Diagnostic values of delayed additional FDG PET/CT scan in the evaluation of cardiac sarcoidosis

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Abstract

Objective

This study aimed to compare the contribution of ^{18}F-fluorodepxyglucose (FDG) positron (PET)/ computed tomography (CT) acquisition of early and delayed scan in patients with cardiac sarcoidosis (CS).

Methods

Twenty-three patients with CS (median age: 69 years; 11 women) were retrospectively evaluated using dual-phase FDG PET/CT. All patients were instructed to consume a low-carbohydrate diet followed by fasting for 18 h before FDG injection to reduce physiological myocardial uptake. PET/CT was acquired at 60 min (early) and 100 min (delayed) after FDG administration. Focal and focal on diffuse uptake on visual analysis was considered positive for CS. A semi-quantitative analysis was performed using the maximum standardized uptake value (SUVmax) of the cardiac lesion and the mean SUV (SUV mean) of the blood pool.

Results

Significant myocardial FDG uptake was observed in 21 patients (91.3%) in the early acquisition group and in 23 patients in the delayed scan group (100%). Compared to the early scan, the delayed scan showed a significantly higher SUVmax of cardiac lesion (median, 4.0; IQR [interquartile range, 2.9 to 7.0] vs. 5.8 [IQR 3.7 to 10.1]; P = 0.0030) and a significantly lower SUVmean of blood pool (median, 1.3 [IQR, 1.2 to 1.4] vs. 1.1 [IQR, 0.9 to 1.2]; P < 0.0001).

Conclusion

Delayed FDG PET/CT acquisition improves detection accuracy in patients with CS compared to early scans with washout of the blood pool activity. Therefore, it can contribute to a more accurate assessment of CS.

Introduction

Sarcoidosis is a chronic granulomatous disease that affects various organs, including the heart. Unfortunately, the cause of sarcoidosis is still unknown, and it can persist for years, causing a variety of symptoms depending on which organs are affected. Cardiac sarcoidosis (CS) is a serious complication that can manifest as a range of symptoms, including chest pain, palpitations, shortness of breath, and arrhythmias. In severe cases, it can cause ventricular tachycardia or heart block leading to sudden death (1).

Although screening with electrocardiography and echocardiography for cardiac involvement has been recommended for patients with extracardiac sarcoidosis, approximately 20% of patients without conduction or morphological abnormalities are missed (2). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is an advanced tool for detecting the early stages of CS. FDG is an analog of glucose; therefore, high FDG accumulation has been observed in active inflammatory lesions, including sarcoidosis (3). In the recommendations from the Japanese Society of Nuclear Cardiology, a whole-body PET scan 60 min after FDG administration and additional cardiac spot imaging that takes approximately 10 min are recommended to evaluate patients suspected of CS (4, 5).

The advantage of additional PET scans has been established in clinical practice for several types of malignant tumors, with the potential to provide more accurate diagnoses than single-time-point FDG PET scan (6–8). Recent studies have demonstrated the usefulness of additional PET scans in assessing large-vessel vasculitis, which involves the precise evaluation of active inflammation with washout of the blood pool activity (9, 10). We recently reported a case of CS highlighting the usefulness of the additional FDG PET scan (11, 12). However, no systematic studies have confirmed the effectiveness of delayed scans in patients with CS. This study aimed to assess the utility of additional scans in identifying active inflammation caused by sarcoidosis in patients with CS.

Material and methods

Patients

This study retrospectively evaluated the medical records of patients admitted to our hospital between June 2021 and September 2022. The Institutional Review Board approved this study and waived the need for written informed consent (IRB#S22-085). Patients with CS based on the diagnostic criteria of the Japanese Circulation Society (JCS) (13), who underwent both early and delayed PET scans, were included. Patients who received anti-inflammatory treatment before the scan were excluded. If a patient underwent multiple tests during this period, only the results from the first test were included.

