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Focal uptake on ^{18}F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis†

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Heart

Aims To evaluate the value of ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) in detecting cardiac sarcoidosis.
Methods and results Thirty-two patients with sarcoidosis and thirty controls were recruited. All subjects underwent cardiac ^{18}F-FDG PET after a 6 h fasting period, and subjects with sarcoidosis underwent blood testing, ECG, echocardiography, and ^{67}Ga and ^{99m}Tc-sestamibi (MIBI) scintigraphy. We classified ^{18}F-FDG PET images into four patterns ('none', 'diffuse', 'focal', and 'focal on diffuse') and found that all the control subjects exhibited either none ($n = 16$) or diffuse ($n = 14$) pattern. In contrast, fifteen subjects with sarcoidosis exhibited none, seven exhibited diffuse, eight exhibited focal, and two exhibited focal on diffuse patterns, with the prevalence of the focal and focal on diffuse patterns being significantly higher in the sarcoidosis group when compared with the control group ($P < 0.001$). None of the 32 subjects with sarcoidosis exhibited abnormal findings on ^{67}Ga scintigraphy, and 4 exhibited abnormal findings on ^{99m}Tc-MIBI scintigraphy.
Conclusion Focal uptake of the heart on ^{18}F-FDG PET images is a characteristic feature of patients with sarcoidosis. Furthermore, ^{18}F-FDG PET has the potential to detect cardiac sarcoidosis that cannot be diagnosed by ^{67}Ga or ^{99m}Tc-MIBI scintigraphy.

Introduction

Sarcoidosis is a systemic disorder of unknown etiology, which is characterized by its pathological hallmark, noncaseating granuloma. Sarcoidosis is associated with a low mortality rate, although cardiac involvement may worsen prognosis because of complications such as congestive heart failure, ventricular tachyarrhythmia, or conduction disturbance leading to sudden death.[1,2] A recent report has shown that cardiac involvement is responsible for as many as 85% of sarcoidosis deaths in Japan.[3] However, cardiac involvement is clinically identified in only 5% of patients with sarcoidosis, but in as many as 25–78.8% on autopsy.[4,5] Because treatment with corticosteroids improves prognosis in some patients,[6,7] early and accurate diagnosis of myocardial sarcoidosis followed by adequate management is desirable.

There are several problems associated with obtaining a definitive diagnosis of cardiac sarcoidosis. Myocardial biopsy is the only technique that allows us to reach pathological diagnosis, but myocardial involvement of sarcoidosis is not homogeneous and diagnostic yield can be as low as 19%.[8,9] Noninvasive modalities such as electrocardiogram (ECG),[10,11] echocardiography (UCG),[12] and cardiac scintigrams[13] offer the potential to identify at-risk patients requiring corticosteroid treatment, but these techniques offer low sensitivity and specificity.

Recently, ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) has been reported to identify sarcoid lesions in hilar lymph nodes,[14] lung parenchyma,[15] and abdominal organs.[16] In addition, Brudin *et al.*[15] reported that ^{18}F-FDG PET has the potential to reflect disease activity in pulmonary sarcoidosis. Because the pathology of cardiac sarcoidosis is similar to that in other organs, we hypothesized that ^{18}F-FDG PET might be useful in assessing cardiac sarcoidosis.

In this study, we compared the accumulation patterns of ^{18}F-FDG in the hearts of sarcoidosis patients with those of

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control subjects, and we examined the potential of ^{18}F-FDG PET to assess cardiac sarcoid lesions.

