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Heterogeneous Myocardial FDG Uptake and the Disease Activity in Cardiac Sarcoidosis

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OBJECTIVES This study evaluated the usefulness of fasting ^{18}F-fluorodeoxyglucose (FDG)–positron emission tomography (PET) in the diagnosis and management of cardiac sarcoidosis (CS) and compared it with FDG uptake in dilated cardiomyopathy (DCM).

BACKGROUND Cardiac sarcoidosis may clinically present as DCM but is amenable to systemic corticosteroid therapy if disease activity is high. Although alterations of FDG uptake have been reported in CS, limited information is available on the quantitative estimates of FDG uptake.

METHODS Fasting FDG–PET was performed in 24 systemic sarcoidosis patients and was compared with 8 age-matched DCM patients. FDG–PET was also performed in 15 age-matched healthy control subjects. Twelve of the 24 sarcoidosis patients had cardiac involvement based on criteria established by the Japanese Ministry of Health and Welfare; the remaining 12 of 24 patients revealed no evidence of cardiac involvement. The myocardial FDG uptake was quantified by measuring the standardized uptake value in 17 myocardial segments in each subject. Coefficient of variation (COV), which equals the standard deviation of uptake divided by the average uptake of 17 segments, was calculated as an index of heterogeneity in the heart.

RESULTS The FDG uptake was distinctly heterogeneous in CS patients. The COV value was significantly greater in CS patients (0.25 ± 0.05) than control subjects (0.14 ± 0.03, $p < 0.01$), sarcoidosis patients without cardiac involvement (0.14 ± 0.03, $p < 0.01$), or DCM patients (0.15 ± 0.02, $p < 0.01$). The COV value in DCM patients was similar to control subjects or sarcoidosis patients without cardiac involvement. The cutoff COV value for the diagnosis of CS was 0.18 (sensitivity: 100%; specificity: 97%). After corticosteroid therapy in CS patients, the COV value was decreased to 0.14 ± 0.06 ($p < 0.05$) and became essentially similar to the other groups.

CONCLUSIONS Heterogeneous myocardial FDG uptake may be a useful diagnostic marker of disease activity for CS. (J Am Coll Cardiol Img 2010;3:1219–28) © 2010 by the American College of Cardiology Foundation

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Sarcoidosis is a multisystem disorder of unknown etiology, characterized by the formation of noncaseating epithelioid cell granulomas in many organs. Sarcoidosis is generally associated with a low mortality rate (1), but cardiac involvement is responsible for more than two-thirds of the deaths (2–5). Cardiac sarcoidosis (CS) has a wide spectrum of clinical manifestations and may frequently present as dilated cardiomyopathy (DCM). It has been reported that the patients initially diagnosed with end-stage DCM were rediagnosed with CS upon histological examination of the resected myocardium after left ventriculoplasty or ventricular assist device implantation (6,7). Some CS patients have been misdiagnosed with DCM, primarily because of difficulties in its diagnosis. The mainstay of treatment for patients with sarcoidosis is systemic corticosteroid if disease activity is high; corticosteroid that impedes the formation of granulomas is effective against most active clinical manifestations of CS and may halt progression of left ventricular (LV) dysfunction and improve LV remodeling and prognosis in CS patients (8,9). As such, early diagnosis and determination of disease activity are desirable in the treatment of CS.

ABBREVIATIONS AND ACRONYMS

COV = coefficient of variation
CS = cardiac sarcoidosis
DCM = dilated cardiomyopathy
FDG = ^{18}F-fluorodeoxyglucose
Ga = ^{67}gallium
LV = left ventricular
PET = positron emission tomography
SUV = standardized uptake value
Tc-MIBI = ^{99m}Technetium sestamibi

^{18}F-fluorodeoxyglucose (FDG) has been shown to accumulate in inflamed tissues. The molecular targeting approach using FDG-positron emission tomography (PET) has been validated for the localization of macrophages and granulomatous inflammation (10,11). Recent studies have revealed that FDG-PET under fasting conditions is a promising modality for identification of CS; a heterogeneous FDG uptake in the heart has been reported to be a characteristic feature of CS (12–14). However, because a diffuse uptake of FDG in the normal heart and DCM can also be observed, it is prudent to compare the quantitative and qualitative features of FDG uptake in sarcoidosis patients with and without cardiac involvement, DCM patients, and normal subjects.