PET/CT acquisition protocol

PET/CT imaging was performed using a Celesteion (Cannon, Japan, Tokyo). All patients were instructed to fast for over 18 h overnight along with a low-carbohydrate diet (less than 5 g per meal the day before scanning) (14). Fasting plasma glucose (FPG) levels were measured before the FDG injection. Approximately 270.5 ± 55.4 MBq FDG was intravenously administered under resting conditions. Immediately after low-dose CT for attenuation correction (50 mAs, 120 kV tube voltage, 2 mm slice thickness, 2 mm increment), whole-body imaging of the area from the head to the lower thigh or toe was performed just under an hour after FDG administration for 2 min per table position, depending on the scanner performance and patient condition. The second acquisition, covering the thoracic region for 15 min per table, was performed approximately 100 min after FDG injection. An identical axial field of view

(554.54 × 554.54 mm) was scanned using PET. The acquired data were reconstructed with an image matrix of 256 × 256 pixels (pixel size: 2.03875 × 2.03875 mm) using Fourier rebinning and ordered subset expectation maximization algorithms. The thicknesses of the PET sections were 2.0 mm. Both PET and CT imaging were performed with the patient in the supine position under free-breathing conditions.

PET/CT imaging analysis

All FDG PET/CT images were reviewed by two nuclear medicine physicians (OM and KT) independently, masked to the other reviewer's interpretations. Visual analysis was performed using an appropriate workstation and software (SYNAPSE VINCENT; Fujifilm Corporation, Tokyo, Japan). Semiquantitative analyses were performed using Metavol (15). Abnormal FDG uptake was classified as positive uptake in the left ventricular (LV) myocardium. In the visual assessment, localized FDG uptake in the myocardium, which was higher than the FDG uptake in the blood pool, was considered as a positive finding. Disagreements in interpretation between the two physicians were resolved by consensus. Subsequently, a nuclear medicine physician (KT) thoroughly reviewed the PET images and selected FDG-avid lesions in the myocardium to measure FDG uptake in the myocardium and blood pool as an indicator of glucose metabolic status. The maximum standard uptake value (SUVmax) was calculated as follows: SUVmax = maximum activity in the region of interest (mBq/g) / (injected dose [mBq]/body weight [g]). The average SUV (SUVmean) of the blood pool in the descending aorta was measured. Cardiac metabolic volume (CMV), defined as the volume within the boundary determined by a threshold (SUVmean of blood pool × 1.5), and cardiac metabolic activity (CMA), calculated by multiplying the SUVmean by the CMV, were measured as previously reported (14). To compare the early and delayed scans, if FDG accumulation was visible only on the delayed images, we referred to the delayed images and placed the volume of interest in the corresponding area on the early images.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR) and were compared using the Wilcoxon rank-sum test. Categorical variables are presented as absolute numbers with percentages and were compared using the Fisher's exact test. Statistical significance was set at $P < 0.05$. JMP ver. 16.1.0 (SAS Institute, Cary, NC) was used for all the data analyses.

Results

Patient characteristics

A total of 45 PET/CT scans were performed in patients with confirmed CS at our hospital between June 2021 and September 2022. Of these scans, 12 were excluded because they were performed on the same patients and 10 were excluded because they were performed after anti-inflammatory treatment. Finally, a total of 23 patients were included in this retrospective study. The baseline characteristics of the study population are summarized in Table 1.

Table 1
Participant's characteristics

Variables	n = 23
Age (y)	69 (50−76)
Male (n)	12 (52.2)
FPG (mg/dl)	100 (85−115)
FDG dosage	282.9 (224.2−325.6)
Fasting time (hour)	18.8 (18−20)
Duration between FDG injection and first scan (minute)	53.3 (48.3−59.0)
Duration between FDG injection and second scan (minute)	96.1 (81.9−118.2)
Values are represented as median (IQR) or n (%).	
FPG, fasting plasma glucose; FDG, ^{18}F-fluorodeoxyglucose	

Visual assessment

The results of the visual evaluation of the early and delayed images are summarized in Table 2. All patients exhibited focal or focal on diffuse uptake in the LV myocardium on delayed scans. In two cases, FDG uptake was observed only in the delayed scan but was not visible in the early scan. None of the patients showed focal uptake in the early scan, but not in the delayed scan. Typical images are shown in Fig. 1.

Table 2
Visual assessment of positive uptake

	early	delay
Uptake (+)	21 (91.3%)	23 (100%)
Uptake (-)	2 (8.7%)	0

Table 3
Semiquantitative assessment between early and delayed images

	early	delay	P value
SUVmax of LV	4.0 (2.9−7.0)	5.8 (3.7−10.1)	0.0030
CMV (mL)	21.8 (2.8−96.5)	45.8 (5.8−106.7)	0.0006
CMA (mL)	74.6 (85.5−305.2)	104.3 (15.7−374.8)	0.0009
SUVmean of blood pool	1.3 (1.2−1.4)	1.1 (0.9−1.2)	P < 0.0001

Values are represented as median (IQR) or n (%).