Materials and methods

Subjects

We recruited 32 patients with sarcoidosis attending our institution between February 2002 and February 2004. All patients with sarcoidosis were diagnosed clinically by blood test, chest X-ray, computed tomography, bronchial alveolar lavage, or by histological examination. Indeed, 28 of 32 patients were diagnosed as having sarcoidosis by lung, skin, or lymph node biopsy. We recruited 30 sex- and age-matched control subjects, comprising 6 healthy volunteers and 24 subjects who were admitted to our institution for examination of possible lung or gastrointestinal diseases during the same period as the patients with sarcoidosis. Among the 24 in-hospital subjects, 8 were found to have benign diseases, such as colon polyp, collagen vascular disease, or pneumonia, and 16 had malignant diseases, including lung, gastric, or colon cancer and rectal or pulmonary carcinoid tumour. In the case of subjects with malignant diseases, those who underwent chemotherapy or radiation therapy were excluded. To maximize the comparability between the groups, we excluded subjects who met one or more of the following criteria: history or suspicion of ischaemic heart disease or myocardial diseases including cardiomyopathy and myocarditis, uncontrolled diabetes mellitus or hypertension, use of steroids, ECG abnormalities, or ongoing active inflammatory disease. The same exclusion criteria, except for ECG abnormalities and use of steroids, were applied to patients with sarcoidosis. In some cases, we performed UCG or 24 h ECG recordings when these tests appeared useful to further exclude heart diseases. The study protocol was approved by the Ethics Committee of Hokkaido University School of Medicine and we obtained written informed consent from each subject prior to the study.

Methods

All patients with sarcoidosis underwent measurement of serum angiotensin-converting enzyme (ACE) levels, chest X-ray, standard 12-lead ECG, 24 h Holter ECG monitoring, UCG, and three types of radionucleotide imaging [^{67}Ga scintigraphy (31 patients), ^{99m}Tc-sestamibi (MIBI) scintigraphy, and ^{18}F-FDG PET]. All assessments were conducted within 1 month and no signs indicated any change in sarcoidosis disease activity. In the case of radionucleotide imaging, we obtained the images within 1 week in order to minimize the influence of changes in disease activity. The 30 control subjects underwent blood sampling, ECG, UCG when needed, and ^{18}F-FDG PET.

Echocardiography

Patients were interrogated with a 2.5 MHz echo-Doppler probe of SONOS 5500 (Agilent Technologies, Andover, MA, USA). Left ventricular (LV) ejection fraction was estimated by Simpson's modified 2D biplane method or M-mode method. Regional wall motion and condition of LV wall were evaluated according to the guidelines provided by the American Heart Association[17] as assessed by two experienced cardiologists.

^{67}Ga and ^{99m}Tc-sestamibi scintigraphy

Patients with sarcoidosis underwent single photon emission computed tomography (SPECT) studies using both ^{67}Ga-citrate for whole-body evaluation and ^{99m}Tc-MIBI for myocardial perfusion.

Two experienced nuclear physicians interpreted the images individually unaware of the findings of ^{18}F-FDG PET. When evaluation of the images differed, agreement was reached by discussion.

^{18}F-FDG PET

In order to reduce the uptake of ^{18}F-FDG by the heart, ^{18}F-FDG PET images were acquired after at least 6 h period of fasting in all of the 62 subjects. In 32 patients with sarcoidosis, we obtained blood samples to measure serum or plasma levels of glucose, free fatty acid (FFA), and immunoreactive insulin (IRI) and then injected 185 MBq of ^{18}F-FDG intravenously. We administered the same dose of ^{18}F-FDG in the 30 controls and measured only fasting plasma glucose (FPG) levels. In an attempt to further reduce physiological ^{18}F-FDG uptake by the myocardium, we intravenously preadministered unfractionated heparin (50 IU/kg) to all patients with sarcoidosis and 6 of the 30 control subjects. To obtain a consistent effect, injection of ^{18}F-FDG was performed 15 min after administration of heparin.

^{18}F-FDG PET was performed with a whole-body PET camera (Siemens EACT EXACT 47; Siemens Medical Systems, Inc., Knoxville, TN, USA). Transmission scanning was performed for attenuation correction (AC) using ^{68}Ge line sources. Data were acquired on 3D-mode 45–60 min after ^{18}F-FDG injection. AC was reconstructed by ordered subset expectation maximization. These images were resliced into a series of short-axis and vertical long-axis images.

