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Imaging the inflammatory activity of sarcoidosis

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ABSTRACT: Accurate assessment of pulmonary and extrapulmonary organ involvement in sarcoidosis is one of the great challenges for clinicians. This assessment includes the evaluation of symptoms and of sarcoidosis activity in a specific organ and its functional consequences.

In this review, radiological and nuclear techniques to image the inflammatory activity of sarcoidosis are described, in particular ^{18}F-FDG positron emission tomography/computed tomography. The current use of this technique in clinical practice is explained, particularly in patients with persistent symptoms, stage IV disease and cardiac sarcoidosis.

KEYWORDS: ^{18}F-FDG positron emission tomography/computed tomography, high-resolution computed tomography, inflammation, sarcoidosis activity

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Sarcoidosis is a chronic granulomatous disease of unknown origin that can affect any organ. Organs most frequently affected include the lymphatic system, lungs, skin, peripheral and central nervous system and eyes [1]. Involvement of the heart is a rare, although potentially life-threatening, manifestation of the disease [2, 3].

Accurate evaluation of pulmonary and/or extrapulmonary organ involvement of sarcoidosis remains one of the great challenges for clinicians. This evaluation includes the assessment of sarcoidosis activity in a specific organ and its functional consequences [4].

In patients with chronic disease, fibrotic changes may occur in the affected organs. These patients in particular might benefit from immunosuppressive treatment to prevent further irreversible organ damage. It is most likely that this organ damage occurs in patients with ongoing inflammatory activity.

To optimise clinical decision making on the type and/or dose of immunosuppressive drugs, it is of utmost importance to have markers that accurately reflect the degree of sarcoidosis activity throughout the body, and ideally at single organ level in case of involvement with symptomatic and/or functional consequences [5]. However, there are currently only a few serum biomarkers that can be used to monitor sarcoidosis acivity. Since none of these markers is ideal, there is a need for further development in this field.

In the past decade, nuclear imaging, particularly positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG), has emerged as a potentially powerful tool to visualise the intensity and extent of inflammatory activity of sarcoidosis throughout the body [6–8]. Radiological and other nuclear techniques are available to assess disease activity. In this article, a review of the literature is given on radiological and nuclear imaging in sarcoidosis, and on ^{18}F-FDG PET/computed tomography (CT) imaging in particular. Additionally, the current application of this technique in our clinical practice is described.

RADIOLOGICAL IMAGING

Conventional chest radiography

Over five decades ago, SCADDING [9] presented a staging system for pulmonary sarcoidosis based on chest radiography. It is a purely descriptive system that uses the presence or absence of lymphadenopathy and parenchymal disease to stage pulmonary sarcoidosis.

A major drawback of this system is that, although it provides some prognostic information, the

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radiographic findings in themselves hardly differentiate between active inflammation and fibrosis or inactive disease [1].

Only serial changes on chest radiography might reveal some information on pulmonary disease activity. Its value as a tool to visualise inflammation in sarcoidosis is therefore mainly based on retrospective analysis.

High-resolution CT

High-resolution CT (HRCT) is superior to conventional radiography in detecting nodules, early fibrosis and parenchymal distortion. Its high spatial resolution provides improved anatomic detail enabling assessment of fine parenchymal changes at the level of the secondary pulmonary lobule. With the advent of multidetector CT scanners, volumetric scanning has become routine in many institutions and enables fast imaging of the whole lungs in one single breath-hold. It has become a powerful tool in the diagnosis of diffuse parenchymal lung disease. In the evaluation of suspected pulmonary sarcoidosis, HRCT enables a more confident first-choice diagnosis with better interobserver agreement when compared to conventional chest radiography [10]. However, the exact diagnostic and prognostic value of HRCT in pulmonary sarcoidosis is still being researched.

Several studies have investigated the prognostic role of HRCT by evaluating disease changes over time with serial CT scanning. These studies, with relatively small numbers of patients, demonstrated that architectural distortion, honeycombing, traction bronchiectasis and large cysts are invariably irreversible, (micro)nodular disease is in most cases reversible, but ground-glass, irregular linear opacities and interlobular septal thickening can be reversible but quite often are not and can progress to fibrosis [11–16]. Thus, evaluating the reversibility of disease by HRCT appears to be possible only in retrospect with serial data. However, some HRCT features might still have the potential to discriminate between reversible disease (active inflammation) and irreversible disease (fibrosis). Additionally, HRCT features may carry predictive information about the response to anti-inflammatory therapy or progress towards fibrosis, though there is a need for large-scale HRCT scoring data including follow-up scans and clinical data such as serial lung function of well-typed patient groups.

NUCLEAR IMAGING

Gallium-67 scintigraphy

In vivo, Gallium-67 (^{67}Ga) acts like an iron analogue and binds to transferrin. In inflammatory lesions, ^{67}Ga will subsequently bind to lactoferrin, which is an important binding protein in polymorphonuclear leukocytes [17].

During the first 24 h after administration, ^{67}Ga citrate is excreted by the kidneys. Subsequently, the hepatobiliary system excretes the radiopharmaceutical. Due to the slow plasma clearance, a substantial amount of ^{67}Ga citrate remains in the body and will be distributed to ''lactoferrin-rich'' tissues. This explains the activity in bone marrow, spleen, liver and lacrimal and salivary glands.