SUVmax, maximum standardized uptake value; CMV, cardiac metabolic volume; CMA, cardiac metabolic activity; SUVmean, mean standardized uptake value

Comparison of FDG uptake between early and delayed scan in patients with CS

Compared to the early scan, the delayed scan had higher SUVmax (5.8 [IQR 3.7 to 10.1] vs. 4.0 [IQR 2.9 to 7.0], P = 0.0030), CMV (45.8 mL [IQR 5.8 to 106.7 mL] vs. 21.8 mL [IQR 2.8 to 96.5], P = 0.0006), and CMA (104.3 mL [IQR 15.7 to 374.8 mL] vs. 74.6 mL [IQR 5.5 to 305.2 mL], P = 0.0009; Fig. 2A-C). Conversely, the SUVmean in the blood pool was significantly lower in the delayed scan compared to the early scan (1.3 [IQR 1.2 to 1.4] vs. 1.1 [IQR 0.9 to 1.2], P < 0.0001) (Fig. 2D).

Discussion

In this study, we observed a significant decrease in the SUVmean of the blood pool and a significant increase in FDG uptake in cardiac lesions during delayed scans, allowing even slight accumulation to be visualized as positive. The increase in CMV and CMA values was attributed to the increased accumulation of CS lesions and a decrease in the threshold value of the region of interest determined by the SUVmean of the blood pool. These findings are consistent with data from previous FDG PET/CT studies on atherosclerosis that have shown that delayed imaging decreases FDG uptake in the blood pool (9), suggesting that FDG PET/CT in the delayed phase may be more appropriate for screening CS compared to that in the early phase.

The diagnostic criteria for CS proposed by the JCS (13) and the Heart Rhythm Society expert consensus statement (1, 16) includes focal uptake on FDG PET and late gadolinium enhancement (LGE) on magnetic resonance imaging (MRI) as positive criteria. FDG PET plays an important role in the assessment of CS activity. A recent meta-analysis suggested that FDG PET/CT is less sensitive than MRI (17). Because of the relatively low resolution, FDG PET/CT may fail to identify some instances of CS, mainly in the early stages of the disease or when sarcoid granulomas are small and cannot be distinguished from blood pool accumulation. However, based on our investigation, we expect that the

detection sensitivity for CS lesions can be improved by adding a delayed scan. Our research group reported a typical case indicating that delayed FDG PET/CT may be sensitive to small CS lesions (11, 12).

Semi-quantitative analyses using SUVmax, CMV, and CMA have been used for the diagnosis, assessment of treatment efficacy, and prognostic prediction of CS (18–20). Osborne et al. found that decreases in SUVmax and CMV, when comparing pre- and post-therapy values, were linked to an improvement in left ventricular ejection fraction (LVEF), indicating that repeated PET scanning could potentially assist in adjusting immunosuppressive therapy to enhance LV function and prevent heart failure in CS (18). Ahmadian et al. demonstrated that patients with lower LVEF and a history of adverse clinical events, such as ventricular tachycardia (VT), sudden cardiac death, and heart block, had higher CMA (19). Furthermore, binary logistic regression analysis with CMA, SUVmax, and the total defect score of perfusion images demonstrated that CMA was the only independent predictor of events, including VT, sudden cardiac death, worsening atrioventricular block, cardiac hospitalization, and new or worsening heart failure. In this study, owing to the limited number of patients, it was difficult to determine which values obtained from the early and delayed images were useful for diagnosis or prognostic prediction. However, considering that the degree of FDG accumulation may vary depending on the time from administration to imaging, it may be necessary to standardize the time interval for evaluating these parameters for follow-up and research.

This study has several limitations. First, due to the retrospective nature of the study, the number of participants was relatively small. Second, obtaining pathological evidence for FDG-avid lesions is difficult; thus, we considered focal uptake as positive according to the JCS criteria, which are widely used in clinical sessions. Third, although the usefulness of delayed imaging was demonstrated, the optimal timing for image acquisition was not investigated. Recently, Adili et al. compared images obtained 1, 2, and 5 h after FDG administration using total-body PET/CT in patients with Takayasu arteritis, and reported comparable detection rates with images acquired 2 and 5 h after administration (21). However, conventional PET/CT may suffer from decreased image quality with longer time intervals between FDG administration and imaging owing to the influence of its half-life. Finally, in this study, patients without a confirmed diagnosis of CS and those with CS who had already received steroid treatment were excluded; therefore, it was not possible to evaluate the usefulness of delayed PET scans in the differential diagnosis or assessment of treatment effectiveness, necessitating further research in this area.

