

## FOCUS ISSUE ON CARDIAC SARCOIDOSIS

## Role of PET/CT for the Identification of Cardiac Sarcoid Disease

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## Abstract

Sarcoidosis reflects a multisystem granulomatous disease of unknown etiology that is characterized by the formation of non-caseating granuloma in various organs. Cardiac involvement may occur in one out of four patients accounting for an increased mortality rate in these patients.  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography ( $^{18}\text{F}$ -FDG-PET) is increasingly applied for the detection and characterization of systemic and cardiac sarcoid disease. In particular,  $^{18}\text{F}$ -FDG-PET has the unique potential to identify early and inflammatory cardiac sarcoid disease before developing structural alterations in the myocardium such as fibrosis and/or scarring.  $^{18}\text{F}$ -FDG-PET is not only suitable for early disease identification but also for installing and guiding immune-suppressive therapy to improve cardiovascular outcome that, however, needs to be further tested in large-scale clinical trials.  $^{18}\text{F}$ -FDG-PET, is likely to introduce an image-guided and personalized preventive medicine approach in sarcoid patients in the near future.

**Keywords:**  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), Granulomatous disease, Inflammation, Positron emission tomography (PET), Sarcoid disease

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Sarcoidosis is described as a multisystem granulomatous disease of unknown etiology that is characterized by the formation of non-caseating granuloma in various organs (1,2). The etiology of cardiac sarcoidosis still remains to be further elucidated, while environmental, occupational, and infectious causes are assumed to trigger an immunologic response in genetically predisposed individuals (2). The prevalence of sarcoid manifestation is quite variable and contingent upon ethnicity, gender and regions (3). For example, the prevalence is 10–40/100'000 persons in the United States and Europe, while there is an increased prevalence of sarcoidosis in African-American as compared to Caucasians with a ratio ranging from 10–17: 1 (1). Interestingly, in the Scandinavian population the prevalence of sarcoidosis is markedly higher than in other whites with 50–60 per 100'000 individuals. In the

japanese population the prevalence of sarcoid is reported to be 1.01 per 100'000 inhabitants and related to gender (prevalence of 0.73 in males and 1.28 in females) (4). Gender has been appreciated to play a pivotal role in sarcoid manifestation as women are more frequently affected with a peak incidence below 40 years of age (5). While systemic sarcoid disease most frequently manifests in the perihilar–mediastinal lymph nodes and in the lungs, the disease can affect also any other organ (6). In one out of four patients with sarcoid disease, cardiac involvement is likely to ensue. Clinically, cardiac sarcoid disease is underdiagnosed but it is anticipated to be the predominant cause of death by sarcoidosis in Japan and in the United States (3,7).

## Clinical manifestation

Cardiac sarcoid disease with inflammatory granuloma

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**Table 1** Indications for Perfusion and  $^{18}\text{F}$ -FDG-PET for the Evaluation of Cardiac Sarcoid Disease

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-Patients <55 years of age presenting with second- or third-degree atrioventricular block of unknown etiology.
-Unexplained monomorphic ventricular tachycardia.
-Patients with extra-cardiac sarcoidosis and abnormal ECG, Holter or Echocardiogram in whom cardiac sarcoidosis is suspected.
-Patients with established cardiac sarcoidosis for evaluation of response to treatment.

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$^{18}\text{F}$ -FDG-PET:  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography, ECG: electrocardiogram.

