

¹⁸F-FDG-PET in Finnish patients with clinical suspicion of cardiac sarcoidosis: female sex and history of atrioventricular block increase the prevalence of positive PET findings

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Abstract

Introduction: Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) is a non-invasive imaging modality that has been shown to be a feasible method to demonstrate myocardial inflammation. The aim of this study was to identify the patients suspected of having cardiac sarcoidosis (CS), who are most likely to benefit from PET imaging.

Materials and methods: 137 patients suspected of having CS underwent a dedicated cardiac FDG-PET examination at Tampere University Hospital between August 2012 and September 2015. These examinations were retrospectively analysed.

Results: 33 and 12 of the 137 patients had abnormal left and right ventricular (LV and RV) FDG uptake respectively. Abnormal LV-uptake and RV-uptake were significantly associated with female sex and a history of advanced AV-block ($p < 0.05$). Abnormal RV uptake was also associated with ventricular tachycardia and atrial fibrillation ($p < 0.05$). 56% of the 27 female patients with a history of AV-block had a pathological PET finding compared to only 6% of the 49 male patients without a history of AV-block. There were 17 female patients with history of both AV-block and ventricular tachycardia, 71% of them had abnormal PET finding.

Conclusions: Abnormal FDG-PET findings were associated with female sex, AV-block and arrhythmias in this clinical cohort.

Abbreviations: CS=cardiac sarcoidosis; EMB=endomyocardial biopsy; FDG-PET=
¹⁸Fluorodeoxyglucose positron emission tomography; RV= right ventricle; LV= left ventricle;
AV=atrio-ventricular; VT= ventricular tachycardia, MPI= myocardial perfusion imaging

Keywords: ¹⁸F-FDG-PET, cardiac sarcoidosis, AV-block

Introduction

Sarcoidosis is a multisystem granulomatous inflammatory disorder that can affect any organ system. The disease most commonly manifests in the lungs, typically as an asymptomatic hilar lymph node enlargement. The incidence of sarcoidosis differs between populations according to their genetic background (1). In Europe, Scandinavians have the highest prevalence (2). At autopsy, 27% of sarcoidosis patients showed cardiac involvement, which is the most frequent cause of sarcoidosis-related death (3, 4, 5, 6). In 40-50% of patients, cardiac sarcoidosis (CS) is diagnosed pre-mortem (7). Due to the difficulty of diagnosing CS, epidemiological literature on the topic is sparse. In Finland, the prevalence of biopsy-confirmed CS is 2.2/100.000. In 65% of such cases, sarcoidosis is confined to the heart without clinical manifestations in other organs. The true incidence of CS is probably higher because all clinically diagnosed cases without biopsy verification were excluded (8).

According to the guidelines issued in 2006 by the Japanese Ministry of Health and Welfare (JMHW) and revised by the Japan Society of Sarcoidosis and Other Granulomatous Disorders, CS can be diagnosed directly by verifying cardiac involvement on biopsy or indirectly via histologically proven extra-cardiac sarcoidosis combined with electrocardiographic and imaging findings (9). The revised criteria were proposed by the Heart Rhythm Society in 2014 (10).

According to both guidelines, CS can only be diagnosed if there is direct proof by endomyocardial biopsy (EMB) or previously diagnosed systemic sarcoidosis combined with clinical and imaging findings indicating cardiac involvement. Given that the sensitivity of EMB is low, a large share of patients with probable CS does not fulfil the current diagnostic criteria (11). Thus, imaging is also needed in the diagnostic workup for CS. Criteria for diagnosing isolated CS relying partly on imaging were proposed by Isobe in 2015 (12).

Cardiac ¹⁸fluorodeoxyglucose positron emission tomography/computerized tomography (18FDG PET/CT) (later referred to as PET) has been used to identify active cardiac inflammation, with a sensitivity and specificity of 89% and 78%, respectively (13). PET is not included in the JMHG guidelines. The demand for cardiac imaging has increased because it has been suggested that CS should be excluded in patients under the age of 55 with unexplained dilated cardiomyopathy, II or III degree atrioventricular (AV-) block or persistent ventricular tachycardia (VT) (10, 11). The aim of the present study was to evaluate the use of PET in the diagnostic workup of patients with symptoms suggestive of CS in a clinical setting. Because PET imaging is relatively expensive and involves radiation, it is clinically relevant to identify the patients who are most likely to benefit from the diagnostic method and to recognize the factors that predict a diagnosis of CS.