Several authors have described the sensitivity and specificity of ^{67}Ga scintigraphy to diagnose sarcoidosis. In the majority of studies, active disease was defined by the presence of symptoms in patients with biopsy-proven sarcoidosis. In order to determine specificity, sarcoidosis was defined as inactive when patients did not have symptoms and chest radiography did not change. The sensitivity of ^{67}Ga scintigraphy ranges between 60–90%, with a low specificity of ~50% [6, 18–22].

However, negative ^{67}Ga scintigraphy combined with normal angiotensin-converting enzyme (ACE) has a high negative predictive value [23, 24].

^{67}Ga scintigraphy correlates with ACE values and clinically effective steroid therapy is associated with an improvement of ^{67}Ga scintigraphy and decrease in ACE [20, 24–26]. RIZZATO *et al*. [27] assessed the predictive value of ^{67}Ga scintigraphy, chest radiography and ACE in 382 patients. ^{67}Ga scintigraphy appeared to be more sensitive than chest radiography in detecting disease progression and improvement. Furthermore, uptake of ^{67}Ga citrate was suppressed by the use of corticosteroids but to a lesser extent than ACE.

The "lambda" and "panda" signs in ^{67}Ga scintigraphy are suggested to be a characteristic feature of sarcoidosis. Bilateral hilar activity combined with predominantly right sided active lymph nodes in the mediastinum represents the lambda sign. The panda sign is based on the symmetrical activity in the lacrimal and parotid glands. However, these signs have demonstrated a poor diagnostic sensitivity in biopsy-proven sarcoidosis patients [28–30]. Furthermore, the panda sign can also be found in patients with HIV, malignant lymphomas and Sjögren's syndrome.

In general, ^{67}Ga scintigraphy is performed with 185 MBq ^{67}Ga citrate, resulting in an effective radiation dose of 18.5 mSv [31, 32].

Somatostatin receptor scintigraphy

Somatostatin receptors are present in several cell types, for example activated macrophages [33]. There are five somatostatin receptor subtypes and *in vitro* autoradiography of histological biopsies of sarcoidosis has revealed that the somatostatin receptor subtype 2 (sst_2) is expressed in epitheloid cells and giant cells [34]. Somatostatin receptor scintigraphy (SRS) is most frequently performed with Indium-111 (^{111}In) pentetreotide. Pentetreotide shows high affinity for the sst_2 receptor and might therefore be used in the imaging of sarcoidosis. In general, SRS is performed with 200 MBq ^{111}In-pentetreotide resulting in an effective radiation dose of 10.8 mSv [35]. Planar whole-body images and single photon emission CT (SPECT) of the chest are performed 24 h after injection.

KWEKKEBOOM *et al*. [36] performed SRS in 46 sarcoidosis patients and demonstrated active lesions in 97% of the disease locations imaged by conventional chest radiography. Additional thoracic and extrathoracic lesions were found, but several other extrathoracic lesions were not properly demonstrated. LEBTAHI *et al*. [37] compared SRS with ^{67}Ga imaging in 18 patients and found that SRS revealed significantly more sarcoidosis lesions at the clinically involved sites than ^{67}Ga imaging (83% and 65% of clinically involved sites, respectively). Although SRS demonstrated additional extrathoracic sites that were not suspected clinically, 40% of the known extrathoracic lesions were not diagnosed. SRS therefore seems to be sensitive in the assessment

of active thoracic sarcoidosis, but the presence of extrathoracic disease can be missed.

^{18}F-FDG PET

^{18}F-FDG PET is widely used in the imaging of malignant tumours. An increased glucose metabolism of malignant cells causes the accumulation of ^{18}F-FDG. Once ^{18}F-FDG is transported through the cell membrane into the cytosol, it is phosphorylated by hexokinase. Here, the ^{18}F-FDG is metabolically trapped as ^{18}F-FDG-6-phosphate. Glucose transporters (GLUT) across the cell membrane account for the transport of ^{18}F-FDG into the cell. In malignant cells, the expression of GLUT-1 is mainly responsible for ^{18}F-FDG accumulation [38–41]. Activated leukocytes also express the GLUT-1 transporter [39]. Consequently, ^{18}F-FDG PET can be used in leukocyte-mediated processes, such as inflammatory lesions.

In 1994, the use of ^{18}F-FDG PET in sarcoidosis was first reported by LEWIS and SALAMA [42]. Although autoradiographic studies of sarcoid lesions are lacking, the accumulation of ^{18}F-FDG in macrophages and $CD4^+$ T-lymphocytes may explain the *in vivo* imaging of this granulomatous process [43, 44].

^{18}F-FDG PET and ^{67}Ga scintigraphy

NISHIYAMA *et al*. [21] compared ^{18}F-FDG PET and ^{67}Ga scintigraphy retrospectively in 18 patients. Histology was used as the gold standard. Sensitivity for the detection of thoracic disease was 100% for ^{18}F-FDG PET and 81% for ^{67}Ga scintigraphy, while extrathoracic lesions were adequately observed in 90% and 48% of sites, respectively. In a similar study, PRAGER *et al*. [22] reported a significantly higher overall detection rate for ^{18}F-FDG PET. Thoracic disease was found in 96% of patients. ^{67}Ga scintigraphy revealed thoracic abnormalities in 88%. 19 extrathoracic locations were found in ^{18}F-FDG PET and 12 in ^{67}Ga scintigraphy.