Analysis of ^{18}F-FDG PET images

We classified ^{18}F-FDG PET images into four patterns: 'none', 'diffuse', 'focal', or 'focal on diffuse'. The none pattern indicates no myocardial uptake of ^{18}F-FDG, whereas the diffuse pattern indicates a pattern in which the outline of the LV wall was visually identified. The pattern was classed as focal only when focal uptake of ^{18}F-FDG was observed, and the focal on diffuse pattern indicates focal ^{18}F-FDG uptake overlying the diffuse pattern described previously. We visually localized the site of ^{18}F-FDG uptake in cases exhibiting the focal or focal on diffuse pattern. Because augmented uptake of ^{18}F-FDG in the lateral wall of LV is known to be observed in healthy humans,[18,19] cases with focal uptake only in the lateral wall of the LV were not classified as having the focal or focal on diffuse pattern. Two experienced radiologists, who were blinded to the clinical characteristics of each subject, independently estimated ^{18}F-FDG uptake. Whenever the two observers' scores differed, a third independent observer was consulted.

Statistical analysis

Data are presented as mean $\pm$ SD, unless otherwise specified. An unpaired *t*-test or Mann–Whitney *U* test was used to examine comparisons between groups when equal variance was shown by the *F*-test or when equal variance was not shown, respectively. The prevalence of either focal or focal on diffuse uptake pattern on ^{18}F-FDG PET images was compared between the controls and patients with sarcoidosis using the χ^2 test. In addition, a χ^2 test was used to compare the presence of any abnormal findings on ECG, Holter ECG, or in UCG between patients with sarcoidosis who exhibited focal or focal on diffuse pattern and those who did not. Analysis of sensitivity and specificity of the three radionucleotide methods was performed using the Guidelines for Cardiac Sarcoidosis of the Japanese Ministry of Health and Welfare as a gold standard. In all tests, *P*-values of <0.05 were considered to be statistically significant.

Results

Characteristics of the controls and patients with sarcoidosis are summarized in *Table 1*. There were no significant differences between the two groups in age, gender, prevalence of comorbid diseases, including diabetes mellitus, hypertension, and hyperlipidaemia, or prior ischaemic heart diseases.

Table 1 Characteristics of controls and patients with sarcoidosis

	Controls ($n = 30$)	Sarcoidosis ($n = 32$)	*P*-value
Sex (male/female)	7/23	6/26	0.66
Age (years)	54 ± 13	55 ± 17	0.75
Height (cm)	159 ± 10	158 ± 9	0.75
Body weight (kg)	58 ± 10	57 ± 13	0.82
BMI	23 ± 3	23 ± 5	0.96
FPG (mg/dL)	91 ± 12	87 ± 11	0.19
Diabetes mellitus	0	2	0.16
Hypertension	9	7	0.47
Ischaemic heart disease	0	0	

Data are mean ± SD or *n*. BMI, body mass index.

Table 2 shows a list of the results obtained from patients with sarcoidosis. Of the 32 individuals, 9 had resting ECG abnormalities such as complete or incomplete right bundle branch block, conduction disturbance, or left-axis deviation. Holter ECG monitoring confirmed that four patients had premature ventricular contraction above Lown's grade 2. On UCG, we identified abnormalities in six patients: two patients had diffuse ventricular wall thickening, one had septal wall thickening, one had septal wall thinning, and two had local reduction of LV wall motion. On ^{67}Ga scintigraphy, none of the patients exhibited abnormal uptake, but focally reduced uptake of ^{99m}Tc-MIBI was seen in four patients. According to the Japanese Ministry of Health and Welfare Guidelines for Diagnosing Cardiac Sarcoidosis[20] (*Table 3*), 5 of the 32 patients with sarcoidosis were diagnosed as having cardiac sarcoidosis.