Materials and methods

Study population

We retrospectively screened all cardiac PET studies performed in the Tampere University Hospital from August 2012 to September 2015. We excluded PET studies if clinical indication was not CS suspicion, where the patient's clinical data could not be obtained or if the PET study was performed to follow up on previously diagnosed CS. Imaging studies were also excluded if the dedicated imaging protocol, as described below, was not followed precisely. Altogether 137 PET examinations were analysed for the present study. It is routine in our hospital to perform PET in the diagnostic workup of possible CS. The reason for a clinical suspicion of CS was one or more of the following: unexplained AV-block (n=61), ventricular (n=39) or supraventricular (n=13) arrhythmia, unexplained dilated cardiomyopathy (n= 27), unexplained low ejection fraction in echocardiography (n=46), other echocardiographic findings suggestive of CS (n=53), or syncope (n=27). Symptoms and clinical findings were considered unexplained by the cardiologist after routine studies including clinical examination, ECG and echocardiography. Coronary angiography was performed in case of clinical suspicion of coronary artery disease.

PET Imaging

All patients underwent an integrated PET/CT (Discovery STE 16, GE Healthcare, Milwaukee, WI, USA) examination. To minimize the physiological myocardial FDG uptake, the patients were instructed not to consume any carbohydrates during the day before the imaging and were fasting for 12 h before the FDG injection. The patients kept a food diary during the diet. The patients were also instructed to avoid heavy physical exercise to minimize FDG uptake in skeletal muscle. The patient's height and weight were measured before the administration of the radiopharmaceutical, and their blood glucose level was tested to be <7 mmol/l. The PET/CT images were acquired

approximately 60 min after the intravenous injection of FDG using the Medrad® Intego PET infusion system (Bayer Medical Care Inc., Indianola, PA, USA). The activity injected is currently based on the patient's weight (3-3.2 MBq/kg). However, the protocol was changed in 2013. Previously, patients were given a fixed dose of 370 MBq. The mean injected activity in our study population was 320 MBq (range 219-460 MBq). The imaging covered a volume of two bed positions around the myocardium approximately from the level of shoulders to the level of the gallbladder. The acquisition of the images was made in the three dimensional (3D) mode with a 128*128 matrix, 70 cm field of view (FOV) and 5 min per bed position. The PET images were reconstructed using the 3D VUE Point reconstruction algorithm (GE Healthcare) with 2 iterations and 28 subsets. Gaussian 6.0 mm FWHM was used as the post-filter. The acquisition parameters of the CT scanner were as follows: tube voltage, 120 kV; tube current automatic exposure control range, 30 – 80 mA; noise index, 33 HU; rotation speed, 35 mm/rot; and pitch, 1.75:1. The CT images were reconstructed to slice thicknesses of 2.50 mm, with 1.25-mm intervals. The total examination time for the PET/CT was approximately 15 min. CT was used for attenuation correction and the accurate localization of uptake.

Analysis of the PET images

We classified the uptake pattern in the left ventricular (LV) myocardium according to the recommendations of the Japanese Society of Nuclear Cardiology (10) as 'none' (no activity exceeding normal blood pool activity), 'global diffuse' (even activity over the whole myocardium) 'focal' (focally increased spot(s) of activity, other regions inactive), 'focal on diffuse' (intense focal spot(s) of activity overlaid on global myocardial activity) or 'diffuse non-global' (faint activity on at least two LV walls but at least some areas of myocardium with no activity over normal blood pool activity). Diffuse non-global uptake is not mentioned in the Japanese Society of Nuclear Cardiology recommendations, but it was considered to be a similar physiological phenomenon as

diffuse uptake. The uptake was called physiological if it was classified as none, global diffuse or diffuse non-global and pathological if it was classified as focal or focal on diffuse. We also classified the uptake in the right ventricle (RV) in a similar manner. The maximum standardized uptake value (SUVmax) in the heart was measured, and its location was determined. The images were interpreted after patient anonymization and randomization. The images were separately interpreted by two experienced nuclear medicine physicians (HT, KS) blinded to all clinical data. In cases where the interpretation of LV uptake differed between the observers, a consensus was formed and used in the further analyses.

