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Evaluation of FDG PET combined with cardiac MRI for the diagnosis and therapeutic monitoring of cardiac sarcoidosis

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AIM: To compare combined 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron-emission tomography (PET) and cardiac magnetic resonance imaging (CMR) for the diagnosis and therapy monitoring of cardiac sarcoidosis (CS).

MATERIALS AND METHODS: Eighty patients with sarcoidosis and a suspicion of CS who underwent PET and CMR were included retrospectively. PET was undertaken after a low-carbohydrate–high-fat diet in all patients using a combined 16-section PET/computed tomography (CT) camera. PET was considered positive (PET+) in cases of focal or multifocal FDG uptake. CMR was considered positive (CMR+) in cases of subepicardial late gadolinium enhancement (LGE). A subgroup of 50 patients (50/80) was monitored during therapy and classified as responders or non-responders.

RESULTS: Eighty-two percent of patients with PET+ (9/11) also had CMR+ imaging, with good spatial agreement (kappa=0,79; 95% confidence interval [CI]: 0.65–0.94). Twenty-seven percent (22/80) had residual physiological FDG uptake, with a standardised uptake value (SUV) not significantly different compared to the SUV from pathological uptake (6.4 versus 6 respectively, p=0,92). The clinical response was more frequent in patients with baseline PET+ compared to baseline PET− (80% versus 45%, p=0.07). PET findings improved in all cases under treatment (7/7), whereas LGE improved in only 33% of patients (3/9).

CONCLUSION: Due to high risk of false-positive or undetermined findings, PET might be performed as a second-line study in cases of LGE, to assess inflammatory load. In addition, PET seems suitable to predict and assess response under therapy.

Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown aetiology characterised by mononuclear and giant cell accumulation, as well as non-caseating granuloma

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formation, with a prevalence of 1–5 in 10,000. The cardiovascular system is the third most frequently disease-targeted organ,[1] affecting on average 25–70% patients with sarcoidosis based on autopsy reports, but is only clinically identified in approximately 5% of patients.[2,3] Cardiac sarcoidosis (CS) is a life-threatening condition, and an accurate diagnosis is crucial because early treatment improves the prognosis.[4,5]

Diagnosis of CS is challenging and usually relies on a combination of clinical findings and imaging abnormalities.[6] The most common clinical presentations of CS are conduction system disease as third-degree atrioventricular (AV) block, ventricular and atrial arrhythmias,[7] and heart failure.[8] The most frequently used diagnostic criteria are those proposed by the Japanese Ministry of Health and Welfare (JMHW), published in 1993 and revised in 2007, and by the Heart Rhythm Society (HRS) [9,10]. These guidelines show the importance of having an underlying diagnosis of sarcoidosis based on histopathological confirmation, in addition to electrocardiographic changes or results from a reliable imaging method, such as cardiac magnetic resonance imaging (CMR) or 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET). Several studies have shown the utility of FDG for the diagnosis of active CS with high diagnostic accuracy (89% sensitivity and 78% specificity), according to a meta-analysis by Youssef *et al.* 11. Additionally, CMR is very sensitive for the diagnosis of CS, mainly through detecting myocardial damage.[12] CMR also has prognostic value for predicting major adverse cardiac events (MACEs) in CS[13,14]; however, CMR is not specific for identifying associated inflammation, which commonly occurs in the early and potentially reversible stages of CS.[15] Recently, Slart *et al.*, published a procedural position statement on imaging in CS, including the use of CMR, FDG PET, and myocardial perfusion imaging (MPI) for diagnosis.[16]

Despite the abundance of literature on CS, the comparative diagnostic value of PET and CMR has not been well studied, due to the limited number of patients included and the heterogeneity of the data, especially regarding the regimen used to suppress cardiac FDG uptake (fasting, heparin and/or a low-carbohydrate diet) and regarding the PET criteria used for the diagnosis of CS. The risk of false-positive results associated with FDG PET is known, and the use of semi-quantitative analysis is a source of debate.[17] Hence, the results are discordant regarding the association between FDG metabolism, late gadolinium enhancement (LGE), and hyperintensity on T2-weighted (W) imaging, and detailed analysis of spatial agreement is not available. Furthermore, although both PET and CMR are recommended for CS evaluation,[18] there is no consensus regarding the use of imaging strategies for assessing therapeutic response.

The objectives of the present study were to compare PET and CMR results in a large population of sarcoidosis patients suspected of having CS and to assess the relevance of the two techniques for therapy monitoring.

Materials and methods

Study population

From May 2009 to October 2014, 209 patients with biopsy-proven sarcoidosis were referred due to suspicion of CS; CS was suspected based on the diagnostic criteria of the European Society of Cardiology (ESC).[6] All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Formal ethics committee approval was not required for this retrospective analysis of the routine use of the PET technology in sarcoidosis. The diagnosis of sarcoidosis was established using the following validated criteria: consistent clinical presentation and chest radiography, histological evidence of non-caseous granulomas in biopsy specimens, and an absence of infection, environmental factors, or medical treatment known to cause granulomatous disease. PET and CMR were performed within a median time interval of 2 weeks. All PET studies were performed after the consumption of a high-fat–low-carbohydrate (HFLC) diet, according to a previous study.[17] Patients who did not completely follow the regimen before PET were excluded from the study.