METHODS

Subjects and study design. Forty-seven subjects were prospectively enrolled in the present study of FDG-PET as follows.

SARCOIDOSIS PATIENTS. Twenty-four of the 47 subjects had systemic sarcoidosis, which was diagnosed clinically and/or histologically. Twelve of the 24 patients with sarcoidosis had cardiac involvement based on guidelines established in 2006 by the Japanese Ministry of Health and Welfare (15) (Table 1). Twelve patients with sarcoidosis had no cardiac involvement (non-CS).

CONTROL SUBJECTS. Of the 23 control subjects, 8 patients had idiopathic DCM (5 men, 3 women; mean age: 58.3 ± 7.9 years; range 44 to 66 years) based on angiographic and histological information. Patients with ischemic and valvular causes of DCM were excluded from this analysis. Clinical information for the individual patients is shown in Table 2. The remaining 15 age-matched healthy control subjects (5 men, 10 women; mean age: 57.7 ± 7.5 years; range 50 to 72 years) were recruited who had no evidence of active inflammatory, coronary, valvular disease; these subjects did not have uncontrolled diabetes mellitus or insulin treatment or severe hepatic, renal, malignant and hematological diseases and were not receiving corticosteroids.

Table 1. Guidelines for Diagnosis of CS (2006)

Histologic diagnosis group

Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis.

Clinical diagnosis group

Although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid cell granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than 1 in 6 basic diagnostic criteria.

1. 2 or more of the 4 major criteria are satisfied.
2. 1 in 4 of the major criteria and 2 or more of the 5 minor criteria are satisfied.

Major criteria

a. Advanced atrioventricular block.
b. Basal thinning of the interventricular septum.
c. Positive ^{67}gallium uptake in the heart.
d. Depressed ejection fraction of the left ventricle (<50%).

Minor criteria

a. Abnormal ECG findings: ventricular arrhythmias (ventricular tachycardia, multifocal or frequent PVCs), CRBBB, axis deviation or abnormal Q-wave.
b. Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening).
c. Nuclear medicine: perfusion defect detected by ^{201}thallium or ^{99m}technetium myocardial scintigraphy.
d. Gadolinium-enhanced CMR imaging: delayed enhancement of myocardium.
f. Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade.

CMR = cardiac magnetic resonance; CRBBB = complete right bundle branch block; CS = cardiac sarcoidosis; ECG = electrocardiogram; PVC = premature ventricular contraction.