Conclusion

An additional delayed FDG PET/CT scan improves the diagnosis of CS, with a higher SUVmax for the active lesion with washout of the blood pool activity. Delayed image acquisition influences the subjective and quantitative interpretation of FDG PET scans in CS as they are more likely to detect CS lesions.

Declarations

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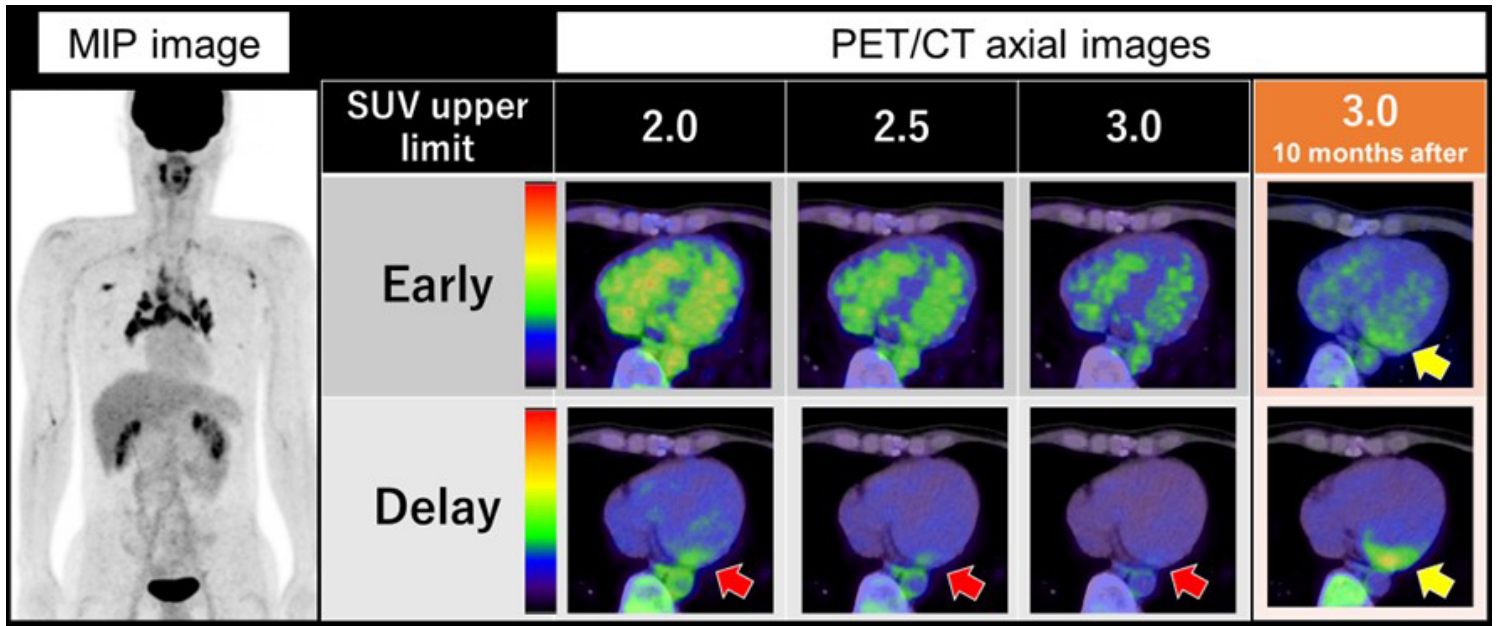
Figures

Figure 1

Representative case of cardiac sarcoidosis.