In a prospective evaluation of both techniques, the overall sensitivity for detecting active sarcoidosis in histologically proven sarcoidosis was 97% for ^{18}F-FDG PET and 88% for ^{67}Ga scintigraphy. Significantly more active lesions in the mediastinum, hila and extrapulmonary regions were detected by ^{18}F-FDG PET, mainly due to lymph node and spleen involvement. Furthermore, interobserver agreement was considerably higher in ^{18}F-FDG PET [45].

Compared to ^{18}F-FDG PET, ^{67}Ga scintigraphy is less sensitive in detecting active sarcoidosis lesions, its radiation dose is three times higher and acquisition is 24 h after administration of the radiopharmaceutical. In addition, ^{67}Ga scintigraphy cannot guide in predicting disease outcome [46–48]. Therefore, ^{67}Ga scintigraphy is no longer the preferred nuclear imaging technique in the assessment of sarcoidosis activity. If conventional activity markers are unable to demonstrate active disease though active sarcoidosis is suspected, ^{18}F-FDG PET is recommended.

^{18}F-FDG PET/CT

It might be suggested that a combined imaging modality of ^{18}F-FDG PET and CT is even more sensitive than PET alone. BRAUN *et al*. [6] retrospectively evaluated ^{18}F-FDG PET/CT in 20 patients, with both new and previously diagnosed sarcoidosis. This technique correctly demonstrated 78% of the biopsy-proven locations, with 100% sensitivity for thoracic and sinonasal disease. Skin lesions were the main reason for the decreased overall sensitivity, probably explained by the skin thickness causing difficulties in granuloma detection. In 12 patients, ^{67}Ga scintigraphy had previously been performed, with a correct detection of biopsy-proven lesions in 58%. Sensitivity for thoracic and sinonasal disease was 71% and 75%, respectively.

TEIRSTEIN *et al*. [8] retrospectively analysed 188 ^{18}F-FDG PET/CT scans in 137 patients and demonstrated that this technique exhibits adequate sites for diagnostic biopsy. In 51 patients, ^{18}F-FDG PET/CT was repeated to evaluate the effect of corticosteroids. Overall, the improvement seen by ^{18}F-FDG PET/CT correlated well with changes in symptoms and clinical findings, although limited data were provided [8].

Quantifying metabolic activity by ^{18}F-FDG PET/CT

Maximum standardised uptake value (SUV_{max}) is a semi-quantitative tool to measure disease activity. However, it only represents the maximum amount of activity in one pixel, corrected for the patient's body weight and injected dose of the radiopharmaceutical. In oncology, SUV_{max} has proven to be a reliable predictor of disease outcome. The difference in SUV_{max} before and after chemo(radiotherapy) as well as the residual SUV_{max} has shown to correlate with survival in several types of malignancy [49–52].

In contrast with sarcoidosis, tumours are well-delineated processes. The pulmonary abnormalities in sarcoidosis can be diffuse as well as focal and appear in one or more lobes. Therefore, an increased metabolic activity with an SUV_{max} of 3 involving all lobes might be more relevant than one small focal lesion with an SUV_{max} of 10. So not only the amount of metabolic activity is relevant, the extent is of great importance as well.

Quantifying the total amount of metabolic activity in one organ might have great clinical value. It might be suggested that the total amount of activity in the lung parenchyma correlates with the degree of deterioration on pulmonary function testing (PFT) in the future. To date, studies correlating quantified ^{18}F-FDG uptake with clinical outcome have not been performed.

Prognostic value of ^{18}F-FDG PET in sarcoidosis

Little is known about the prospective value of ^{18}F-FDG PET in sarcoidosis. The metabolic activity in the lung parenchyma correlates with the number of neutrophils in bronchoalveolar lavage (BAL) fluid [53]. The number of neutrophils in BAL fluid is known to be associated with a worse outcome in sarcoidosis, which might suggest that metabolic activity in the lung parenchyma imaged by ^{18}F-FDG PET is correlated with a poorer prognosis as well [54, 55].

In one study, lung parenchymal activity imaged by ^{18}F-FDG PET was correlated with PFT after 12 months [56]. A significant decrease in diffusion capacity of the lung for carbon monoxide ($D_{L,CO}$) was found in 11 untreated patients with diffuse parenchymal activity. All patients showed stage II/III sarcoidosis on chest radiography. No change in vital capacity (VC) or forced expiratory volume (FEV_1) was observed.

16 patients with parenchymal activity, who were treated with immunosuppressive therapy, showed a significant increase in

VC, FEV1 and $D_{L,CO}$. Chest radiography demonstrated stage I disease in nine patients and stage II/III in six patients. This finding suggests that ^{18}F-FDG PET is able to assess the potential functional improvement that can be achieved if immunosuppressive therapy is applied. Conversely, 16 untreated patients without parenchymal activity did not show any change in PFT. In these patients, stage 0 disease was seen in one patient, stage I in nine and stage II/III in six patients. These findings might suggest that the absence of metabolic activity imaged by ^{18}F-FDG PET justifies a policy of watchful waiting.