The presence of cardiac involvement was suspected based on cardiac symptoms (chest pain, palpitation, malaise, or subacute congestive heart failure) and the presence of atrioventricular or intraventricular conduction defects (right bundle branch block, atrioventricular block, intraventricular conduction defect), or ventricular arrhythmias upon electrocardiogram (ECG) or 24-h Holter monitoring. Abnormal wall motion, regional wall thinning or thickening, and dilatation of the left ventricle upon echocardiography were also considered as possible manifestations of CS. Patients with a history of ischaemic heart disease were excluded from the study. Stress myocardial perfusion imaging or X-ray coronary angiography was performed at the discretion of the physicians when necessary. All clinical data (demographics, history, symptoms, ECG and Holter-ECG) and imaging data (echocardiography, PET, and CMR) were collected. All patients were then classified as having CS using the JMHW and HRS criteria.[9,10]

HFLC diet protocol

A menu of permitted (eggs, fish, chicken, meats) and proscribed (bread, cereal, cookies, toast, pasta, rice, cakes, fruit, potatoes) foods was given to sarcoidosis patients according to a previous study.[17] A reminder of the instructions was given at the time of a confirmation call. Patients observed the HFLC diet protocol for dinner before the day of PET and during breakfast approximately 4 hours before PET. Patients were also told to avoid exercise the day before the PET study. The consumption of the HFLC diet for dinner was not supervised. To verify adherence to the diet, a physician asked the patients about their complete diet on the day of

PET. A standardised breakfast meal was supervised in the nuclear medicine department 4 hours before PET. Patients taking medications for diabetes (insulin or oral drugs) did not take their treatment on the day of the PET examination and were monitored based on serum glucose levels.

PET

FDG-PET was acquired after the above-described regimen. After obtaining blood samples to measure serum or plasma levels of glucose, 3 MBq/kg of FDG was injected intravenously. All patients had a serum glucose level <1.4 g/l at the time of injection. PET images were obtained using a combined 16-section PET/computed tomography (CT) camera (GEMINI TF PET/CT, Philips, Best, the Netherlands) 60 minutes following the intravenous injection, with 2 minutes per bed position. The field of view was from the base of skull to mid-thigh. CT images were obtained without contrast media injection using the following parameters: 120 kV, 100 mAs, collimation of 16×1.5 mm, pitch of 0.69, section thickness of 3 mm, and increment of 1.5 mm. Transmission scanning was performed for attenuation correction.

Two experienced nuclear physicians independently estimated FDG uptake while blinded to the clinical characteristics of each subject. In the case of disagreement, the images were reviewed in consensus. According to personal experience and data from the literature, PET images were classified as positive if there was focal or multifocal FDG uptake and negative if there was no myocardial uptake or residual physiological FDG uptake. Diffuse, circumferential basal, papillary muscle, or homogeneous lateral wall uptake was defined as residual physiological uptake, as previously reported in the literature.[19] A positive PET examination was considered to indicate active CS. The localisation of FDG uptake was evaluated according to the 17 segments model. PET images were reviewed in consensus by two nuclear medicine physicians (M.S., B.S.). A quantitative analysis was also performed, in which a maximum standardised uptake value (SUVmax) was obtained in the myocardium with a manual volume of interest (VOI).

CMR

All patients underwent CMR using a 1.5T MRI system (Philips Intera). Images were acquired with ECG gating during repeated breath-holds of 10–15 seconds, depending on the heart rate. After localising scout imaging, spin-echo T2W sequences with chemical shift selective suppression of fat (700 ms repetition time [TR], 70 ms echo time [TE], 5 mm section thickness, 350 mm field of view, 192×256 matrix) was acquired in multiple short-axis views with a section distance of 10 mm, covering the entire left ventricle from base to apex, to assess the presence of myocardial inflammation. Increased signal intensity on the T2W images was suggestive of the inflammatory phase of CS. Cine-MR acquisition was also performed, which allowed quantitative analysis of left ventricle ejection fraction (LVEF) and the left ventricular volume in diastole and systole. Then, T1W contrast-enhanced images were acquired 5–15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-based contrast agent in the same view used for T2W, using the two-dimensional segmented inversion-recovery prepared gradient-echo sequence (700 ms TR, 1.49 ms TE, 250–400 ms inversion time). The inversion time was determined on an individual basis to obtain the optimal nulling of the unenhanced myocardial signal. CMR was considered positive (CMR+) for CS if LGE was observed, limited to the middle or subepicardial portion, or transmural, and sparing the subendocardium portion. The presence of T2W hyperintensity was also recorded. Then, to simplify comparison with PET results, the positivity, location, and extent of LGE were evaluated according to the 17-segment model. CMR was also reviewed in consensus by two experienced observers blinded to clinical history and PET findings (M.S., P.-Y.B.).