Table 2 Characteristics of 32 patients with sarcoidosis

Case no.	Age (years)	Sex	ECG	Holter ECG	UCG	^{18}F-FDG PET	^{99m}Tc-MIBI	^{67}Ga	Cardiac sarcoidosis[a]
1	25	F	ICRBBB	—	—	RV	—	—	No
2	70	F	CRBBB	—	Hypokinesis of anteroseptal wall	Anterior wall	Anteroseptal wall	—	Yes
3	56	F	CRBBB	—	Thickening of IVS	IVS	—	—	Yes
4	64	F	—	—	—	None	—	—	No
5	67	F	—	—	—	None	Anterior wall	—	No
6	64	F	—	—	—	None	—	—	No
7	64	F	—	—	—	None	—	—	No
8	31	M	—	—	—	None	—	—	No
9	73	M	1st degree AVB	—	—	None	—	—	No
10	59	F	—	—	—	Diffuse	—	—	No
11	65	F	—	—	—	Apex	—	—	No
12	75	F	—	—	—	None	—	—	No
13	69	F	—	—	—	None	Anterior wall	—	No
14	35	F	—	Lown 4A	—	Diffuse	—	—	No
15	43	F	—	—	—	Diffuse	—	—	No
16	47	M	—	—	—	Diffuse	—	—	No
17	57	F	—	—	—	None	—	—	No
18	48	F	—	—	—	None	—	—	No
19	66	F	—	—	—	None	—	—	No
20	69	F	Left-axis deviation	Lown 4B	Diffuse hypertrophy	Diffuse	—	—	No
21	60	F	CRBBB, 1st degree AVB	—	Diffuse hypokinesis except anterior wall	IVS	—	—	Yes
22	66	F	—	—	—	None	—	—	No
23	68	M	Left-axis deviation	Lown 2	—	Apex	—	—	No
24	39	F	—	—	—	None	—	—	No
25	53	F	—	—	—	None	—	—	No
26	76	F	CRBBB + LAH	Lown 3	—	Apex	—	—	Yes
27	73	F	—	—	—	Diffuse	—	—	No
28	27	M	—	—	—	Apex	—	—	No
29	22	M	—	—	Diffuse hypertrophy	Diffuse	—	—	No
30	31	F	—	—	—	None	—	—	No
31	25	F	—	—	—	Inferior wall	—	—	No
32	75	F	CRBBB	—	Thinning of anteroseptal wall	Anterior wall	Anteroseptal wall	NA	Yes

ICRBBB, incomplete right bundle branch block; RV, right ventricle; AVB, atrioventricular block; LAH, left anterior hemiblock; IVS, interventricular septum; NA, not available; '—' indicates no abnormal findings.

[a]Diagnosed according to the Guidelines for Diagnosis of Cardiac Sarcoidosis from the Japanese Ministry of Health and Welfare.[20]

Representative illustrations of the four patterns (none, focal, diffuse, and focal on diffuse) on ^{18}F-FDG PET images are shown in *Figure 1*. Among the 30 controls, 16 (53%) and 14 (47%) individuals exhibited the none and diffuse patterns, respectively, but none exhibited the focal or focal on diffuse pattern on ^{18}F-FDG PET images. On the other hand, 15 (47%) and 7 (22%) patients with sarcoidosis showed the none and diffuse patterns, respectively, but there were 8 (25%) patients exhibiting the focal pattern and 2 (6%) exhibiting the focal on diffuse pattern, with the prevalence of the focal and focal on diffuse patterns ($n = 10$, 31%) being statistically higher in the sarcoidosis group when compared with the control group (χ^2 test; $P < 0.001$). The locations of the focal ^{18}F-FDG accumulation were as follows: right ventricle, 1; anterior LV wall, 2; interventricular septum, 2; inferior LV wall, 1; and apex, 4 (*Table 2*). In 2 of these 10 subjects, the location of the focal ^{18}F-FDG uptake was mostly identical to that of the reduced uptake of ^{99m}Tc-MIBI, but the other 2 exhibited abnormal findings at a distant site on ^{99m}Tc-MIBI images. Furthermore, 6 of the 10 patients with positive ^{18}F-FDG PET findings had no abnormalities on ^{99m}Tc-MIBI images.

Table 3 Guidelines for Diagnosis of Cardiac Sarcoidosis from Japanese Ministry of Health and Welfare[20]

Histologic diagnosis group	Cardiac sarcoidosis is diagnosed when histologic analysis of operative or endomyocardial biopsy specimens demonstrates epithelioid granuloma without caseating granuloma
Clinical diagnosis group	In patients with histologic diagnosis of extracardiac sarcoidosis, cardiac sarcoisdosis is diagnosed when item (a) and one or more of items (b–e) are present (a) Right bundle branch block, left-axis deviation, atrioventricular block, ventricular tachycardia, premature ventricular contraction (>grade 2 in Lown's classification), or abnormal Q or ST-T changes on ECG or Holter ECG (b) Abnormal wall motion, regional wall thinning, or thickening, or dilatation of LV on UCG (c) Perfusion defect on ^{201}Tl myocardial scintigram or abnormal accumulation on ^{67}Ga-citrate or ^{99m}Tc-pyrophosphate myocardial scintigram (d) Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of LV (e) Interstital fibrosis or cellular infiltration over moderate grade in endomyocardial biopsy even if findings are nonspecific