The prognostic value of dual time-point PET imaging in persistant pulmonary involvement was evaluated by UMEDA *et al* [48]. PET images were obtained at 60 min and 180 min after injection and SUV was measured. The retention of SUV was expressed as the SUV retention index (RI-SUV) and was correlated with changes on chest CT after 1 year. In addition, initial ^{67}Ga uptake was correlated, as was soluble interleukin-2 receptor (sIL-2R). The diagnostic accuracy of RI-SUV was significantly higher than early SUV or ^{67}Ga uptake. Furthermore, sIL-2R showed a significant correlation with RI-SUV, but not with early SUV, which is in line with previous results [7].

However, a prospective study with large numbers of patients to demonstrate the exact predictive role of ^{18}F-FDG PET/CT is lacking.

^{18}F-FDG PET/CT acquisition

The patient fasts for at least 6 h, preceded by a carbohydrate-restricted diet for at least 24 h. Before the intravenous injection of ^{18}F-FDG, 5 mg of diazepam is administered to reduce muscle activity and accumulation of ^{18}F-FDG in brown fat. In order to reduce radiation exposure and accelerate ^{18}F-FDG excretion by the kidneys, 20 mg of furosemide is injected intravenously. Subsequently, ^{18}F-FDG is administered based on the patient's body weight, with a maximum of 400 MBq. 60m min after administration of ^{18}F-FDG, low-dose CT is performed from the subinguinal region to the head. Low-dose CT is used for attenuation correction and to optimise localisation when interpreting the images. The emission scan is performed from the subinguinal region to the head with an acquisition time of 2.5 min per bed position. In our clinic, a Philips Gemini Time of Flight ^{18}F-FDG PET/CT machine (Philips Healthcare, Best, The Netherlands) is used. Reconstruction is performed in accordance with the 3D-RAMLA protocol applying four iterations with a 144×144 matrix [57].

Radiation dose

The radiation dose of ^{18}F-FDG PET is approximately 5.8 mSv for the first-generation, standalone PET scanners. In the current PET/CT systems, the administered ^{18}F-FDG activity is reduced and is based on the patient's body weight in accordance with European guidelines [58]. A body weight of 80 kg results in an effective radiation dose of 3.8 mSv [31].