Therapy response assessment

A subgroup of 50 patients was assessed for the response to therapy at a median time of 12 months. These patients received immunosuppressive treatment that was introduced, increased, or maintained after the baseline evaluation: corticosteroids (n=30); corticosteroids + immunosuppressive drug (methotrexate, azathioprine) (n=12); immunosuppressive drugs (methotrexate, azathioprine) (n=7); or hydroxychloroquine (n=1). Clinical and imaging follow-up data (CMR, 50/50 and PET, 29/50) were reviewed. These patients were evaluated for pulmonary and cardiac symptoms: symptomatic arrhythmia defined as ventricular tachycardia leading to cardioversion (based on stored ECG), symptomatic bradycardia leading to pacemaker implantation, and death from cardiac cause. Then, the patients were classified as responders or non-responders according to a combination of clinical and functional criteria adapted from the literature,[20] which are detailed in Table 1.

Statistical analysis

Variables are presented as the arithmetic mean ± standard deviation unless otherwise specified. Comparisons

Table 1
Criteria for the classification of patients as responder or non-responder under immunosuppressive therapy.

Responders	Non-responder
Regression of pulmonary symptoms	Persistent or worsening of pulmonary symptoms
Regression of cardiac symptoms	Persistent or worsening of cardiac symptoms
No VT episode after 1 month of prednisolone therapy	Recurrence of VT episode despite 1 month of corticosteroid therapy
Improvement in left ventricular ejection fraction by 10% in patient with LV systolic dysfunction on follow up	No improvement in LVEF
Decrease of ACE by 20%	Persistent or worsening of ACE

VT, ventricular tachycardia; LV, left ventricle; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme.

were performed using Mann–Whitney tests. Fisher's exact test was used to compare the clinical and imaging features of the CS population at baseline and for therapy evaluation. The imaging response to therapy was defined as regression or disappearance of LGE or FDG uptake, through visual and qualitative analysis. The overall and segmental agreement between CMR and PET parameters was assessed using Cohen's kappa coefficients. A p-value of <0.05 was considered significant. Statistical tests were performed using GraphPad.

Results

Population characteristics

A total of 209 patients with biopsy-proven sarcoidosis and suspicion of CS were recorded during the period of inclusion (Fig 1). Among these patients, 129 were excluded: 98 did not have a baseline CMR and/or PET; in 10 patients, PET and CMR were performed with a time interval of >2 months; for 18 patients, the HFLC diet was not followed; and three patients had a history of ischaemic heart disease. The remaining 80 patients met all inclusion criteria. Depending on the results of the PET and CMR examinations, four groups were established according to the imaging results: CMR+/PET+, CMR+/PET−, CMR−/PET+, and CMR−/PET−. The baseline features of the patients in the four groups are presented in Table 2. Briefly, all of the patients had chronic sarcoidosis (median of 6 years since diagnosis); 80% (64/80) were symptomatic, and 58% (46/80) were treated with steroids and/or other immunosuppressive treatment at the time of inclusion. The PET+/CMR+ patients exhibited more electrical abnormalities than the PET−/CMR+ patients (9/9 versus 14/25, $p=0.07$), but showed no significant differences in terms of cardiac symptoms ($p=0.44$). The PET+/CMR+ patients also displayed higher angiotensin-converting enzyme (ACE) levels ($p<0.05$) and a trend of more extracardiac pathological FDG uptake ($p=0.1$) than the PET−/CMR+ patients (Table 2).

Intermodality agreement

Among the patients, 43% (34/80) exhibited LGE upon CMR, which was associated with T2W hyperintensity in 5/34 patients; 14% (11/80) of the patients were PET+. The two techniques were both positive in 11% of patients (9/80). Thirty-one percent of the patients (25/80) were CMR+ and PET−. Only 2/80 patients were PET+ and CMR−. Among all patients of the study population ($n=80$), intermodality agreement regarding segment involvement was low, with a kappa at 0.41 (95% CI: 0.36–0.45). This low spatial agreement was due to the 25/80 patients who were PET− and CMR+.

Conversely, among the PET+ patients, 11% (21/187) of segments were positive, including 86% (18/21) located in the same area as LGE upon CMR, leading to good intermodality agreement: kappa score of 0.79 (95% CI: 0.65–0.94).

Among the five patients with positive T2W, only two patients were in the PET+/MRI+ group. The other three patients were in the PET−/MRI+ group. Of the two patients with a T2 hyperintensity associated with PET+, only one exhibited good spatial correlation between T2W and PET.

In 27% of the patients (22/80), residual FDG uptake with a physiological pattern was observed, including diffuse and homogeneous patterns (13/22), circumferential basal pattern (6/22), diffuse lateral wall uptake (6/22), or papillary muscle (2/22) uptake. CMR was negative in all of these patients. Importantly, the SUVmax of the PET+ patients was not significantly different than the SUVmax of patients with residual FDG uptake: 6±2.9 and 6.4±3.9, respectively ($p=0.92$; Fig 2). In patients with residual uptake, no correlations were found between cardiac factors, such as the LVEF or cardiac volume, upon CMR and residual FDG uptake.