Table 2. Clinical Information of All Patients

Age (yrs)	Sex	ECG Findings	LV Thinning	LVEF (%)	BNP (pg/ml)	Tc-MIBI	Ga Uptake in the Heart	ACE (IU/L/37°C)	CRP (mg/dl)	COV	Number of Criteria	
											Major	Minor
Sarcoidosis without cardiac involvement												
61	F	WNL	Absent	66	11	Nml	Negative	15.5	0.07	0.163	0	0
44	M	WNL	Absent	69	6	Nml	Negative	42.4	1.03	0.069	0	0
72	F	LAH + IRBBB	Absent	80	23	Nml	Negative	23.7	0.21	0.176	0	1
62	F	PVC	Absent	64	43	Nml	Negative	15.1	0.11	0.159	0	1
80	F	3rd° AVB, PM	Absent	72	55	Nml	Negative	30.9	0.06	0.119	1	0
27	M	WNL	Absent	63	4	Nml	Negative	18.7	2.71	0.147	0	0
56	F	WNL	Absent	68	31	Nml	Negative	9.4	2.64	0.157	0	0
54	F	WNL	Absent	68	24	Nml	Negative	33.1	0.04	0.148	0	0
28	M	ST-T change	Absent	70	25	Nml	Negative	19.5	0.23	0.110	0	0
43	M	nsVT	Absent	61	15	Nml	Negative	16.4	0.13	0.168	0	1
79	F	PAC, PVC	Absent	67	69	Nml	Negative	25.8	0.05	0.185	0	0
75	F	A.Fib, PVC	Absent	66	110	Nml	Negative	20.7	1.18	0.091	0	0
Cardiac sarcoidosis												
44	F	ST-T change, VT, AICD	Present	43	185	Hypo	Positive	6.2	1.05	0.182	3	3
62	M	LAH + CRBBB, 1st° AVB	Absent	77	152	Hypo	Negative	41.3	0.24	0.200	1	3
78	M	3rd° AVB, nsVT, PM, AICD	Present	32	300	Hypo	Positive	14.3	0.08	0.245	4	3
69	M	3rd° AVB, VT, PM, AICD	Absent	53	141	Hypo	Negative	1.1	0.18	0.195	1	2
60	F	3rd° AVB, VT, PM, AICD	Present	65	137	Hypo	Positive	23.0	0.04	0.302	3	3
55	F	LAH + CRBBB, PVC	Present	36	92	Hypo	Positive	22.4	0.30	0.348	3	4
56	F	3rd° AVB, PVC, PM	Absent	62	104	Hypo	Negative	14.4	0.07	0.292	1	2
62	F	ST-T change, VT	Present	53	367	Hypo	Negative	45.3	0.05	0.205	1	4
53	F	ST-T change, PVC	Present	40	105	Hypo	Negative	26.2	0.14	0.263	2	3
77	F	Wide QRS complex, nsVT	Present	32	528	Hypo	Negative	16.0	0.04	0.293	2	3
80	F	3rd° AVB, A.Fib, VT, PM, AICD	Present	51	254	Hypo	Negative	19.2	0.28	0.226	2	3
60	F	ST-T change, nsVT	Present	60	35	Hypo	Negative	45.7	0.13	0.240	1	2
Idiopathic dilated cardiomyopathy												
66	F	3rd° AVB, VT, PM	Present	22	775	Hypo	Negative	14.9	0.04	0.148	—	—
62	F	A.Fib, ST-T change	Absent	49	644	Nml	Negative	20.0	0.04	0.161	—	—
63	M	ST-T change, PAC, VT, AICD	Absent	40	24	Nml	Negative	10.3	0.62	0.139	—	—
62	M	Wide QRS complex, VT, AICD	Absent	24	401	Hypo	Negative	2.3	0.04	0.171	—	—
59	M	CLBBB, PVC	Absent	40	204	Hypo	Negative	9.6	0.04	0.131	—	—
64	M	ST-T change, nsVT	Absent	29	22	Hypo	Negative	14.6	0.04	0.144	—	—
46	M	LAH, ST-T change	Absent	33	32	Nml	Negative	13.2	0.06	0.113	—	—
44	F	Transient 3rd° AVB, VT	Present	30	83	Hypo	Negative	10.1	0.04	0.162	—	—

ACE = angiotensin-converting enzyme; A.Fib = atrial fibrillation; AICD = automatic implantable cardioverter-defibrillator implanted; AVB = atrioventricular block; BNP = B-type natriuretic peptide; COV = coefficient of variation; CRP = C-reactive protein; Ga = ^{67}gallium; IRBBB = incomplete right bundle branch block; LAH = left anterior hemiblock; LV = left ventricular; LVEF = left ventricular ejection fraction; Nml = normal; nsVT = nonsustained ventricular tachycardia; PAC = premature atrial contraction; PM = permanent pacemaker implanted; Tc-MIBI = ^{99m}technetium sestamibi; VT = ventricular tachycardia; WNL = within normal limit; other abbreviations as in Table 1.

Serum calcium, C-reactive protein, angiotensin-converting enzyme, and B-type natriuretic peptide levels were measured in all patients. All patients underwent chest X-ray, resting 12-lead electrocardiogram, transthoracic echocardiography, and 3 types of radionucleotide imaging using ^{99m}technetium sestamibi (Tc-MIBI) for myocardial perfusion, ^{67}gallium (Ga), and FDG for whole-body evaluation. All these evaluations were performed within 2 weeks. All subjects gave informed consent. The Ethical Committee for the Clinical Research of Kurume University approved this study.

Echocardiography. A comprehensive transthoracic echocardiography examination was performed in all patients using a standardized approach with an echocardiograph (Sonos 5500, Philips Medical Systems, Inc., Bothell, Washington) interfaced with a multifrequency megahertz transducer. The LV end-diastolic and -systolic dimensions were determined from M-mode or B-mode echocardiograms. The LV ejection fraction was obtained via the modified biplane Simpson method. Echocardiographic findings were blindly evaluated by 2 experienced cardiologists.