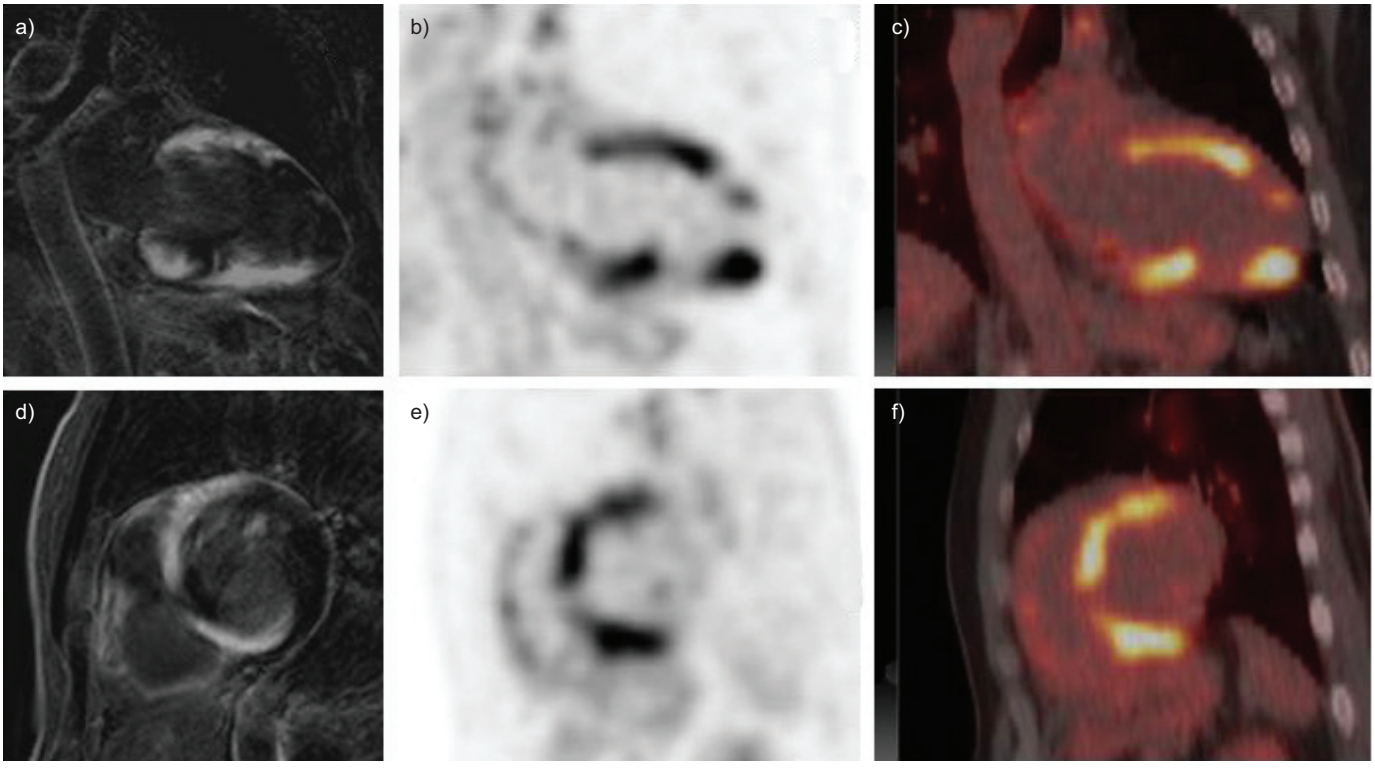

FIGURE 1. a, d) Magnetic resonance imaging (MRI) and b, c, e, f) ^{18}F-fluorodeoxyglucose position emission tomography/computed tomography (^{18}F-FDG PET/CT) of a 49-yr-old male with sarcoidosis and ventricular arrythmias. MRI demonstrated a diffuse hypokinetic left ventricle with an ejection fraction of 35% and enhancement in T2 weighted images in the anterior, inferior and interventricular septal wall. ^{18}F-FDG PET/CT after a carbohydrate-restricted diet revealed that the majority of these lesions were still active. An implantable cardioverter defibrillator was implanted because of the arrhythmias and immunosuppressive therapy was started given the presence of active inflammation in the myocardium.

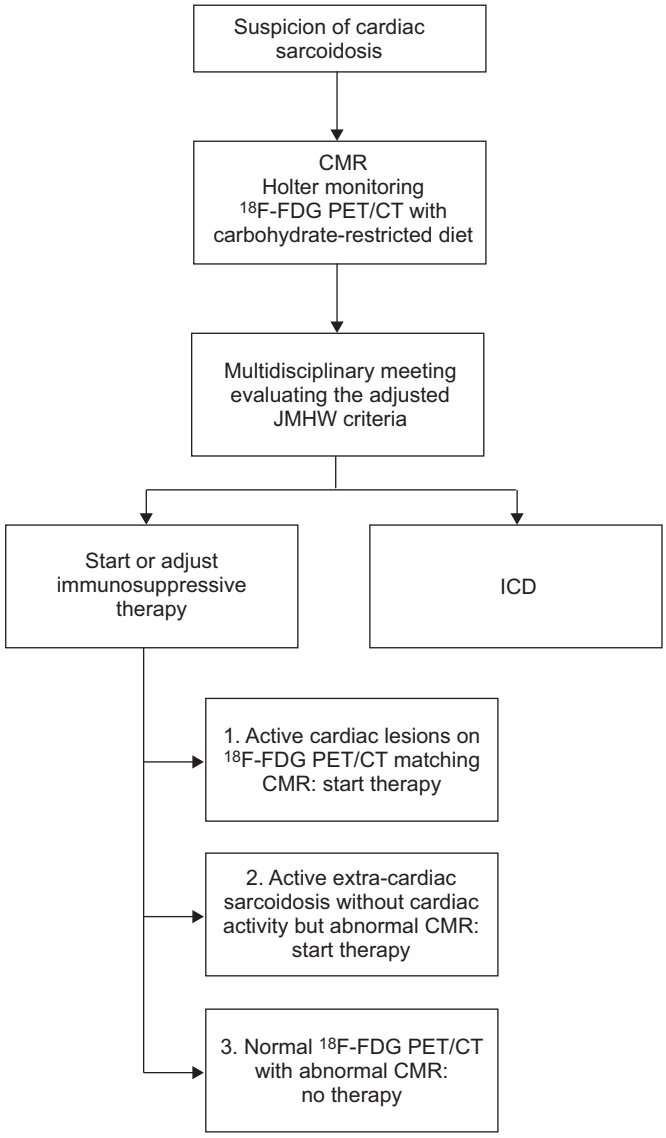

FIGURE 2. Flowchart showing the authors' approach to patients with cardiac sarcoidosis. ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; JMHW: Japanese Ministry of Health and Welfare; ICD: implantable cardioverter defibrillator; CMR: cardiac magnetic resonance imaging.

TABLE 1 Indications for ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in sarcoidosis

Obtaining histological proof of sarcoidosis
Determining the presence of active disease in symptomatic patients with normal conventional markers
Assessing the presence of active cardiac sarcoidosis, combined with CMR
Evaluating disease activity in symptomatic patients with longstanding sarcoidosis or stage IV disease

CMR: cardiac magnetic resonance imaging.

More accurate disease location can be achieved by the concurrently obtained whole-body CT, also performed for attenuation correction. This low-dose CT adds approximately 2.9 mSv to the radiation dose [59].

Even though ^{18}F-FDG PET/CT is a noninvasive technique, it should be applied with care in evaluating sarcoidosis activity. ^{18}F-FDG PET/CT is more expensive than other available tests and radiation exposure should not be ignored. Frequent repetition of ^{18}F-FDG PET/CT is therefore not recommended.

^{18}F-FDG PET/CT AND MAGNETIC RESONANCE IMAGING IN CARDIAC SARCOIDOSIS

Evaluating the presence of active sarcoidosis lesions in the myocardium is challenging, though crucial since this is one of the major causes of sarcoidosis-related death [60]. Clinical involvement of the heart is reported in 5% of sarcoidosis patients in the USA, but autopsy studies have shown myocardial granuloma formation in at least 25% of patients [61]. Incidence varies strongly with race and is most common in Japan.