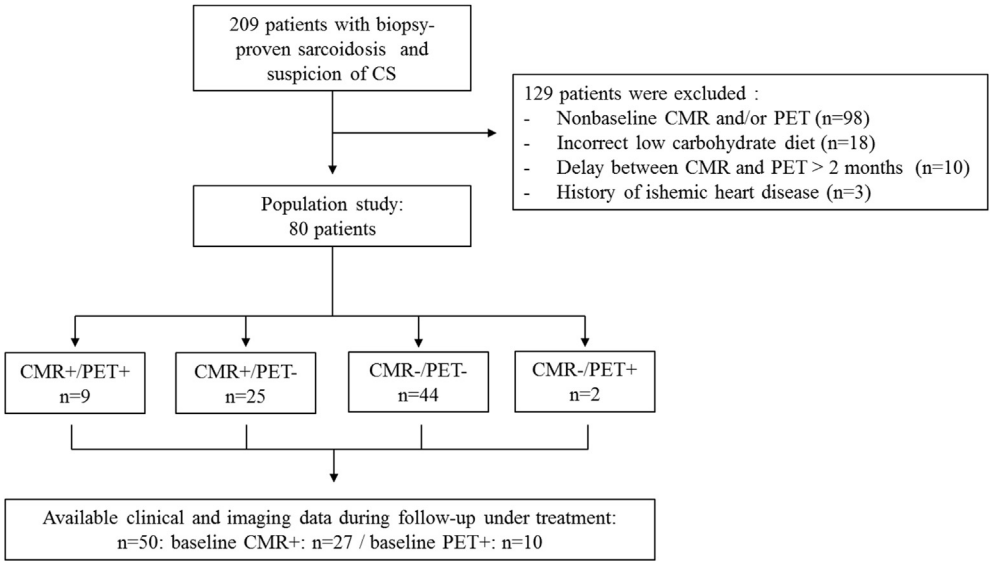

Figure 1 Flow Chart.

Table 2
Baseline characteristics of the 80 patients included in the study.

	MRI+/PET+ (*n*=9)	MRI+/PET- (*n*=25)	MRI-/PET- (*n*=44)	MRI-/PET+ (*n*=2)	Overall (*n*=80)
Baseline characteristics					
Age (years)	43 [27–61]	44,6 [24–79]	42 [12–75]	45 [39–50]	50,1 [28–82]
Males, *n* (%)	6 (67)	14 (56)	25 (57)	1 (50)	46 (58)
Diabetes, *n* (%)	2 (22)	5 (20)	6 (14)	0 (0)	13 (16)
Cardiac symptoms, *n* (%)	6 (67)[a]	11 (44)	21 (48)	1 (50)	39 (49)
None	3 (33)	14 (56)	23 (52)	1 (50)	41 (51)
Chest pain	3 (33)	8 (32)	16 (36)	1 (50)	28 (35)
Palpitation	3 (33)	3 (12)	13 (30)	1 (50)	20 (25)
Syncope	0 (0)	2 (8)	1 (2)	0 (0)	3 (4)
Electrical abnormalities, *n* (%)	9 (100)[b]	14 (56)	28 (64)	0 (0)	51 (64)
None	0 (0)	11 (44)	16 (36)	2 (100)	29 (36)
Left BBB	0 (0)	2 (8)	3 (7)	0 (0)	5 (6)
Right BBB	1 (11)	3 (12)	10 (23)	0 (0)	14 (18)
AV block I	0 (0)	2 (8)	3 (7)	0 (0)	5 (6)
AV block II-III	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ST-T changes	2 (22)	7 (28)	10 (23)	0 (0)	19 (24)
PVCs	5 (60)	9 (36)	7 (16)	0 (0)	21 (26)
Supraventricular arrhythmias	2 (22)	6 (24)	5 (11)	0 (0)	13 (16)
ACE (mean), µg/l	104 (30–335)[c]	49 (10–220)	58 (6–224)	32 (32–32)	61 (6–335)
Echocardiography, *n* (%)					
Decreased LVEF (<60%)	0 (0)	5 (20)	1 (2)	0 (0)	6 (8)
Regional abnormal wall motion	4 (44)	9 (36)	1 (2)	0 (0)	14 (18)
Wall thickening	1 (11)	2 (8)	7 (16)	0 (0)	10 (13)
Immunosuppressive therapy, *n* (%)					
No medication	4 (45)	10 (40)	20 (46)	0 (0)	34 (43)
Steroids	2 (22)	9 (36)	16 (36)	2 (100)	29 (36)
Steroids + other IS agents	3 (33)	6 (24)	8 (18)	0 (0)	17 (21)
PET					
Type of pattern, *n* (%)					
Focal	5 (56)	0	0	2 (100)	7 (9)
Multi-focal	4 (44)	0	0	0	4 (5)
Extra-cardiac FDG uptake, *n* (%)	6 (67)[d]	8 (32)	28 (64)	2 (100)	44 (55)
Residual uptake, *n* (%)	0	6 (24)	16 (36)	0 (0)	22 (27)
Cardiac MRI					
Ventricular function					
LVEF mean, %	54 (42–62)	53 (28–64)	56 (44–73)	52 (45–58)	54 (28–73)
End diastolic volume, ml	118 (49–145)	109 (49–194)	125 (51–228)	81 (59–103)	118 (51–228)
LGE, *n* (%)	9 (100)	25 (100)	0	0	34 (43)
T2W hyperintensity, *n* (%)	2 (22)	3 (12)	0	0	5 (6)
2006 JMHW criteria met, *n* (%)	6 (67)	12 (48)	4 (9)	0 (0)	22 (27)
2014 HRS criteria met, *n* (%)	9 (100)	25 (100)	4 (9)	2 (100)	40 (50)

[a]p=0.44, [b]p=0.017, [c]p=0.04, [d]p=0.1 MRI+/PET+ versus MRI+/PET−.
NYHA, New York Heart Association; BBB, bundle branch block; AV, atrioventricular; PVCs, premature ventricular contractions; LVEF, left ventricular ejection fraction; JMHW, Japanese Ministry of Health and Welfare; HRS, Heart Rhythm Society.