may be ensued by fibrosis or scarring that clinically may lead to different manifestations dependent on the extension and location of the disease. The clinical manifestation of cardiac sarcoidosis may range from subclinical disease to sudden cardiac death (3,8). For example, only 40–50% of patients with cardiac sarcoidosis, as detected at autopsy, have indeed clinically-manifest cardiac disease (9). The most commonly affected regions are found in the ventricular septum and free lateral wall, typically in the basal segments (3,10). Involvement of the septum is likely to cause conduction abnormalities most frequently a third-degree atrioventricular block (14–30%) in young and middle-aged adults (11,12). Such middle-aged patients (<55 years) with sarcoid induced third-degree atrioventricular block are at high risk to suffer cardiac death, heart failure, ventricular fibrillation, or ventricular tachycardia as previous investigations have shown (12). Of note, ventricular tachycardia has been reported in up to 23% of cardiac sarcoid patient and it reflects the second most common clinical finding (13). Unfortunately, sudden cardiac death may manifest in up to 40% as first clinical manifestation (14). Apart from arrhythmic complications, the development of congestive heart failure is not seldom and it manifests in 73% of patients with lethal outcome. Congestive heart failure in cardiac sarcoidosis may be primarily related to extensive myocardial infiltration but also due to pulmonary arterial hypertension induced right heart failure, or valve insufficiency due to papillary muscle involvement. Generally, an involvement of the heart in sarcoid disease portends a worse prognosis, if not detected and treated in a timely manner with corticosteroids and/or other immunosuppressive agents (15). Temporary or permanent pacemaker placement may be needed when atrioventricular conduction abnormalities present, while in clinically manifest cardiomyopathy implantable defibrillator to prevent sudden cardiac death need to be considered. In progressive and advanced stages of heart failure cardiac transplantation may be the ultimate choice. The timely identification of cardiac sarcoidosis remains a difficult challenge and is contingent on the integration of both clinical and imaging findings. Sarcoid

disease most commonly manifests in the thoracic lymphatic nodes and lungs followed by the cardiovascular system (3). When systemic sarcoid disease is present, the prevalence of cardiac involvement may reach up to 25% (16). Conversely, 40–50% of patients with cardiac sarcoid affection at necropsy may not have any clinical symptoms (3,8). Asymptomatic cardiac sarcoidosis, however, is associated a mortality rate up to 19% and, thus, carries an increased risk for poor cardiovascular outcome (17). Thus, a timely identification of cardiac sarcoid disease and the monitoring of its treatment response to immuno-suppressive therapy with cardiac PET/CT imaging is likely to improve cardiovascular outcome in these patients but needing large-scale clinical trials.

In general, PET/CT imaging for cardiac sarcoid disease should be considered in patients having second- or third-degree atrioventricular block of unknown etiology in patients <55 years of age and when non-ischemic, monomorphic ventricular tachycardia manifests (Table 1). Also, when extra-cardiac sarcoidosis is associated with abnormal electrocardiogram, Holter or echocardiogram, further cardiac evaluation with PET/CT imaging may be indicated. In particular, an early identification of cardiac sarcoid involvement with PET/CT imaging may be crucial to install immunosuppressive therapy and thereby prevent the development of severe cardiomyopathy and heart failure symptoms (18).

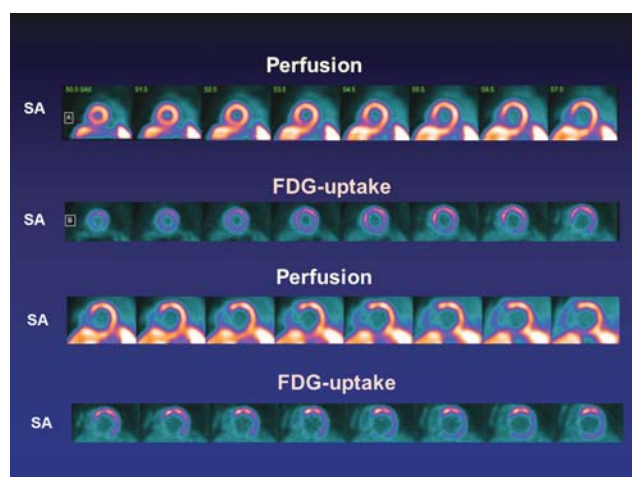
### Identification of cardiac sarcoidosis

As there is no definite gold standard or reference in the identification of cardiac sarcoid disease, it poses major problem in clinical routine. While a histological proof of cardiac sarcoid disease is desirable for definite identification, the diagnostic yield of myocardial biopsies is low and in the end it cannot rule out cardiac sarcoidosis (3,8). In this respect, the Guidelines of the Japanese Ministry of Health and Welfare (JMHWG), as revised by the Japan Society of Sarcoidosis and Other Granulomatous Disorders in 2006, serve as a worldwide standard for clinical detection of cardiac sarcoidosis (19,20). According to these guidelines, either a direct