In the early 1990s, the Japanese Ministry of Health and Welfare (JMHW) published diagnostic guidelines to assess the presence of cardiac sarcoidosis [62]. However, this guideline has not been validated and is now fairly outdated since more recently developed techniques, such as ^{18}F-FDG PET/CT and magnetic resonance imaging (MRI), are not incorporated.

In our current practice, JMHW criteria are still used. However, echocardiography and ^{67}Ga scintigraphy are replaced by cardiac MRI (CMR) and ^{18}F-FDG PET/CT, respectively. The principles and advantages of these two techniques will be discussed below.

CMR has become an important modality for the detection and functional evaluation of cardiac disease. Several studies have shown the value of gadolinium-diethylenetriaminepenta-acetic acid (DTPA) T1 and T2 weighted imaging for diagnosing cardiac sarcoidosis [63, 64]. However, the role of CMR in discriminating active from inactive, *i.e.* fibrotic, lesions in the myocardium has been insufficiently investigated. Most patients with evidence of cardiac sarcoidosis receive an implantable cardioverter defibrillator (ICD) or pacemaker to prevent sudden death caused by ventricular tachyarrhythmia or conduction blocks. After implantation of the device, these patients are no longer suitable for CMR. With the advent of MRI-conditional pacemakers and ICD devices, more data on disease reversibility will undoubtedly become available. To date, study results on disease reversibility and imaging of active disease are limited. However, it has been shown that after steroid treatment both contrast enhancement and later on T2 signal intensity can disappear, suggesting that these imaging findings reflect active disease.

Mammalian metabolism depends on glucose and fatty acids [65]. ^{18}F-FDG uptake in the myocardium is therefore a merely physiological process. Several methods have been shown to reduce this physiological uptake of ^{18}F-FDG, *i.e.* the use of unfractionated heparin, prolonged fasting or a carbohydrate-restricted diet for at least 24 h prior to scanning [66–71]. The latter has been proven to be the most effective method. Only fat