Comparison with JMHW and HRS criteria

Only 28% of patients (*n*=22/80) exhibited positive JMHW criteria: 55% of the patients with positive PET (*n*=6) and 53% of the patients with positive CMR (*n*=18). According to the JMHW criteria, the sensitivity and specificity were 27.3% and 91.4%, respectively, for PET, and 81.8% and 72.4% for CMR. Furthermore, 47% of the patients (38/80) exhibited positive HRS criteria. According to the HRS criteria, the sensitivity and specificity were 28% and 100%, respectively, for PET, and 85% and 100% for CMR.

Clinical and imaging follow-up under immunosuppressive treatment

In the subgroup of 50 patients followed under treatment, baseline PET and CMR were positive in 10/50 and 27/50 individuals, respectively. In the group with baseline PET+ (*n*=10), there was a trend toward better clinical response in comparison with the baseline PET− group (*n*=40): 80% (8/10) versus 45% (19/40), respectively (p=0.07) (Table 3 and Fig 3). Similarly, in the baseline PET+ group, 100% (7/7) of follow-up PET examinations improved under treatment, and the imaging response was well correlated with clinical improvement in most of the patients (6/7). In the group with baseline CMR+ (*n*=27), there was no significant difference in the clinical response in comparison with the baseline CMR− group (*n*=23): 52% (14/27) versus 57% (13/23), respectively (p=0.48; Table 3, Fig 3). Among the two patients with positive T2W in the PET+/CMR+ group, 1/2 was a responder to the treatment. In comparison, among the other three patients with positive T2W in the PET−/CMR+ group, only one patient was a responder. The PET and CMR results under treatment are illustrated in Fig 4.

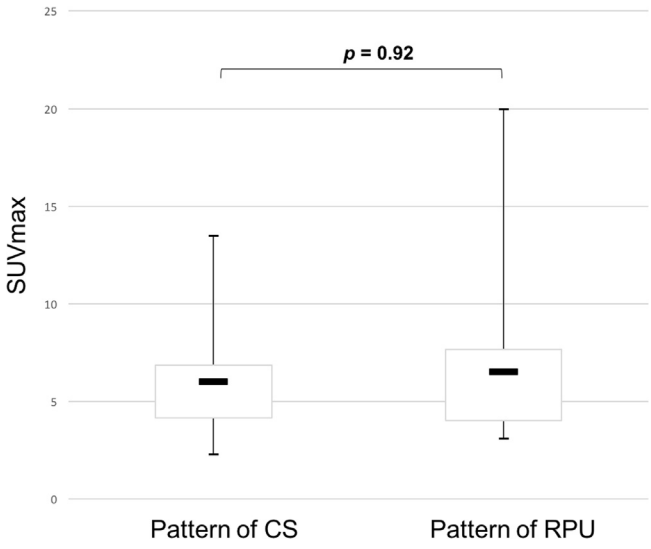

Figure 2 Box plots (mean, extremes) of SUVmax in CS and in residual physiological uptake patterns.

MACEs

Overall, 96% (77/80) of the patients were followed from inclusion to the end of study, with a mean follow-up time of 28±22 months. Four MACEs were recorded, in four patients with negative PET and positive (n=3) or negative (n=1) CMR. Two patients died from cardiac causes, and two others exhibited symptomatic bradycardia leading to pacemaker implantation.

Discussion

The aim of the present study was to compare CMR to PET results systematically in a population of sarcoidosis patients with clinically/ECG-suspected cardiac involvement. The motivation for the present study was the difficulty of withdrawing physiological cardiac FDG uptake after a low-carbohydrate regimen, possibly resulting in either false-positive results or a false negative in cases of physiological uptake in an area of true cardiac inflammation. Indeed, a significant number of cases of failed cardiac FDG suppression under a well-completed regimen is observed in the literature and confirmed in the present study (22/80, 27%).

Table 3
Clinical and imaging (CMR and PET) modifications under treatment according to the clinical response at 12 months (n=50).

Baseline scans	Assessment of response under therapy at M12	
	Clinical response	Imaging response
PET+ (n=10)	8 (80)[a]	7/7 (100)[c]
PET- (n=40)	19 (47)[a]	21/22 (95)
CMR+ (n=27)	14 (52)[b]	7 (26)[c]
CMR− (n=23)	13 (57)[b]	23 stays (100)

Results are shown as number (frequency).
[a]p=0.07 baseline PET+ versus baseline PET−.
[b]p=0.48 baseline CMR+ versus baseline CMR−.
[c]p<0.001 Imaging response under treatment between baseline PET+ and baseline CMR+.