Table 4 shows a comparison of the two groups of patients with sarcoidosis: those with either the focal or focal on diffuse pattern on ^{18}F-FDG PET images ($n = 10$) and those with either the none or diffuse pattern ($n = 22$). Although serum ACE levels in subjects with either the focal or focal on diffuse pattern were lower than in those with either the none or diffuse pattern, there were no significant differences in serum levels of FFA, IRI, and FPG between the two groups. However, notable abnormalities in resting ECG, Holter ECG, UCG, or ^{99m}Tc-MIBI scintigraphy were consistently found more often in patients who had the focal or focal on diffuse pattern, although the differences reached statistical significance only for ECG and UCG. In addition, 5 of the 10 patients (50%) who had either the focal or focal on diffuse pattern on ^{18}F-FDG PET images met the criteria of cardiac sarcoidosis, but none with the none or diffuse pattern met the criteria (0%).

Table 5 shows the sensitivity and specificity for each radionuclear image using the Guidelines for Cardiac Sarcoidosis from the Japanese Ministry of Health and Welfare as a gold standard. The sensitivity and specificity of ^{18}F-FDG PET were 100 and 81.5%, respectively, which were comparable or superior to the values for ^{67}Ga scintigraphy and ^{99m}Tc-MIBI scintigraphy.

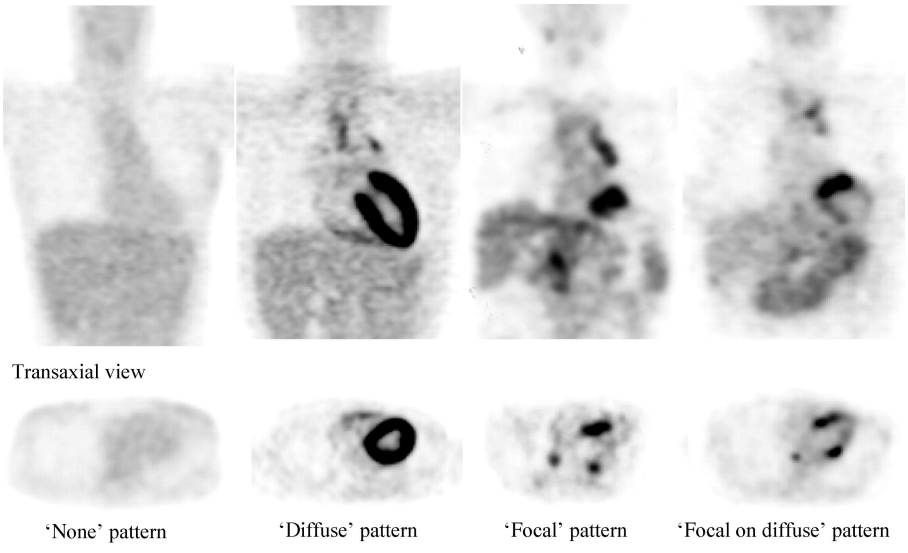

Figure 1 Four patterns on ^{18}F-FDG PET images. The top images are coronal slices and the bottom images are transaxial slices through the heart. The none pattern indicates no myocardial uptake of ^{18}F-FDG, and the diffuse pattern indicates that the outline of the LV wall was visually identified. The focal pattern was assigned when only focal uptake of ^{18}F-FDG was observed, and the focal on diffuse pattern indicates focal ^{18}F-FDG uptake overlying the diffuse pattern described earlier.