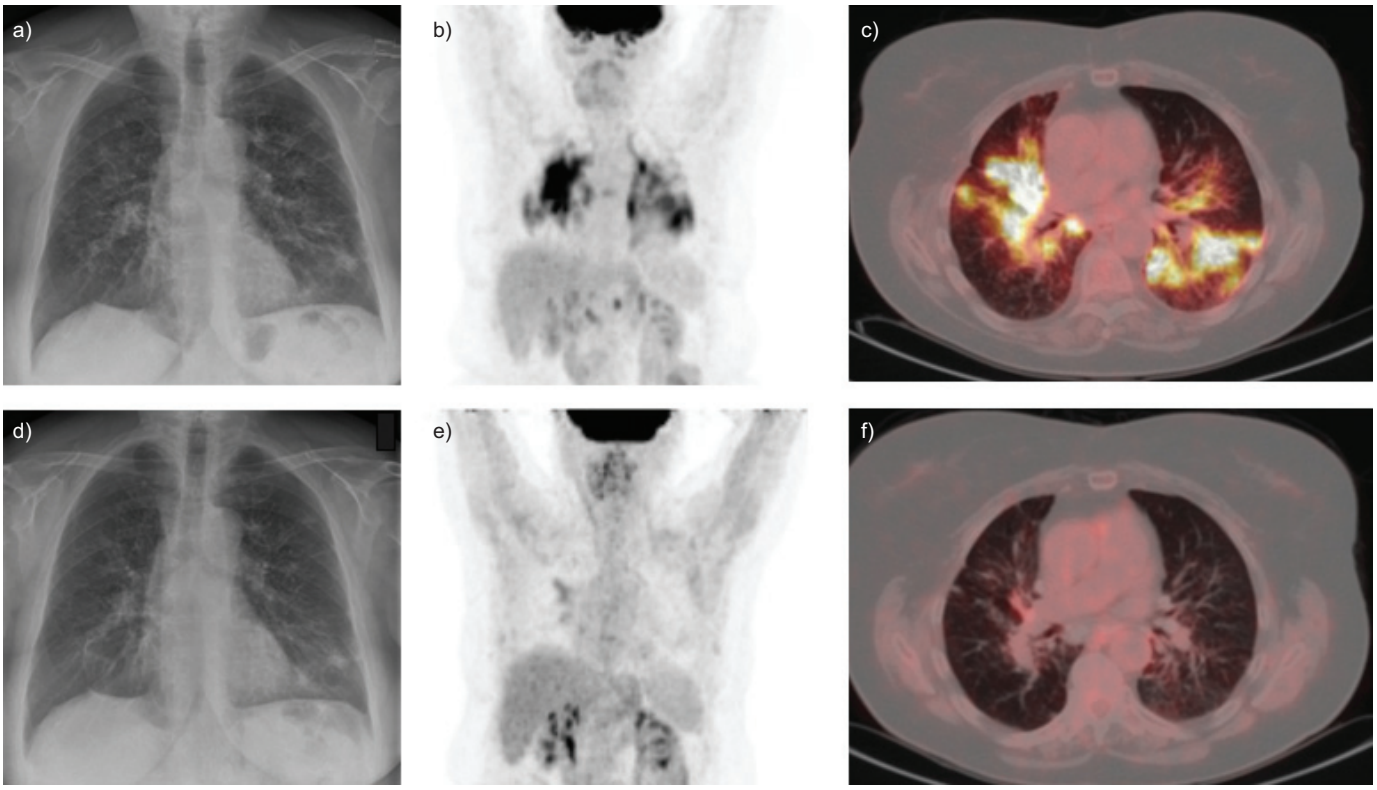

FIGURE 3. a, d) Chest radiography and b, c, e, f) ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) of a 67-yr-old female diagnosed with sarcoidosis 2 yrs before referral to the authors' tertiary centre. The use of 10 mg prednisone per day for 2 yrs, later combined with methotrexate had not prevented a serious decrease in pulmonary function. She suffered from severe dyspnoea on exertion and fatigue. At presentation, chest radiography revealed a diffuse nodular pattern with mild fibrotic changes predominating in the mid lobes without lymphadenopathy. Serum angiotensin-converting enzyme and calcium were normal while soluble interleukin-2 receptor (sIL-2R) was only slightly increased. ^{18}F-FDG PET/CT however demonstrated severely increased metabolic activity in the lung parenchyma. Active lymph nodes were seen in the mediastinum, hila, upper abdomen and left inguinal region. Combined with pulmonary function testing, 6-min walk distance (6-MWD), symptoms and findings, infliximab was started. After six cycles, the increase in forced expiratory volume in 1 s was 11%, and in vital capacity was 21%. Diffusing capacity of the lung for carbon monoxide remained stable. Maximum distance during the 6-MWD showed an increase of 21%. Chest radiography and ^{18}F-FDG PET/CT demonstrated improvement, seen most impressively on ^{18}F-FDG PET/CT (d, e, f). These findings show that ^{18}F-FDG PET/CT is able to reveal the ongoing inflammatory activity of sarcoidosis thereby demonstrating the potentially reversible lesions.

and proteins are allowed, while all carbohydrates, including vegetables, should be avoided.

When the intake of carbohydrates is limited, fatty acids will be used and physiological uptake of ^{18}F-FDG is reduced. Without any physiological uptake in the myocardium, only pathological processes, like active granulomas, will become evident. This is the basis of imaging active cardiac sarcoidosis with ^{18}F-FDG PET/CT.

At this time, a limited number of studies evaluating the use of ^{18}F-FDG PET/CT in cardiac sarcoidosis is available.

In a recent meta-analysis, ^{18}F-FDG PET/CT of 164 sarcoidosis patients was compared to the JMHW guidelines. A sensitivity of 89% and specificity of 78% was found for ^{18}F-FDG PET/CT in the detection of active cardiac sarcoidosis [72]. Physiological myocardial uptake was reduced by the use of the three aforementioned methods.

Figure 1 shows the ability of CMR to demonstrate sarcoidosis in the myocardium while ^{18}F-FDG PET/CT provides information about the activity of these lesions. The presence of sarcoid lesions in the myocardium might give rise to the implantation of a cardioverter defibrillator, while the presence of active granulomas supports treatment with immunosuppressive drugs.

In figure 2, a flowchart shows the authors' approach to patients suspected of having cardiac sarcoidosis. First, CMR, Holter monitoring and ^{18}F-FDG PET/CT preceded by a carbohydrate-restricted diet are performed. Modified JMHW criteria are discussed by the pulmonologist, cardiologist, nuclear medicine physician and radiologist. In these modified criteria, CMR and ^{18}F-FDG PET/CT are incorporated, the latter replacing ^{67}Ga scintigraphy.

In patients with cardiac sarcoidosis based on CMR, an ICD is implanted when ventricular arrhythmias are inducable during electrical stimulation of the ventricle. Active cardiac sarcoidosis is suggested when active cardiac lesions on ^{18}F-FDG PET/CT match CMR. Then immunosuppressive therapy is started.

If ^{18}F-FDG PET/CT shows active sarcoidosis without increased ^{18}F-FDG uptake in the myocardium, but with an abnormal CMR, immunosuppressive treatment is started as well.

The resolution of current ^{18}F-FDG PET/CT systems is approximately 5 mm [73, 74]. Smaller, though relevant cardiac sarciodosis lesions might therefore be missed.

When CMR is abnormal but ^{18}F-FDG PET/CT does not show any increased activity, no immunosuppressive therapy will be started.

CURRENT USE OF ^{18}F-FDG PET/CT IN CLINICAL PRACTICE

^{18}F-FDG PET/CT should not be used in the standard work-up of all sarcoidosis patients. However, when appropriately indicated, application of ^{18}F-FDG PET/CT can provide valuable information and optimise patient treatment. In our opinion, ^{18}F-FDG PET/CT might be useful in the following situations (table 1):

1) ^{18}F-FDG PET/CT can guide the clinician to obtain histological proof of sarcoidosis. Biopsy from metabolically active lesions is more likely to yield the diagnosis than biopsy from inactive lesions.

2) In sarcoidosis patients with persistent symptoms and slightly increased or even normal biomarkers, ^{18}F-FDG PET/CT might help to demonstrate sites of ongoing disease activity (fig. 3). MOSTARD *et al*. [75] evaluated ^{18}F-FDG PET/CT in 89 patients with unexplained, persistent and disabling symptoms and found that ^{18}F-FDG PET/CT demonstrated active lesions in 73% [75]. In 20% of these patients, serum markers of activity were normal.