As a very sensitive and specific method, PET was correlated with CMR to increase the diagnostic confidence in cardiac PET imaging in the setting of CS as suggested by the study of Slart *et al.*[16] The present results showed that when PET was positive, CMR was also positive in 82% of the patients (9/11), with very good spatial intermodality agreement (kappa=0.79). Only two patients exhibited PET+ with CMR−. These two patients showed clinical suspicion of CS (thoracic pain with palpitations), but no electrical abnormalities, normal ACE levels, and normal transthoracic echocardiography, while no MACE was recorded during follow-up. Focal FDG uptake in the lateral wall of the left ventricle was observed in these two patients; this location has been described previously as a potential location of residual FDG uptake under a low-carbohydrate regimen and in some healthy subjects. These retrospective arguments indicate a probable false-positive PET result.

The disagreement between PET and CMR may be explained by the fact that these two methods allow the detection of different pathological processes. FDG-PET shows inflammatory cardiac infiltrates, while LGE upon CMR mainly detect fibrotic and non-viable myocardia.[18] This difference explains the low sensitivity of PET when using the JMHW or HRS criteria as the reference standard, of 27% and 28%, respectively, whereas these values are higher for CMR, at 81.8% and 85%, respectively. This low sensitivity of PET should improve when using FDG PET to detect inflammation, in a similar fashion to myocardial perfusion imaging using rubidium PET to detect fibrosis in the case of perfusion defects, as suggested by Slart *et al.*[16] CMR with T2W imaging has been shown to be accurate in the detection of inflammatory processes in the myocardium; however, in the present study this sequence had low sensitivity compared to LGE, consistent with previous reports.[21,22] The recent introduction of T1 and T2 mapping in addition to traditional CMR sequences might provide a more robust assessment of altered T1 and T2 relaxation times in cardiomyopathy.[23] T1 and T2 mapping is optional in the recent recommendations of Slart *et al.*[16]

The selected criteria for retaining a positive result are crucial. The present results showed that quantitative analysis with SUVmax was not accurate enough for the diagnosis of CS because no significant differences in SUVmax values were observed between patterns suggestive of CS and patterns suggestive of residual physiological uptake (p=0.92). Another critical issue is that residual FDG uptake can mask a possible pathological hotspot. This point is another reason for recommending the use of PET as a second-line evaluation, after pathological CMR. Consequently, visual analysis for the detection of active cardiac sarcoidosis is advised; this method also shows good inter-observer agreement when detailed pre-scan dietary preparation is available.[24]

Another unsolved issue is the choice of the imaging technique for assessing treatment response. The present results showed that PET is suitable for evaluating patients with a positive baseline scan and that the PET response is well correlated with clinical and electrical improvements. This statement is supported by the results of a study by Orii

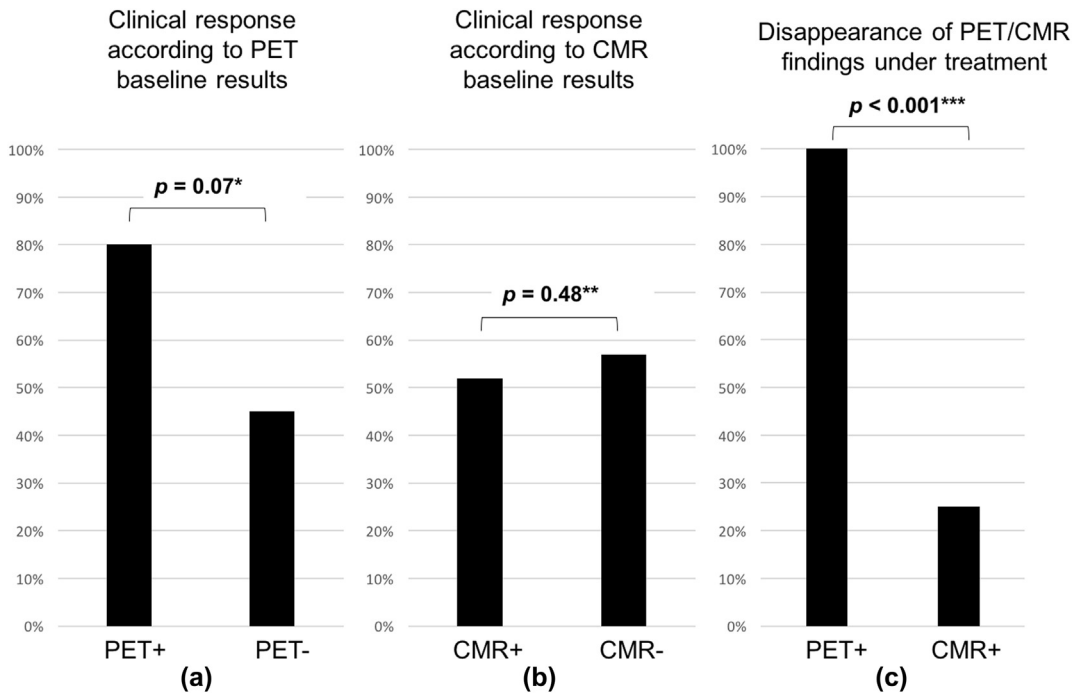

Figure 3 Clinical response according to PET (a) or CMR (b) baseline status. (c) The percentage of disappearance under treatment of FDG uptake or LGE.

et al. showing that pretreatment FDG uptake is predictive of the resolution of a complete heart block under treatment.[25]

Previous studies compared the results of CMR and PET for CS diagnosis. A review of the literature is shown in Table 4. Review of the results shows global disagreement between the two methods. The first interesting point is that FDG PET is more often positive in the setting of new-onset cardiac conduction system disorders than in chronic cardiac