Tc-MIBI and Ga scintigraphy. All patients underwent myocardial perfusion imaging with Tc-MIBI and Ga scintigraphy for whole-body imaging. Single-photon emission computed tomography images of myocardial perfusion scan at rest was acquired 3 h after intravenous injection of Tc-MIBI (740 MBq) after at least 12 h of fasting. To remove Tc-MIBI accumulation in the gallbladder, all patients drank milk 45 min after the tracer injection. ^{67}Gallium scintigraphic imaging was performed 48 h after intravenous injection of Ga citrate (74 MBq) for whole-body planar and single-photon emission computed tomography images. Three experienced nuclear radiologists blindly interpreted the images without knowing their clinical findings. When evaluations of the images differed, an agreement was reached by discussion.

FDG-PET. FDG-PET images were acquired after at least a 12-h period of fasting in order to minimize the myocardial FDG uptake in all 47 subjects. Plasma glucose levels were measured before the injection of the tracer. Each subject received an intravenous administration of 4.2 MBq of FDG per kilogram of body weight and had to be kept in a resting state before PET images were taken. One hour after the FDG injection, PET imaging for evaluation of 3-dimensional heart and whole body was carried out using a PET scanner (Allegro, Philips Medical Systems [Cleveland], Inc., Cleveland, Ohio). We performed an attenuation correction for the PET imaging by a rotating rod of activity in the PET scanner. PET imaging was performed for review on a workstation (Sun Blade 2000, Sun Microsystems, Inc., Santa Clara, California). The FDG-PET images were visually evaluated for the presence of FDG uptake in the heart on the basis of the agreement of 2 cardiologists blinded to other clinical information and treatment assignment of each subject. We classified the FDG-PET images into 4 patterns, as previously described (14), by uptake: "none," "diffuse," "focal," and "focal on diffuse." To ensure that the regions of FDG uptake in CS patients correlate with sites of Ga uptake in the heart, we coregistered the PET images with the Ga images. Next, reorientation of the axial images to a standard cardiac orientation was undertaken and then the standardized uptake value (SUV) was determined. The intensity of myocardial FDG uptake was quantified by measuring the SUV in all 17 segments followed by a scientific statement from the American Heart Association (16). Analysis of myocardial FDG uptake was performed by recognition of endomyocardial and epimyocardial borders and by subdividing the LV in each segment. We determined SUV of each segment in all 17 segments for each subject and then calculated the average of SUV and SD of SUV for each patient. Thereafter, the coefficient of variation (COV) of SUV in each patient was calculated by dividing SD of SUV by average of SUV as an index of heterogeneity of the FDG uptake. Two nuclear radiologists blindly measured SUV, and the measurements were averaged. The intraobserver and interobserver variability of SUV measurements were $<5\%$.

Evaluation for the effect of corticosteroids therapy. Nine of 12 patients with CS were treated with corticosteroid. Initially, the patients were treated with 30 mg/day of prednisolone orally for the first 4 weeks. Then the dose was decreased to 20 mg/day for the next 4 weeks and maintained at 10 mg/day thereafter. The other medications were not altered during the course of the corticosteroid treatment. Although corticosteroid is regarded as the first-line drug, 3 patients did not receive corticosteroid: 1 had chronic hepatitis C and the other 2 refused the treatment. In 9 patients with CS, FDG-PET was repeated 1, 3, 6, and 12 months later. One untreated CS patient underwent FDG-PET 12 months later.

Statistical analysis. Data were described as mean ± SD. Categorical variables were compared by the use of chi-square analysis. Continuous variables were logarithmically transformed if necessary and compared using analysis of variance followed by Scheffe comparison test between groups. The COV values at each time point were analyzed by repeated measures analysis of variance with Scheffe test for comparisons over a time course. Values of <0.05 were considered statistically significant. The diagnostic performance was analyzed using receiver-operator characteristic curves, displaying sensitivity and specificity at different cutoff values, and the area under the curve values were computed.