3) ^{18}F-FDG PET/CT is helpful in the detection of active cardiac sarcoidosis. As described previously, MRI is able to demonstrate cardiac involvement and might give rise to the implantation of a cardiac defibrillator. ^{18}F-FDG PET/CT on the other hand, reveals the activity state of the cardiac lesions and helps indicating whether immunosuppressive treatment should be started or adjusted.

4) In patients with long-standing and symptomatic pulmonary sarcoidosis or signs of fibrosis, the clinician might be challenged to prove the presence of active disease and decide on the usefullness of (additional) immunosuppressive therapy. Retrospective analysis of ^{18}F-FDG PET/CT in symptomatic patients with stage IV disease, revealed persistent parenchymal disease activity in 14 out of 15 patients [75]. In addition, patients with increased metabolic activity in the lung parenchyma show a significant increase in VC and $D_{L,CO}$ after treatment [56, 76]. These findings suggests that ^{18}F-FDG PET/CT is able to demonstrate the potential functional improvement that can be achieved even when fibrosis, *i.e.* end-stage disease, is present. Figure 4 illustrates this potential role of ^{18}F-FDG PET/CT in one patient of this particular population.

FUTURE PERSPECTIVE

Predicting the effect of immunosuppressive therapy might be of great value, particularly in expensive treatment such as anti-TNF-α. Anti TNF-α drugs can be labelled with 99m-technetium (^{99m}Tc) and scintigraphy prior to therapy might predict whether this specific treatment will be successful. In rheumatoid arthritis, scintigraphy with ^{99m}Tc-labelled infliximab demonstrated a significantly higher activity in the affected joints than in those that were not affected [77]. Studies evaluating the role of ^{99m}Tc labelled anti TNF-α scintigraphy in sarcoidosis are lacking, although the success in other TNF-mediated diseases suggests a promising technique.

Since ^{18}F-FDG PET/CT is a whole-body technique, active granulomas could be detected in a single study. Consequently, this technique might be able to determine the total granuloma load in sarcoidosis patients.

But not only is the total amount of active disease relevant: quantification of the inflammatory mass per organ might also help the clinician to titrate immunosuppressive therapy on an individual basis. Since ^{18}F-FDG PET is nowadays combined with CT, the target organ is easier to delimit and the sum of activity in the organ of interest can be calculated. Future studies are undoubtedly warranted to correlate quantification with functional outcome, and to test this concept.

Although available in only a few hospitals worldwide, PET/MRI is the latest hybrid imaging technique. Since MRI compatible leads and devices have become available, repetitive CMR could be performed in patients with cardiac sarcoidosis. Combining the high sensitivity of ^{18}F-FDG PET with the exact anatomical localisation of MRI has great potential in the

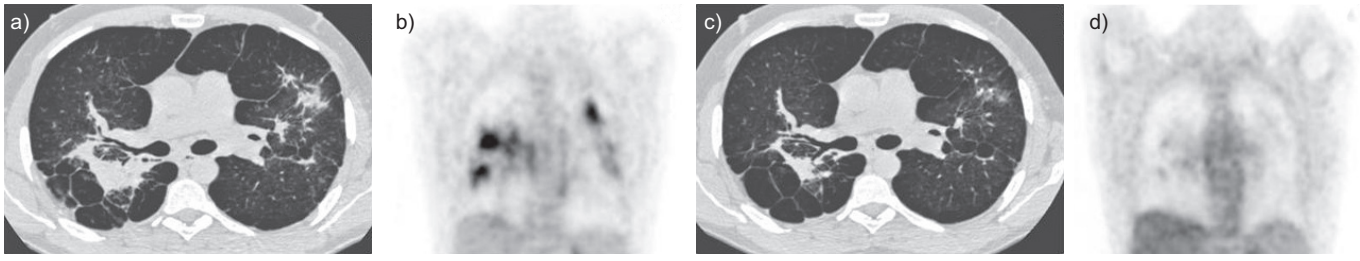

FIGURE 4. A 40-yr-old male with progressive pulmonary sarcoidosis was treated with prednisone and methotrexate. After 2 yrs of treatment, pulmonary function tests remained stable. Vital capacity (VC) was normal, forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) were decreased. Angiotensin-converting enzyme and soluble interleukin-2 receptor were normal. This patient was considered to have inactive disease with pulmonary scarring. a) High-resolution computed tomography (HRCT) showed a perihilar mass-like consolidation with central traction brochiectasis, cystic changes and distortion of the lung parenchyma. No nodular disease was present and the changes were interpreted as being fibrotic without active disease. b) ^{18}F-fluorodeoxyglucose position emission tomography/computed tomography (^{18}F-FDG PET), however, showed increased metabolic activity in the lung parenchyma combined with active lymphadenopathy in hila and the mediastinum. Based on these findings, infliximab therapy was initiated. After 6 cycles, VC, FEV_1 and $D_{L,CO}$ showed considerable increases of 15%, 11% and 8% respectively. c) HRCT demonstrated a significant improvement, while d) only slight metabolic activity remained visible on ^{18}F-FDG PET.

detection and follow-up of patients with cardiac sarcoidosis [78]. Although promising, to date, no such studies have been performed.

STATEMENT OF INTEREST

None declared.

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