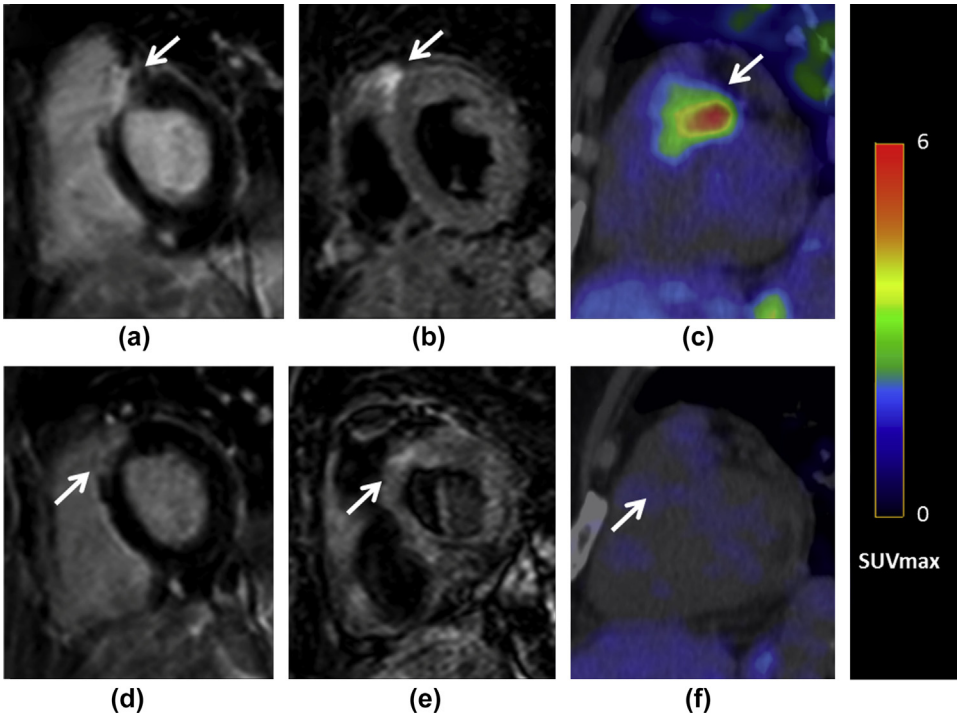

Figure 4 Suspicion of cardiac sarcoidosis in a 66-year-old man presenting with chest pain and an increased ECA level of 154 μg/l, with normal ECG and echocardiography. Antero-septal LGE upon (a) CMR and (b) T2W hyperintensity with (c) FDG uptake (SUVmax: 6.4) in the same location (2/17 segments). After 4 months of steroid treatment, a decrease in the intensity of LGE (d) and T2W hyperintensity (e) was observed and complete disappearance of FDG uptake. This patient was considered to be a responder and did not exhibit any MACE.

Table 4
Review of the main studies of the literature about the comparison of FDG PET and CMR for assessing cardiac sarcoidosis.

Study	Study population	Regimen protocol	PET diagnostic criteria	CMR diagnostic criteria	Results
Ohira (2008) [30]	21 patients suspicion of CS	Fasting $\geq$ 6h UFH 50UI/kg (n=19)	Focal or Focal-on-diffuse pattern	Increased T2W signal LGE	LGE: 8/21; T2: 2/21; PET+: 15/21. PET+/LGE: 8/21; PET+/no LGE: 7/21.
Orii (2015) [25]	15 CS CHB+ 17 CS CHB−	Low-carbohydrate meal Fasting $\geq$ 18h UFH 50UI/kg	Cardiac uptake > Liver uptake	T2W: > 2 SDs above the mean DE: > 5 SDs above the mean	Focal inflammation in IV septum associated with CHB - CHB+: LGE (100%), T2 (60%), PET (87%) - CHB−: LGE (100%), T2 (12%), PET (76%)
Ohira (2016) [31]	30 suspicion of CS: 18 cCSD + 12 new-onset AVB	Fasting $\geq$ 12h HFLC diet	Focal pattern (excluding the lateral wall)	LGE in 2 orientations	PET+/CMR+ in - 72 % (13/18) in cCSD - 58 % (7/12) in AVB
Zandieh (2016)[32]	7 patients with CS	Fasting $\geq$ 12h	Patchy uptake consistent with CS	LGE consistent with CS	PET+: 3/7; CMR+: 5/7, T2+: 2/7
Bravo (2017)[14]	56 patients: high suspicion of CS	High fat, High protein, no carbohydrate and no sugar diet $\geq$ 24h Fasting $\geq$ 12h	Combination of metabolic (M) and perfusion imaging (P): Focal or multifocal pattern for M PET	Sub-epicardial patchy LGE	CMR+: 36/56, PET+: 16/56 LGE versus M/P PET: good agreement (k=0.75) LGE versus M PET: low agreement (k=0.47) CS patients with LGE alone or in association with FDG were at similar risk of future events
Wicks (2018) [33]	51 patients with suspected CS	HFLC diet + Fasting $\geq$ 12h	none, diffuse and focal or focal-on-diffuse" pattern	Presence of LGE	PET+: 28/51; CMR+: 32/51 PET+ with CMR+: 17/51 MACE: 18/51 PET+/CMR+ group: predictor of MACE
Vita (2018) [34]	107 patients with suspected CS	HFLC diet + Fasting $\geq$ 4h	None, focal or multifocal uptake	Focal or multifocal LGE	LGE: 91/107; PET 60/107 When PET findings were added to CMR, 48/107 (45%) were reclassified as having a higher or lower likelihood of CS MACE: 27/107
Dweck (2018) [35]	25 patients with suspected CS	Dietary preparation	None, focal or multifocal uptake TNMR	Focal or multifocal LGE T2 mapping	- PET+/CMR+: 8 (aCS) - PET−/CMR+: 1 (iCS) - PET−/CMR−: 8 - RPU: 6/25 (24%) TNMR higher in aCS (p<0.001) Non-significant correlation between T2 mapping and TNMR (p=0.14)