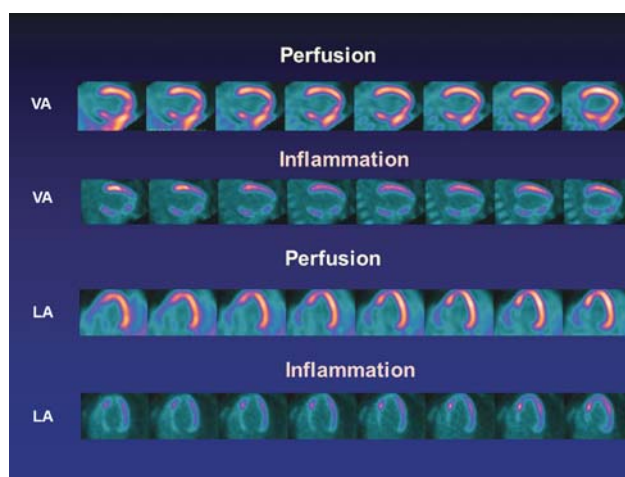
biopsy-proven confirmation of cardiac sarcoidosis or direct histologically proven extra-cardiac sarcoidosis combined with indirect evidence of an inflammatory myocardial lesion is warranted. Although direct proof of cardiac sarcoidosis via endomyocardial biopsy is highly desirable and specific, it is hampered by a reduced sensitivity of about 20% due to a patchy myocardial involvement and selective sampling from the septum. Until more recently, indirect evidence for cardiac sarcoid involvement was derived by imaging of inflammation with the radiotracer Gallium-67, regional myocardial perfusion defects on SPECT images indicative of regional fibrosis or even scarring, and regional wall motion or conduction abnormalities (21). Importantly, updated guidelines have included evidence of regional cardiac fibrosis and/or wall motion abnormalities on magnetic resonance imaging (MRI) studies as minor criteria (20). Somehow surprising, however,  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET to image sarcoid associated myocardial inflammation is not included in current guidelines, despite its well documented sensitivity and specificity in cardiac sarcoid detection (22). In a meta-analysis of seven studies involving 164 patients of whom 50% had diagnosed systemic sarcoidosis, the sensitivity and specificity of  $^{18}\text{F}$ -FDG-PET in the detection of cardiac sarcoid involvement was reported to be as high as 89% and 78%, respectively (22). In this respect, the Japanese health insurance system has approved more recently the reimbursement of  $^{18}\text{F}$ -FDG-PET for identification of inflammation sites in cardiac sarcoidosis (23) but not yet the application  $^{18}\text{F}$ -FDG-PET to diagnose patients with suspected cardiac sarcoidosis. The Japan Society of Sarcoidosis and other Granulomatous Disorders is about to add a positive  $^{18}\text{F}$ -FDG-PET finding as one of the criteria for the diagnosis of cardiac sarcoidosis (23).

$^{18}\text{F}$ -FDG is a glucose analogue that in concert with PET/CT is increasingly applied to identify and characterize systemic and cardiac sarcoid disease (15,18,19). This diagnostic approach with  $^{18}\text{F}$ -FDG-PET/CT is most suitable for active sarcoid disease detection as up-regulation of glucose metabolism is observed at sites of macrophage-mediated inflammation (24). It is important to note that the energy production of the heart depends on various factors such as fasting state, neurohormonal conditions, and systemic regulation. Although that most part of the energy consumption of the heart is extracted from oxidation of free fatty acids under aerobic conditions, glucose and amino acids may also contribute to this. The glucose uptake of about 15–20% under aerobic conditions may in fact lead to a