Collection of clinical data

We aimed to study the diagnostic yield of PET in relation to different patient characteristics (demographics, clinical history and reason for referral). The clinical data were retrospectively collected from the electronic medical records of Tampere University Hospital, which contains information from 2008 onwards. We collected demographic information, echocardiography findings, relevant diagnoses, symptoms and EMB findings.

Statistical methods

Statistical analyses were performed using IBM SPSS statistics version 22.0 (Armonk, NY, USA) and R software version 3.2.2. Chi-square and t-tests were used to compare the results. Data are expressed as the mean (\pm SD) for the continuous variables and percentages for the dichotomous variables. Inter-observer agreement was calculated using kappa statistics.

Results

The inter-observer agreement in analysing the LV uptake in the PET studies was good (kappa 0.762). The mean follow-up time (interval between PET imaging and data collection) was 692.8 days (1 year, 10.8 months) (SD 347 days).

104 patients had no pathological LV-uptake: 85 had no visible uptake, three had diffuse uptake and 16 had diffuse non-global uptake pattern. Pathological LV-uptake was observed in 33 patients: 28 had focal uptake and five had focal on diffuse uptake pattern. The mean SUVmax in the heart was 8.5 (SD 4.1) in those with pathological uptake compared to 3.4 (SD 1.3) in those with no pathological uptake ($p < 0.001$).

Alltogether 29 (21 %) patients had focal uptake outside myocardium. Uptake foci were encountered in hilar, mediastinal, axillary, subclavicular and abdominal lymph nodes, lung parenchyma, spleen and skeleton. 16 of the 33 patients with pathological myocardial uptake had pathological extracardiac foci compared to 13 of those 104 who had no pathological myocardial uptake ($p < 0.001$).

The proportions of patients with pathological PET findings according to the demographic information and patient history are presented in Tables 1 and 2. 13 (16 %) of the male and 20 (35 %) of the female patients had abnormal LV uptake. Twelve patients had uptake in the RV free wall, ten of them were female. All patients with abnormal RV uptake also had pathological LV uptake. The patients with pathological PET findings were more often female and had more frequently a history of 2nd or 3rd degree AV-block than the patients with normal PET findings (Tables 1 and 2, Figure 1). Of the 137 patients 56 (41 %) had a history of 2nd or 3rd degree AV-block and 41 % of them had a pathological PET finding. 27 of the patients with advanced AV-block were female and 56% of them had pathological LV-uptake. Of the 49 male patients without AV-block only 6% had

pathological LV-uptake. In our population, there were 75 patients with a history of VT. 31% of them had abnormal LV uptake and 15% had abnormal RV uptake. Abnormal RV uptake was significantly associated with ventricular tachycardia (Table 2). There was also a borderline significant ($p=0.053$) association between abnormal LV uptake and ventricular tachycardia (Table 1). There was a subgroup of 17 female patients who had a history of both advanced AV-block and VT. 71 % of them had a pathological PET-finding. Abnormal RV uptake was also significantly associated with the history of atrial fibrillation (Table 2). AV-block was the only reason for referral significantly associated with abnormal PET findings (Tables 1 and 2).

EBM was obtained from 21 patients. Histology was suggestive of CS in seven patients. Six of those had pathological LV-uptake and four also had pathological RV-uptake. However the association between abnormal FDG uptake and positive EMB finding was not statistically significant.