Maximum intensity projection (MIP) and axial PET/CT images with modified standardized uptake value (SUV) limits are arranged in the upper row for early phase images and in the lower row for delayed phase images. The accumulation of the blood pool was greater in the early images than in the delayed images. Focal FDG uptake in the posterior left ventricular wall was observed only on delayed-phase images (red arrows). Focal accumulation was confirmed only in the posterior wall of the left ventricular myocardium on the delayed images. Follow-up FDG PET/CT performed 10 months later showed increased accumulation in the same lesion (yellow arrows), indicating worsening of the cardiac sarcoidosis
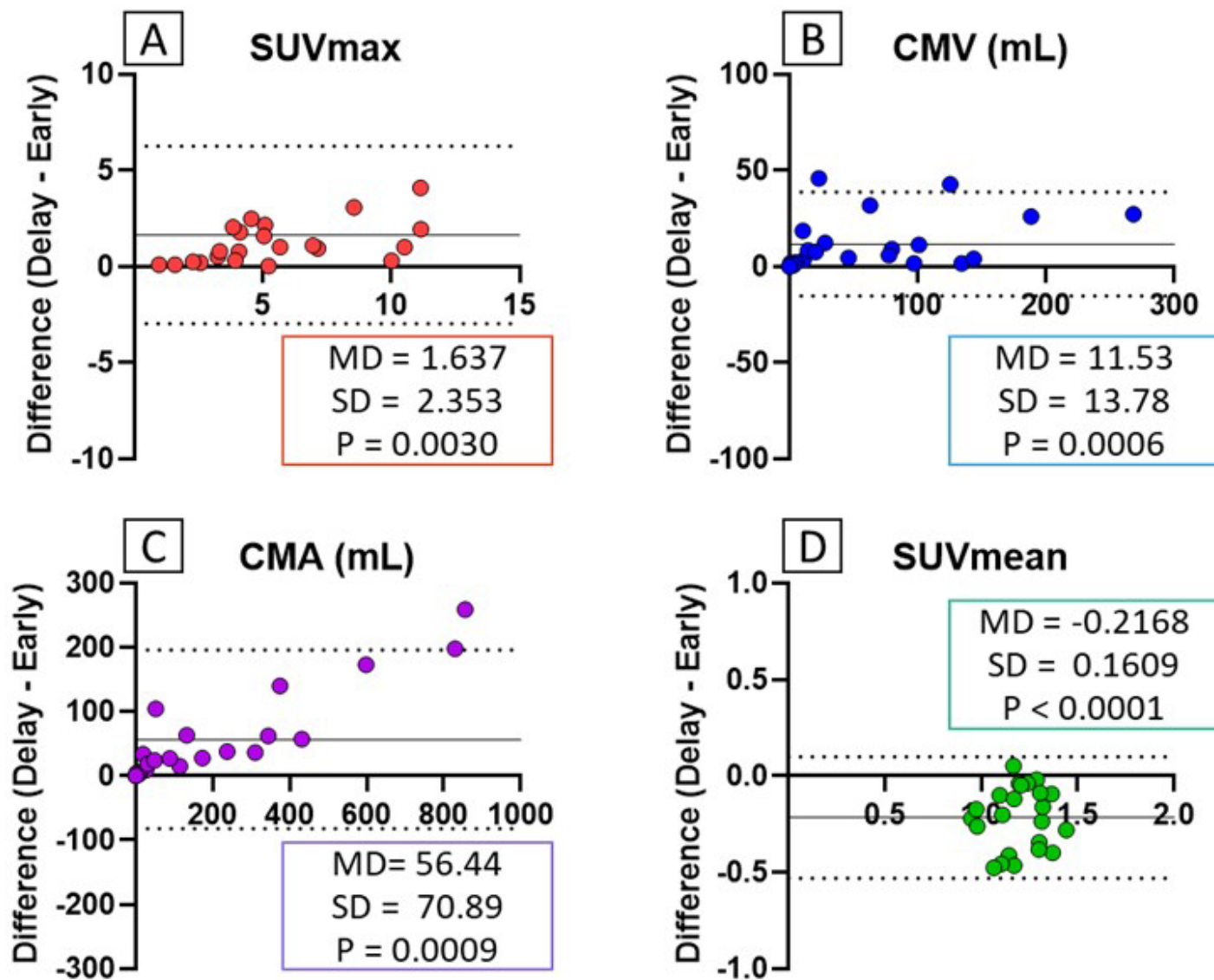
Figure 2

Bland-Altman plots to compare the early and delay values.

The vertical axis of the graph represents the difference between the late and early images, and the horizontal axis indicates the average. The mean differences are represented by the lines, whereas the dotted lines indicate the 95% confidence limits. For the delayed images, the SUVmax (A), CMV (B), and CMA (C) of cardiac sarcoidosis were significantly higher, and the mean SUV of the blood pool (D) was significantly lower than those of the early images. SUVmax, maximum standardized uptake value; CMV, cardiac metabolic value; CMA, cardiac metabolic volume; SUVmean, mean standardized uptake value; MD, mean difference; SD, standard deviation