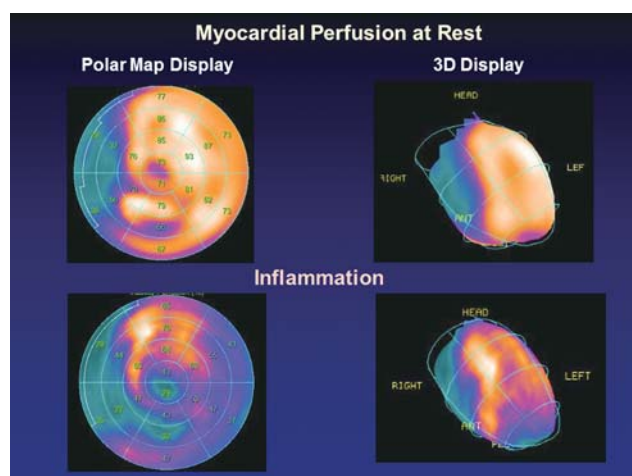
“physiologic”  $^{18}\text{F}$ -FDG uptake in the myocardium even under a fasting state. Not surprisingly, fasting studies in normal volunteers (25) and in oncologic patients (26) have reported diffuse, inhomogeneous, but also focal  $^{18}\text{F}$ -FDG uptake. The focal  $^{18}\text{F}$ -FDG was predominantly seen in the infero-lateral and basal part of the left-ventricle (26). In order to avoid this confounding factor of physiologic  $^{18}\text{F}$ -FDG uptake that, in fact, may lead to false positive detection of cardiac sarcoidosis, strategies for enhanced myocardial suppression of glucose uptake have been developed (3,8,21). These include prolonged fasting (27), dietary modifications (28,29), and a heparin load before PET imaging (8,30). In particular, a very high-fat, low-carbohydrate, protein-permitted diet has been reported to effectively suppresses physiologic myocardial  $^{18}\text{F}$ -FDG uptake more effectively than overnight or 4-h fasting in an oncologic cohort (29). In another study, the effectiveness of myocardial  $^{18}\text{F}$ -FDG suppression owing to a high-fat, low-carbohydrate, and protein-permitted diet was compared with a prolonged fasting over 12 hours in an oncologic patient cohort (28). As it was observed, dietary restriction better suppressed  $^{18}\text{F}$ -FDG cardiac uptake than an extended fasting state (28). Thus, combining a high-fat, low-carbohydrate, and protein-permitted meal followed by a prolonged fasting state of at least 12 hours is considered to be effective in suppressing physiologic  $^{18}\text{F}$ -FDG, providing the basis to apply  $^{18}\text{F}$ -FDG PET/CT for the detection of inflammatory sarcoid disease (3,8). Such approach may also be enhanced by additional heparin application shortly before the  $^{18}\text{F}$ -FDG PET/CT (8). Administration of unfractionated heparin intravenously may promote the increase in free fatty acids plasma levels and its utilization in the myocardium instead of glucose. Unfractionated heparin, in fact, activates the lipoprotein lipase with lipolytic effects leading to a substantial increase in free fatty acids in the circulation. While the use of intravenous heparin application to stimulate a free fatty acids loading prior to the PET scanning is variable between institutions, one possibility is to administer 700–1000 IU intravenously in divided doses 30 and 15 minutes prior to scanning in patients where there is no contraindication. Overall, if patient preparation is performed appropriately,  $^{18}\text{F}$ -FDG PET/CT is a reliable tool in the diagnosis of active and inflammatory cardiac sarcoid disease (22). Nevertheless, it is important to keep in mind that the distribution of cardiac sarcoid disease is quite variable and commonly does not follow coronary vascular territories (3,8). A focal and patchy distribution of  $^{18}\text{F}$ -FDG in the left ventricular wall is suggestive of



(A)



(B)



(C)

**Fig. 1** PET/CT study in an individual with biopsy-proven and isolated cardiac sarcoid disease that led to end-stage heart failure raising the need for potential heart transplantation. **A-B)** Reanulated  $^{13}\text{N}$ -ammonia PET/CT perfusion images signify a moderate-to-large sized (4-5 segments) perfusion defect of the septum in the basal and mid-segment with some extension into the inferior wall likely to reflect severe fibrosis and/or scar tissue. Corresponding  $^{18}\text{F}$ -FDG-PET/CT images with predominant and pronounced  $^{18}\text{F}$ -FDG uptake in the anterior wall to suggest myocardial inflammation. **C)** Polar map display and 3D display of perfusion and inflammation findings in this patient.

cardiac sarcoid disease (Fig. 1). In addition, focal  $^{18}\text{F}$ -FDG uptake in the basal segments of the septum or lateral wall but also of the papillary muscles is frequently encountered and widely characteristic for cardiac sarcoid activity (3,31,32).

