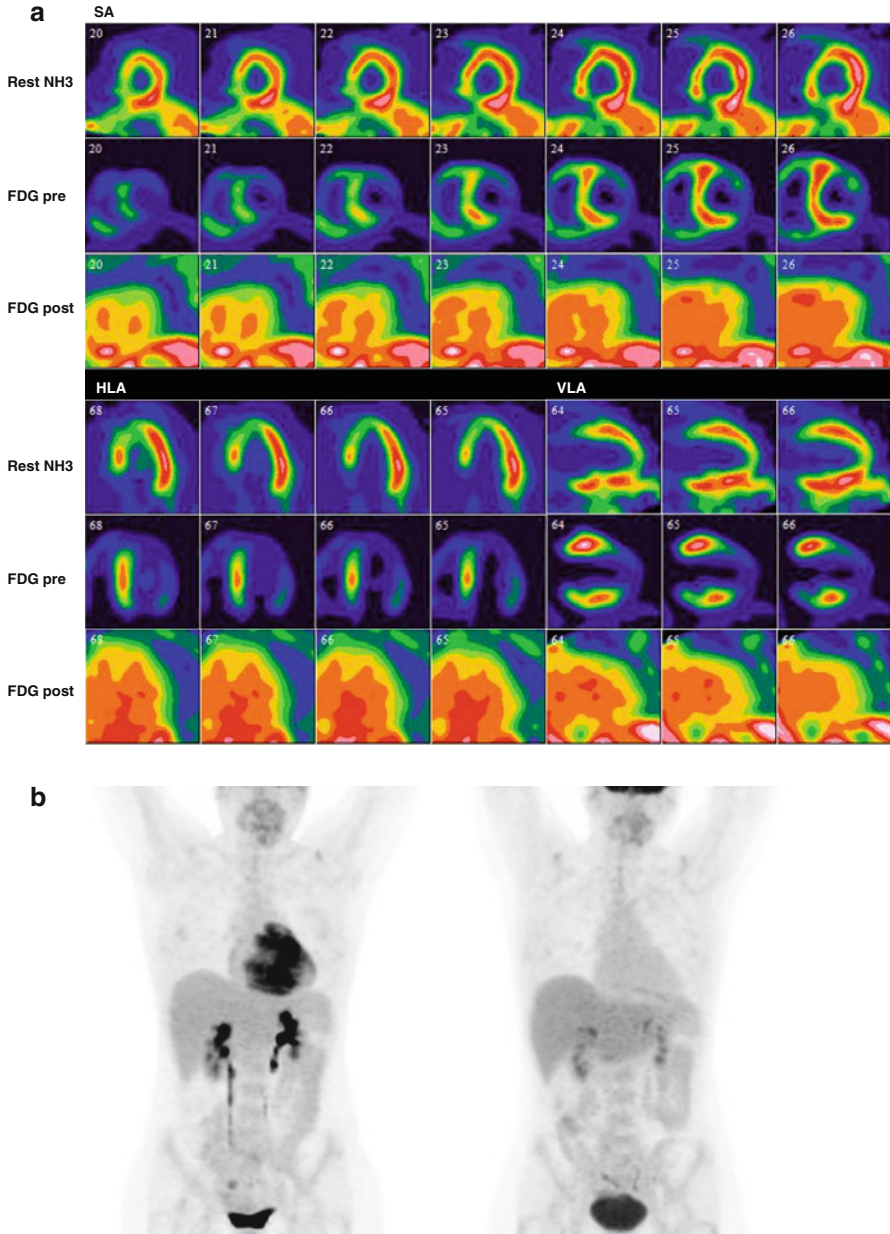


Fig. 4.12 (a) Baseline rest ammonia-N13 perfusion images with (b) corresponding FDG-PET images of a patient with diagnosis of cardiac sarcoidosis. Following a treatment of 9 months of corticosteroid, a FDG-PET study was repeated 13 months following baseline evaluation, showing no evidence of active inflammation in the myocardium. The LVEF, as measured by radionuclide ventriculography prior to each FDG-PET scan, remained unchanged, from 53 to 51 %

lesions [20, 42–45] and cardiac lesions (Fig. 4.12) [73]. Resolution of FDG uptake in the basal septum has been associated with resolution of third-degree atrioventricular block and progression of FDG uptake after steroid tapering was associated with VT in case reports [112, 113].

In a retrospective study of 23 patients with cardiac sarcoidosis treated with immunosuppressive therapies guided by serial PET scans, reduction in the intensity and extent of inflammation, as quantified by FDG uptake, was associated with an increase in LVEF [107]. These results reinforce the potential role of FDG-PET in guiding the duration and intensity of immunosuppressive treatment. Nonetheless, further validation of the role of FDG-PET in assessment of response to therapy by prospective trials is necessary.