Discussion

Few studies have dealt with the utilization of PET in the diagnostic workup of CS in a clinical setting. A prospective study by Yokoyama et al described the characteristics of a population of 92 patients with a suspicion of CS (14). In that population, 40% of patients were diagnosed with CS. Pathological PET findings were observed in 36/37 of the patients diagnosed with CS compared with 16/55 non-CS patients, resulting in a sensitivity of 97% and specificity of 71%. Blankstein et al (15) studied 118 patients with suspected CS. They found pathological LV uptake or perfusion defects in 60% of the patients, but only 40% of those fulfilled the JMWH criteria, which resulted in low specificity. The authors speculated that these findings were a result of low sensitivity of the JMWH criteria because PET was a better predictor of future adverse events. In our population of 137 patients, 33 had pathological LV uptake. The lower proportion of abnormal PET findings compared with the previously mentioned studies probably reflects our relatively unselected population; we included all PET studies in which there was a suspicion of CS based on patients symptoms. The awareness of CS as a possible cause of otherwise unexplained cardiac symptoms has resulted in an increased demand for cardiac PET studies at our institution during the last few years.

AV-block was significantly associated with pathological PET findings in the present study. In our population, 56 patients had a history of 2nd or 3rd degree AV-block; 41% of them had pathological LV-uptake. Unexplained AV-block has previously been shown to indicate possible CS. In a study by Kandolin et al. inflammatory myocardial disease was diagnosed in 22 of 76 patients (<55 years old) with advanced AV-block (16). Correlation between AV-block and FDG-uptake in the interventricular septum has also been reported previously (17). AV-block often causes symptoms resulting in referral for imaging studies in the active phase of the disease. This may in part explain why advanced AV-block is the most specific symptom predicting abnormal PET finding. PET

findings are pathological only in the active phase of myocardial inflammation but may be normal in the chronic fibrotic phase.

In a previous study by Tung et al, 103 cardiomyopathy patients with ventricular arrhythmias underwent FDG-PET (18). In that cohort 49% of the patients had abnormal LV uptake. Nery et al. studied 15 patients with unexplained monomorphic VT and found that 42% had pathological LV uptake (19). The authors also found that CS was most often diagnosed in patients with a history of AV-block in combination with VT. In our population there was an association between the history of VT and pathological PET findings, which is in line with the previous literature. Interestingly, 71% of the female patients with a history of both VT and AV-block had a pathological PET-finding in our study.

9% of patients in the present study showed pathological uptake in the RV free wall in addition to pathological LV uptake. Ten of those patients were female and nine had a history of AV-block. Interestingly one third of patients with abnormal RV-uptake were later diagnosed with EMB-verified CS. This percentage is rather high considering the low diagnostic yield of the EMB. In a study by Blankstein et al (15), pathological RV uptake was encountered in 11 of the 118 patients, which is a similar proportion as that found in our study. Blankstein et al. also observed an elevated risk of VT and death in patients with abnormal RV uptake, regardless of whether they fulfilled the JMWH criteria for CS or not. In another study, which included 59 patients with systemic sarcoidosis, the proportion of patients with pathological RV uptake was 22%, and 85% of them fulfilled the JMWH criteria for CS (20).

There are limitations related to this study. In some cases the conclusion was different between the two image interpreters. Cardiac FDG-PET has previously been shown to be difficult to interpret (21). In this study, a consensus was formed in cases where the interpretation differed between the readers. This is common practice when interpreting borderline studies in clinical situations. Because of the cross-sectional nature of this study, causality could not be assessed. Reflecting the ethnic

background of the majority of the Finnish population, our study group consisted of mainly white Caucasians; therefore, these results cannot be directly generalized in other populations. One major limitation concerning all studies investigating CS is the lack of accurate diagnostic gold standard. As the diagnosis of CS was biopsy-proven in only seven of the patients, one cannot be certain of the underlying cause of all abnormal PET findings. In the case of pathological PET findings, perfusion imaging might improve diagnostic accuracy (10). However, in our institution it is not routinely performed in combination with cardiac PET. Furthermore, this particular study dealt with PET only; perfusion imaging would not have changed the categorization of the findings.