In a recent article by Ishida et al. (23), diagnostic criteria for cardiac regions with visual assessment of  $^{18}\text{F}$ -FDG uptake have been established. According to this, the distribution of myocardial  $^{18}\text{F}$ -FDG uptake for sarcoid detection can be evaluated on the basis of following classifications:

1. Classification into two types of patterns: diffuse and focal.
2. Classification into three types of patterns: none, diffuse, and focal.
3. Classification into four types of patterns: none, diffuse, focal, and focal and diffuse.

For example, if an exam demonstrates an  $^{18}\text{F}$ -FDG uptake distribution that is focal or that has a focal and diffuse pattern according to classifications 2 and 3, this exam is considered to signify an abnormal  $^{18}\text{F}$ -FDG

uptake in an inflammatory myocardial sarcoid lesion. Conversely, cardiac exams revealing both focal and diffuse  $^{18}\text{F}$ -FDG uptake distribution patterns in classification 1 are also estimated to demonstrate abnormal  $^{18}\text{F}$ -FDG uptake. As regards the classification 3 of  $^{18}\text{F}$ -FDG uptake distribution into four types of patterns (30), it is the most frequently adopted determination criteria in Japan. Applying the latter classification with  $^{18}\text{F}$ -FDG uptake pattern and exclusion of cases with focal uptake only in the lateral wall,  $^{18}\text{F}$ -FDG PET/CT imaging may have a diagnostic capability of 100% and specificity of 81.5% (30).

For the detection of cardiac sarcoid disease, however, it is recommended to add resting myocardial perfusion imaging to  $^{18}\text{F}$ -FDG PET/CT (3,8,15). While  $^{18}\text{F}$ -FDG-PET/CT following a high-fat, low-carbohydrate, and protein-permitted diet with a prolonged fasting over at least 12 hours provides important information of active and inflammatory sarcoid disease, the assessment of resting myocardial perfusion aims to identify regional perfusion defects suggestive of myocardial areas with



Rest Perfusion	FDG	Frequency	Example		Interpretation / Comment
			Perfusion	FDG	
Normal perfusion and metabolism					
Normal	Normal (negative)	32 (27%)			Normal
Normal	Diffuse (non-specific)	15 (12%)			Diffuse FDG most likely due to failure to suppress FDG from normal myocardium
Abnormal perfusion <u>or</u> metabolism					
Normal	Focal	20 (17%)			Nonspecific pattern; focal increase in FDG may represent early disease vs. normal variant
Positive	Negative	17 (14%)			Rest perfusion defect may represent scar from cardiac sarcoidosis or other etiologies
Abnormal perfusion <u>and</u> metabolism					
Positive	Focal increase ("mismatch pattern")	23 (19%)			Presence of active inflammation ± scar in the same location
Positive	Focal on diffuse	6 (5%)			Similar to above but also areas of inability to suppress FDG from normal myocardium vs. diffuse inflammation
Positive	Focal increase (different area)	5 (4%)			Presence of both scar and inflammation but in different segments

**Fig. 2** Classification of cardiac PET/CT perfusion and metabolism imaging for the detection of cardiac sarcoid involvement. Normal perfusion and metabolism (category 1), abnormal perfusion or metabolism (category 2), abnormal perfusion and metabolism (category 3). (With kind permission from reference 14)

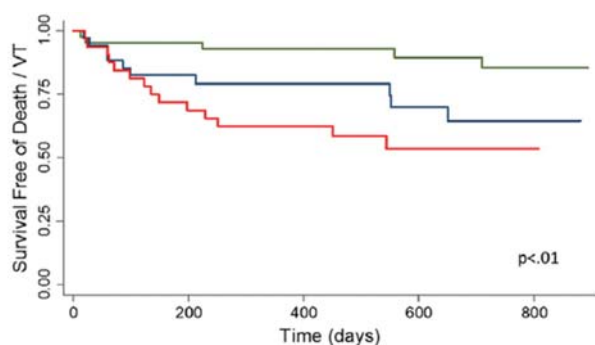
fibrosis or due to inflammation induced edema associated with a compression of the coronary arteriolar vessels (23). Assessing three patterns of myocardial perfusion and  $^{18}\text{F}$ -FDG-uptake is most helpful to increase the confidence in diagnosing cardiac sarcoid disease. In this respect, images are commonly divided into following patterns (Fig. 2) (15):