Table 4 Comparison of two groups among patients with sarcoidosis

	Focal or focal on diffuse ($n = 10$)	Diffuse or none ($n = 22$)	*P*-value
Sex (male/female)	2/8	4/18	0.90
Age (years)	55 ± 21	55 ± 16	0.94
FPG (mg/dL)	86 ± 6	88 ± 12	0.53
IRI (μU/mL)	4.3 ± 2.1	4.7 ± 3.1	0.73
FFA (mEq/L)	1839 ± 701	2099 ± 805	0.43
ACE (IU/L)	15.3 ± 4.6	20.6 ± 7.4	0.048
Number of subjects with abnormal findings			
ECG	7 (70)	2 (9)	<0.001
Holter ECG	2 (20)	2 (9)	0.32
UCG	4 (40)	0 (0)	0.002
^{99m}Tc-sestamibi	2 (20)	2 (9)	0.39
^{67}Ga	0 (0)	0 (0)	
Diagnostic criteria[a]	5 (50)	0 (0)	<0.001

Data are mean ± SD or *n* (%).
[a]Guidelines for Diagnosis of Cardiac Sarcoidosis from Japanese Ministry of Health and Welfare.[20]

Table 5 Sensitivity and specificity of three scintigraphy techniques based on Guidelines for Diagnosis of Cardiac Sarcoidosis from Japanese Ministry of Health and Welfare[20]

	Sensitivity (%)	Specificity (%)
^{99m}Tc-sestamibi	40	92.6
^{67}Ga	0	100
^{18}F-FDG PET (focal)	100	81.5

Discussion

In the analysis of ^{18}F-FDG PET images, we noted either focal or focal on diffuse cardiac uptake pattern in 10 of the 32 patients with sarcoidosis (31%) but in none of the 30 controls (0%), and this difference is statistically significant (χ^2 test; $P < 0.001$). In addition, patients with sarcoidosis exhibiting either focal or focal on diffuse uptake pattern had a higher frequency of abnormal findings on 12-lead ECG, Holter ECG, and UCG when compared with those exhibiting the none or diffuse pattern. When the Japanese Ministry of Health and Welfare Guidelines for Cardiac Sarcoidosis was used as a gold standard, the sensitivity and specificity of ^{18}F-FDG PET were higher or equivalent to the values for ^{67}Ga and ^{99m}Tc-MIBI scintigraphy (*Table 5*). We thus conclude that focally increased uptake of ^{18}F-FDG indicates the presence of cardiac involvement of sarcoidosis and that ^{18}F-FDG PET may have a novel role in the diagnosis and assessment of cardiac sarcoidosis.

Yamagishi *et al.*[21] recently reported the usefulness of ^{18}F-FDG PET in the diagnosis and observation of cardiac involvement in patients with sarcoidosis, but there are several differences between their study and ours. First, we recruited 30 control subjects and 22 patients having sarcoidosis without any abnormalities on 12-lead or Holter ECG for comparison with those having cardiac sarcoidosis. By enrolling control subjects and patients without cardiac involvement for this study, we were able to obtain sensitivity and specificity data for ^{18}F-FDG PET as a diagnostic tool of cardiac sarcoidosis. In addition, we recognized that about half of the control subjects showed diffuse cardiac uptake of ^{18}F-FDG. Although the mechanism of uptake is not fully clarified, this should be kept in mind when we use ^{18}F-FDG PET as a method to evaluate cardiac involvement of sarcoidosis. Secondly, we administered intravenous heparin prior to obtaining ^{18}F-FDG PET images in all patients with sarcoidosis. Because heparin increases serum FFA levels and possibly minimizes background myocardial uptake of ^{18}F-FDG,[22,23] we might have increased the sensitivity for detecting sarcoidosis-associated lesions when compared with images obtained without heparin.

Although ^{67}Ga scintigraphy is a well-known imaging technique for diagnosing and assessing disease activity of sarcoidosis,[13,24,25] there were no patients who showed abnormal cardiac uptake in the present study. Indeed, normal images were seen even in the 10 patients with 12-lead or Holter ECG abnormalities and in all patients who met the criteria of the Japanese Ministry of Health and Welfare Guidelines for Cardiac Sarcoidosis. Although ^{67}Ga scintigraphy is thought to detect active sarcoid lesions in other parts of the body, this does not appear to be true in the heart. ^{67}Ga scintigraphy appeared to offer lower sensitivity, at least in this study. On the other hand, decreased uptake on ^{99m}Tc-MIBI scintigraphy generally indicates reduced perfusion or, in the case of sarcoidosis, fibrotic changes replacing normal myocardium.[26] In our study, two cases had an area in the heart that exhibited augmented accumulation on ^{18}F-FDG images, but showed reduced uptake on ^{99m}Tc-MIBI images. The simultaneous presence of an active inflammatory lesion and fibrotic changes is suggested in such cases. On the other hand, the presence of focal ^{18}F-FDG uptake and ^{99m}Tc-MIBI defects at a distant location indicated the coexistence of active and fibrotic changes at different sites in the heart. Because ^{18}F-FDG does not accumulate in areas with no blood flow, the two nuclear imaging techniques appear to be a desirable combination to accurately assess cardiac involvement of sarcoidosis.