Conclusion

Abnormal LV-uptake and RV-uptake were associated with female sex and a history of advanced AV-block. Especially abnormal RV-uptake was predominantly encountered in female patients. Abnormal RV uptake was also associated with ventricular tachycardia and atrial fibrillation. One third of the patients with abnormal RV-uptake were later diagnosed with EMB-verified cardiac sarcoidosis. These results can be utilized in diagnostic work-up of cardiac sarcoidosis.

New Knowledge Gained

Highest frequency of pathological cardiac PET-findings was encountered in female patients with history of both advanced AV-block and VT.

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Compliance with Ethical Standards

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Ethical approval: This article does not contain any studies with human participants performed by any of the authors

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Table 1. Baseline variables in patients with pathological or normal left ventricle FDG-PET-finding.

Variable	Abnormal LV-uptake (n =33)	Normal LV-uptake (n=104)	p
Gender, female/male	20/13 (61/39%)	37/67 (36/64%)	0.002*
Age, years	45.8 ±12.1	43.7 ±13.2	0.401
Body mass index	26.2 ±3.9	28.3 ±5.9	0.053
History of:			
II or III degree AV-block	23 (70%)	33 (32%)	<0.001
Ventricular tachycardia	23 (70%)	52 (50%)	0.053
Atrial fibrillation	16 (49%)	37 (36%)	0.185
Heart failure	14 (42%)	53 (51%)	0.393
Pulmonary sarcoidosis	10 (30%)	17 (16%)	0.208
Any heart disease	22 (67%)	64 (62%)	0.595
Reasons for referral:			
AV-block	25 (76%)	35 (34%)	<0.001*
Supraventricular arrhythmia	3 (9%)	10 (10%)	0.541
Ventricular arrhythmia	5 (15%)	34 (33%)	0.052
Dilated cardiomyopathy	6 (18%)	22 (21%)	0.712
Abnormal echo findings	14 (43%)	39 (38%)	0.613
Syncope	6 (18%)	22 (21%)	0.712
CS-positive EMB (n=21)	6 (18%)	1 (1%)	0.190

Figures are n (%) for dichotomous and mean (+/- SD) for continuous variables.

Abbreviations: CS=cardiac sarcoidosis; EMB=endomyocardial biopsy; FDG-PET=¹⁸Fluorodeoxyglucose positron emission tomography; LV= left ventricle; AV=atrio-ventricular

Table 2. Baseline variables in patients with or without pathological right ventricular FDG-PET-finding.

Variable	Abnormal RV-uptake (n =12)	Normal RV-uptake (n=125)	p
Gender, female/male	10/2 (83/17%)	49/76 (39/61%)	0.004*
Age, years	44.7 ±8.2	44.1 ±13.3	0.878
Body mass index	28.0 ±5.7	25.8 ±4.1	0.188
History of:			
II or III degree AV-block	9 (75%)	47 (37%)	0.014*
Ventricular tachycardia	11 (92%)	64 (52%)	0.006*
Atrial fibrillation	8 (67%)	45 (36%)	0.040*
Heart failure	5 (42%)	62 (50%)	0.413
Pulmonary sarcoidosis	4 (33%)	23 (18%)	0.249
Any heart disease	10 (83%)	76 (61%)	0.106
Reasons for referral:			
AV-block	10 (83%)	50 (40%)	0.004*
Supraventricular arrhythmia	1 (8%)	12 (10%)	0.682
Ventricular arrhythmia	4 (33%)	35 (28%)	0.461
Dilated cardiomyopathy	1 (8%)	27 (22%)	0.250
Abnormal echo findings	5 (43%)	48 (38%)	0.527
Syncope	4 (33%)	24 (19%)	0.209
CS-positive EMB (n=21)	4 (33%)	3 (2%)	0.537

Figures are n (%) for dichotomous and mean (+/- SD) for continuous variables.

Abbreviations: CS=cardiac sarcoidosis; EMB=endomyocardial biopsy; FDG-PET=

¹⁸Fluorodeoxyglucose positron emission tomography; RV= right ventricle; AV=atrio-ventricular

Figure 1. Abnormal FDG uptake in left ventricular (A) and right ventricular (B) wall in different groups.