1. Normal perfusion and metabolism
2. Abnormal perfusion or metabolism
3. Abnormal perfusion and metabolism

Following the conventional sarcoid preparation, normal metabolism was defined as no or diffuse FDG uptake without any areas of focal uptake. In general, reduced regional perfusion associated with an abnormal FDG-uptake signifies a "mismatch" between a focal decrease in myocardial perfusion and abnormal FDG-uptake (inflammation), that is widely characteristic and diagnostic for acute and inflammatory cardiac sarcoid disease. In the differential diagnosis, however, subacute myocardial infarction and myocarditis need to be considered and ruled out clinically. The distribution pattern of cardiac sarcoid disease is quite helpful as reductions in regional myocardial perfusion do not follow an ischemic or coronary artery disease pattern. As mentioned before, cardiac sarcoid activity is com-

monly encountered in the basal segments of the septum or lateral wall but may affect also any other myocardial segments. Conversely, normal perfusion and no abnormal  $^{18}\text{F}$ -FDG widely excludes cardiac sarcoid disease. The diagnostic challenge, however, arises for the intermediate classification with abnormal perfusion or  $^{18}\text{F}$ -FDG uptake. Abnormal regional myocardial perfusion most pronounced in the basal segments and following a non-ischemic pattern can be widely related to old or acute sarcoid disease. Conversely, isolated  $^{18}\text{F}$ -FDG uptake without any perfusion abnormality may pose a diagnostic problem. In the absence of regional myocardial perfusion abnormalities, isolated  $^{18}\text{F}$ -FDG uptake may certainly signify sarcoid disease induced myocardial inflammation but it may also, at least in part, be related to incomplete suppression of physiologic  $^{18}\text{F}$ -FDG uptake despite sarcoid preparation diet and fasting period, accounting for some false positive findings. In order to avoid or reduce false positive findings, isolated  $^{18}\text{F}$ -FDG of the myocardium needs to be cautiously evaluated and interpreted in the appropriate clinical context for the decision-making process. Since isolated myocardial  $^{18}\text{F}$ -FDG uptake, indicative of early and inflammatory sarcoid disease, may be associated with worse cardiovascular outcome (15), specific attention is needed and immunosuppressive therapy may be installed, if clinically appropriate, even in the absence of biopsy-proven cardiac sarcoid disease.

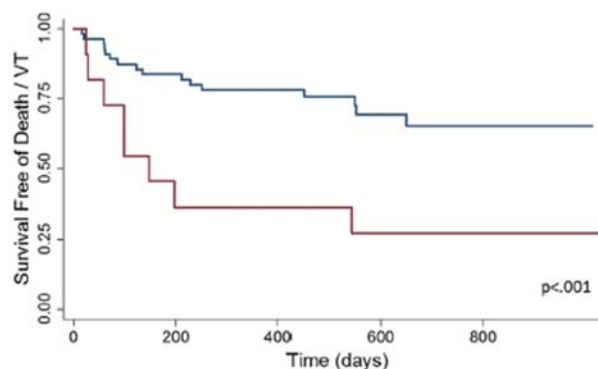
Despite the potential of cardiac  $^{18}\text{F}$ -FDG PET in the detection and treatment of patients with cardiac sarcoidosis (3,8), until more recently it was not known whether the use of  $^{18}\text{F}$ -FDG PET will truly identify sarcoid patients at a higher risk of adverse cardiac events. In this direction, Blankstein et al. (15) reported of first clinical observations in that cardiac sarcoid identification with perfusion and  $^{18}\text{F}$ -FDG-PET/CT carries indeed important prognostic outcome information (Fig. 3). Overall, 118 consecutive patients with no history of CAD were studied at baseline with  $^{82}\text{Rb}$  rubidium perfusion and  $^{18}\text{F}$ -FDG PET/CT for cardiac sarcoid detection with a median follow-up of 1.5 years (15). The presence of both a regional myocardial perfusion defect and abnormal  $^{18}\text{F}$ -FDG uptake (29% of patients) was associated with a hazard ratio of 3.9 ( $p < 0.01$ ). In particular, perfusion abnormalities and/or abnormal  $^{18}\text{F}$ -FDG uptake on cardiac PET images remained significant for the occurrence of ventricular tachycardia and cardiac death even after adjusting for left ventricular ejection fraction and clinical criteria (15). The study also signified that abnormal focal  $^{18}\text{F}$ -FDG uptake in the right ventricle to suggest inflammation was associated