Of interest is that some individuals exhibited the none pattern whereas others showed the diffuse pattern on ^{18}F-FDG PET images, in both the control and the patient groups. With regard to this issue, we speculated that the myocardial uptake of ^{18}F-FDG varied according to blood levels of glucose, IRI, or FFA, because these factors are known to influence myocardial uptake of glucose.[27] However, subjects exhibiting the none pattern and those exhibiting the diffuse pattern had similar levels of plasma FPG among the controls, and similar levels of FPG, IRI, and FFA among patients with sarcoidosis. In addition, the degree of insulin resistance, as defined by the homeostasis model assessment index, did not differ among the subjects with different patterns on ^{18}F-FDG PET images. We therefore speculate that the different patterns of myocardial ^{18}F-FDG uptake were caused by intersubject variation in glucose metabolism exclusively at the cardiac level. Nuutila *et al.*[28] reported that myocardial uptake of glucose is not necessarily associated with uptake of glucose at the whole-body or skeletal muscle level.

Several types of cells are thought to cause focal uptake on ^{18}F-FDG PET images in patients with sarcoidosis. According to the *in vitro* study by Kubota *et al.*,[29] ^{18}F-FDG was found to accumulate in inflammatory cells such as lymphocytes, neutrophils, and macrophages. Alternatively, increased

^{18}F-FDG uptake may also be associated with augmented glucose metabolism in the myocardium.[30] Indeed, ^{18}F-FDG PET is a well-known tool to identify myocardial viability, particularly in patients with ischaemic heart disease,[31] and ^{18}F-FDG uptake is enhanced in the ischaemic state because of increased utilization of glucose together with the decreased utility of FFA.[32]. Thus, focal or focal on diffuse uptake pattern on ^{18}F-FDG PET images might reflect the enhanced uptake of ^{18}F-FDG by inflammatory cells and/or by modestly damaged myocardium. In any case, focally enhanced cardiac uptake on ^{18}F-FDG PET indicates the presence of active lesions, rather than progress of fibrotic lesions, in patients with sarcoidosis.

There are some limitations in the present study. First, not all of the controls were completely healthy, and recruiting only healthy subjects as controls would have strengthened the conclusions of the present study. However, we used strict exclusion criteria and excluded any factors known to be influential to myocardial uptake of ^{18}F-FDG. We therefore believe that our methodology in selecting the controls would not significantly affect the central conclusion of this study. Secondly, diffuse uptake pattern of ^{18}F-FDG was observed in about half of control subjects, and this may have decreased the sensitivity of ^{18}F-FDG PET in identifying cardiac involvement of sarcoidosis. However, we were able to identify two patients with sarcoidosis exhibiting focal on diffuse cardiac uptake pattern, which suggests the potential of ^{18}F-FDG PET to detect cardiac involvement of sarcoidosis, even in individuals with diffuse uptake pattern. The third limitation of this study is that we performed myocardial biopsy in only four patients with sarcoidosis. Although myocardial biopsy should have been performed in all suspected patients with cardiac sarcoidosis in order to confirm diagnosis, the diagnostic yield of such biopsies is not as high as expected.

In conclusion, we propose that focal cardiac uptake on ^{18}F-FDG PET images is a characteristic feature of patients with sarcoidosis. Because focally enhanced accumulation of ^{18}F-FDG suggests the presence of active inflammatory processes, ^{18}F-FDG PET, particularly in combination with ^{99m}Tc-MIBI scintigraphy, may be better suited to the diagnosis and assessment of the disease activity of cardiac sarcoidosis.

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