4.3.7 When to Consider PET/CT in Patients with Sarcoid Disease

Metha et al. studied prevalence of cardiac symptoms, ECG findings, Holter monitoring, and transthoracic echocardiography findings of 62 patients with known sarcoidosis [109]. Description of abnormalities studied is presented in Table 4.9. They showed that patients with cardiac sarcoidosis had more cardiac symptoms and more findings on Holter monitoring and on transthoracic echocardiography compared to patients without cardiac sarcoidosis. All patients with cardiac sarcoidosis had symptoms or at least one abnormal test result [109]. Based on these results, the HRS expert consensus recommends screening of patients with established extracardiac sarcoidosis with clinical symptoms, ECG and echocardiography; [99] if one or more of these screening tests is abnormal, the patient is then referred for further cardiac imaging with FDG-PET or cardiac MRI.

Table 4.9 Screening tests with accompanying abnormalities associated with cardiac sarcoidosis

Screening test	Description of abnormalities
Cardiac symptoms	Significant palpitation Presyncope Syncope
Abnormal ECG	RBBB LBBB Second- or third-degree AV block Q waves in two consecutive leads Ventricular tachycardia
Abnormal Holter monitoring	Supraventricular tachycardia Excessive PVCs AV block Ventricular tachycardia
Echocardiography findings	LV systolic dysfunction Segmental wall motion abnormalities LV diastolic dysfunction RV systolic dysfunction

4.3.8 When to Consider PET/CT in Patients Without Evidence of Sarcoid Disease

Multiple studies have reported cardiac manifestations as the initial presentation of patients with sarcoidosis [54, 114]. These patients were younger than 55 years old and initially presented with new onset of unexplained atrioventricular block and VT [115]. Nery et al. prospectively evaluated patients younger than 60 years old who presented with unexplained second- or third-degree atrioventricular block, with no previous history of sarcoidosis [55]. Of the 32 patients studied, CS was diagnosed in 11 (34 %) subjects and 11/11 were subsequently diagnosed with extracardiac sarcoidosis. Similar results were obtained in patients presenting with sustained VT of unknown etiology [116]. Nery et al. prospectively evaluated patients presenting with monomorphic VT of unknown etiology, excluding patients with idiopathic VT, ischemic VT, or known sarcoidosis. In their sample, 6 out of 14 (28 %) patients had CS as the underlying etiology. Based on these results, it is recommended to perform advanced cardiac imaging with FDG-PET or cardiac MRI in patients younger than 60 years old presenting with unexplained second- or third-degree atrioventricular block, and it could be useful in patients with VT of unknown etiology [99].

4.4 Future Directions

The rationale behind detection of patient with cardiac sarcoidosis is prevention of life-threatening arrhythmias and to preserve left ventricular function. Over the past decade, FDG-PET has been playing a central role in detecting cardiac sarcoidosis. Nevertheless, the current criteria used in the diagnosis of CS require further refinement. For example, an optimal pretest preparation protocol should be determined and image interpretation should be standardized. Additionally, understanding physiological uptake after preparation is central to improve accuracy. Some authors reported the possibility of FDG uptake in areas without inflammation due to regional substrate availability [92]. Furthermore, very little data is available on accuracy of FDG-PET in patients with insulin resistance. Given the high prevalence of diabetes and that corticosteroids can induce insulin resistance, many patients referred for FDG-PET imaging may present with insulin resistance. For this reason, understanding the effects of insulin resistance on FDG-PET accuracy and optimization of pretest preparation in these patients is necessary.

Although promising results have emerged so far, further prospective studies to establish the role of FDG uptake in therapy monitoring are needed. Using FDG-PET to differentiate between quiescent granulomas and active inflammation could be used to adjust therapy dosage, and decision to discontinue treatment could be based on assessment of inflammation rather than fixed time periods.

New hybrid imaging systems combining PET and MRI are now available, allowing combination of tissue characterization capabilities of MRI with PET. Two reports have highlighted the complementary role of PET and MRI in cardiac sarcoidosis with PET-MRI hybrid imaging [117, 118].

Although FDG-PET is an effective tool in the diagnosis of CS, FDG remains a nonspecific marker and interpretation of results should always be conducted in light of clinical information. Some authors have described combination of FDG with other PET tracers including ¹¹C-methionine [119, 120], fluorine-18-alpha-methyltyrosine (FMT) [121], and ¹⁸F-fluorothymidine (FLT) [122] to improve specificity of FDG imaging in extracardiac sarcoidosis. Clinical trials are under way to assess the potential role of ⁶⁸Ga-DOTANOC, a neuroendocrine tumor marker, in cardiac sarcoidosis. To this day, only anecdotal reports are available on imaging sarcoidosis with other tracers than FDG. In order to replace FDG in clinical practice, a new PET tracer would need to be more specific and less dependent on patient preparation and not require on-site cyclotron. Until then, FDG-PET remains an accurate and efficient way of imaging patients for sarcoidosis.

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