**Fig. 3A** Survival free of death or ventricular tachycardia (VT) stratified by cardiac PET examination results. Myocardial perfusion defects at rest, as indicating structural alterations such as interstitial fibrosis and/or pronounced edema. In addition, myocardial inflammation as signifies on FDG-PET images was associated with a pronounced lower survival free of death or ventricular tachycardia compared with normal cardiac PET findings. (With kind permission from reference 14)

with a 5-fold higher event rate than in those with normal perfusion and metabolism (Fig. 3). Taken together, it appears that abnormal cardiac PET findings in patients with sarcoid disease are predictive of survival free of death and ventricular tachycardia that goes beyond the Japanese Ministry of Health and Welfare clinical criteria, the presence of extra-cardiac sarcoidosis and left ventricular ejection fraction (15).

Importantly, the use of cardiac  $^{18}\text{F}$ -FDG-PET may also play a decisive role not only in the identification of early and inflammatory sarcoid activity but also to guide the success of immunosuppressive therapy of systemic and/or active cardiac sarcoid disease. A first follow-up study in sarcoid disease patients has demonstrated some success of monitoring immunosuppressive treatment in concert with standard heart failure therapy (18). A reduction in the intensity and extent of myocardial inflammation on  $^{18}\text{F}$ -FDG-PET was indeed associated with an improvement in left-ventricular ejection fraction (18). A longitudinal regression analysis revealed a significant inverse linear relationship between maximum standardized uptake value (SUV) and left-ventricular ejection fraction with an expected increase in EF of 7.9% per SUV reduction of  $10 \text{ g} \cdot \text{mL}^{-1}$  ( $p=0.008$ ). These initial findings, although low in numbers ( $n=23$ ), outline the potential of serial PET scanning to identify the success of immunosuppressive treatment in the prevention and treatment of heart failure due to cardiac sarcoid involvement. Whether this PET-guided approach to detect and monitor treatment success in cardiac sarcoidosis is likely to improve the clinical outcome in these patients still remains to be



**Fig. 3B** Survival Free of Death or Ventricular Tachycardia According to Focal Right-Ventricle Inflammation. Survival free of death or VT stratified by the presence or absence of focal right ventricular FDG uptake among individuals with abnormal cardiac PET examination findings. RV = right ventricular. (With kind permission from reference 14)

clinically tested. As  $^{18}\text{F}$ -FDG PET/CT signifies active inflammatory disease, however, it is most suitable for early disease identification, guiding immunosuppressive therapy, and image-guided biopsy (8).

## Conclusions

The identification of cardiac sarcoid involvement or isolated cardiac sarcoid disease with cardiac perfusion and  $^{18}\text{F}$ -FDG PET/CT is increasingly appreciated as it portends a worse cardiovascular outcome. While  $^{18}\text{F}$ -FDG PET/CT is more sensitive than delayed enhancement cardiac magnetic resonance (CMR) imaging, CMR is more specific in the detection and characterization of cardiac sarcoid disease. With the advent of PET/MR further advances and refinement in sarcoid disease detection is likely to ensue.  $^{18}\text{F}$ -FDG-PET, however, has the unique potential to identify early and inflammatory cardiac sarcoid disease before structural alterations in the myocardium such as fibrosis and/or scarring may manifest. Initial observations also indicate that the use of  $^{18}\text{F}$ -FDG-PET is a helpful tool in guiding immunosuppressive therapy to eliminate sarcoid-induced myocardial inflammation in heart failure patients is indeed associated with a mild improvement in left-ventricular systolic function. Whether the application of such diagnostic approach in guiding immunosuppressive therapy will also result into an improved cardiovascular outcome, however, remains to be further tested in large-scale clinical trials. Myocardial perfusion imaging combined with  $^{18}\text{F}$ -FDG-PET, is likely to further introduce image-guided and personalized preventive medicine in sarcoid patients in the near future.

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No potential conflict of interest exists.

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