CS, cardiac sarcoidosis; UFH, unfractionated heparin; LGE, late gadolinium enhancement; CHB, complete heart block; SDs, standard deviations; DE, delayed enhancement; cCSD, chronic conduction system disease; AVB, atrioventricular block; HFLC, high fat and low carbohydrate; RPU, residual physiological uptake; CMR, cardiac magnetic resonance; T2W, T2-weighted imaging; MACE, major adverse cardiac event; TNMR, target-to-normal myocardium ratio; aCS, active CS; iCS, inactive CS.

disease.[25,26] Second, systematic analysis of the agreement between PET positivity and the presence of pathological findings in CMR (LGE and/or T2W hyperintensity) is problematic. One study showed a high rate of PET positivity with negative CMR, which is in disagreement with the present results. One explanation is the regimen (fasting and heparin perfusion) employed in this study, which was not efficient enough to suppress physiological cardiac uptake, as shown in recent studies suggesting that the combination of fasting and a low-carbohydrate diet is the most efficient way to suppress physiological cardiac FDG uptake.[27] Third, in line with the present results, Bravo *et al.* showed that the overall agreement of PET and CMR appears to be reasonably good. Furthermore, the authors observed that PET positivity is always associated with the presence of LGE upon CMR. Hence, the present study agrees with Bravo *et al.* regarding the categorisation of three groups of sarcoidosis patients: (1) those with no myocardial damage (negativity of PET and CMR), with the best prognosis; (2) those with myocardial damage with inflammation, related to active CS, with a significantly higher risk of MACEs than those without myocardial damage; and (3) those with myocardial damage without inflammation, suggestive of fibrotic lesions of previously treated sarcoidosis. In the third group of patients, Bravo *et al.* observed that the risk of adverse events was significantly higher than in those without myocardial damage, but was comparable to that in patients with LGE associated with FDG uptake. In the present study, only 4/80 MACEs were observed during the follow-up period, and CMR LGE was observed in 3/4 patients without FDG uptake; this low rate of events precludes a robust prognostic analysis.

There are some limitations of this study. First, it is retrospective in design. Second, 58% of the patients were treated with immunosuppressive therapy at the time of PET, a condition that could impair the detection of active disease; however, in a meta-analysis by Youssef *et al.*,[11] most of the patients with CS under treatment exhibited positive PET, suggesting that steroids did not reduce the initial diagnostic power of FDG PET. Third, PET and CMR were not performed at the same time, but with a maximum time interval of 2 months (mean time interval of 12±48 days). Hybrid imaging with PET/MRI could solve the problem of this temporal difference between PET and CMR, as shown in recent studies by White *et al.*[28] and Nensa *et al.*[29] Fourth, the sample size in this study was relatively small, and 55% of the subjects presented negative imaging, which could partially explain the low rate of MACEs. Finally, PET was used only for the detection of inflammation and no associated PET perfusion study (with rubidium, for example) was conducted. The study of Slart *et al.* suggests that FDG PET associated with perfusion imaging may be useful for monitoring the progression of scarring and inflammation, but further studies are needed to establish more accurate methods of monitoring.[16]

New knowledge gained

There is no difference in SUVmax between pathological and residual FDG uptake in CS patients, suggesting that semi-quantitative evaluation with FDG PET is inappropriate for assessing CS. Pathological FDG uptake based on visual analysis shows good spatial agreement with CMR LGE for the diagnosis of CS. A clinical response is more frequent in patients with baseline PET+, in whom FDG uptake was shown to be improved in all cases under treatment. This observation suggests that PET is suitable for assessing the inflammatory nature of myocardial damage and can predict response under immunosuppressive therapy. Finally, due to the significant risk of false-positive results or undetermined findings, the present results suggest that FDG PET should be performed as a second-line evaluation in the presence of LGE upon CMR.

In conclusion, the present study shows that FDG uptake presents good spatial agreement with LGE CMR; that quantitative analysis is not a reliable criterion for the diagnosis of inflammatory cardiac sarcoidosis; and that FDG uptake is more sensitive than LGE upon CMR for assessing therapeutic response. The present results suggest that PET should be performed as a second-line evaluation after positive CMR to improve lesion characterisation and decrease the risk of false-positive and false-negative results. Then, FDG PET might be employed as a therapeutic response tool in the case of positivity.

Conflict of interest

None.

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