Table 3. Summary of Clinical Variables

Variables (Normal Value)	Non-CS (n = 12)	CS (n = 12)	DCM (n = 8)
Age, yrs	56.8 ± 17.6	63.0 ± 10.6	58.3 ± 7.9
Age (range), yrs	27–80	44–80	44–66
Women, n (%)	8 (67)	9 (75)	3 (38)
Cardiothoracic ratio, %	48.1 ± 6.0	53.4 ± 4.3	58.0 ± 5.5*
Fast blood sugar,† [80–109] mg/dl	95.9 ± 7.4	99.0 ± 7.6	103.6 ± 7.9
HbA_{1C}, [4.3–5.8] %	5.39 ± 0.17	5.65 ± 0.66	5.46 ± 0.36
BNP,† [<18.4] pg/ml	23.5 ± 1.8	160.2 ± 12.3*	123.5 ± 9.5*
CRP, [<0.20] mg/dl	0.71 ± 0.95	0.22 ± 0.27	0.12 ± 0.19
Serum calcium, [8.7–10.3] mg/dl	9.17 ± 0.26	9.83 ± 0.97	9.18 ± 0.30
ACE, [8.3–21.4] IU/ l/37°C	23.2 ± 8.9	24.7 ± 14.2	11.9 ± 4.8
LV end-diastolic diameter, mm	48.1 ± 6.3	53.8 ± 7.3	64.9 ± 9.6*‡
LV end-systolic diameter, mm	29.9 ± 5.0	40.0 ± 9.9	54.8 ± 10.5*§
LV ejection fraction, %	67.8 ± 4.7	50.3 ± 13.6*	33.3 ± 8.5*‡
LV wall thinning, n (%)	0 (0)	9 (75)*	2 (25)
Advanced AVB, n (%)	1 (8)	5 (42)	2 (25)
Ventricular tachycardia, n (%)	1 (8)	8 (67)*	5 (63)*
Myocardial perfusion defect, n (%)	0 (0)	12 (100)*	5 (63)*
Cardiac Ga accumulation, n (%)	0 (0)	4 (33)	0 (0)
Medication use, n (%)			
Digitalis	0 (0)	3 (25)	2 (25)
Diuretics	2 (17)	7 (58)	5 (63)
ACE inhibitor	0 (0)	3 (25)	1 (13)
ARB	1 (8)	6 (50)	7 (88)*
Beta blockers	0 (0)	2 (16)	5 (63)*
Calcium channel blockers	4 (33)	1 (8)	0 (0)
Antiarrhythmic agents	0 (0)	4 (33)	2 (25)
Warfarin	1 (8)	5 (42)	4 (50)

Categorical variables are summarized by frequency and percentage. Continuous variables are summarized by mean ± SD unless otherwise noted. Analyses were performed with analysis of variance post hoc tests, except categorical variables, for which chi-square analysis was used. *$p < 0.01$ versus Non-CS. †Log-transformed value was used for the calculation of means and SD. ‡$p < 0.05$ versus CS. §$p < 0.01$ versus CS.
ARB = angiotensin receptor blockers; CS = cardiac sarcoidosis; DCM = dilated cardiomyopathy; HbA_{1C} = glycosylated hemoglobin A_{1C}; other abbreviations as in Table 2.

RESULTS

Baseline characteristics. Characteristics of the 24 patients with systemic sarcoidosis (non-CS: n = 12, CS: n = 12) and the 8 DCM patients are presented in Tables 2 and 3. There were no significant differences in age, fasting blood sugar, glycosylated hemoglobin A_{1C}, C-reactive protein, serum calcium, and angiotensin-converting enzyme between the 3 groups. Female pre-dominance was observed in patients with systemic sarcoidosis. In non-CS patients, serum levels of B-type natriuretic peptide were lower than those of CS ($p < 0.01$) and DCM ($p < 0.01$) patients. Advanced atrioventricular block requiring permanent pacemaker was frequent in CS ($p = 0.11$ for trend). The incidence of ventricular tachycardia was similar between CS and DCM. Tc-MIBI abnormalities were common in both CS and DCM. All CS patients, none of the non-CS patients, and 5 of 8 (63%) DCM patients exhibited abnormal myocardial perfusion. According to abnormal myocardial perfusion, the sensitivity and specificity for diagnosing CS were 100% and 76%, respectively. The diagnostic accuracy is relatively high, but it is not specific to CS and lacks assessment of disease activity. Ga scintigraphy, a well-known imaging modality for diagnosing and assessing disease activity of cardiac involvement, was positive in only 4 of 12 (33%) CS.

All patients were on optimal and stable doses of digoxin, diuretics, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers or beta-blockers. A list of the medications except for corticosteroid is shown in Table 3.

Echocardiographical data. CS patients had lower LV systolic function than non-CS patients ($p < 0.01$) did. DCM patients demonstrated ventricular enlargement and reduced ejection fraction on echocardiography (Table 3). Echocardiograph septal

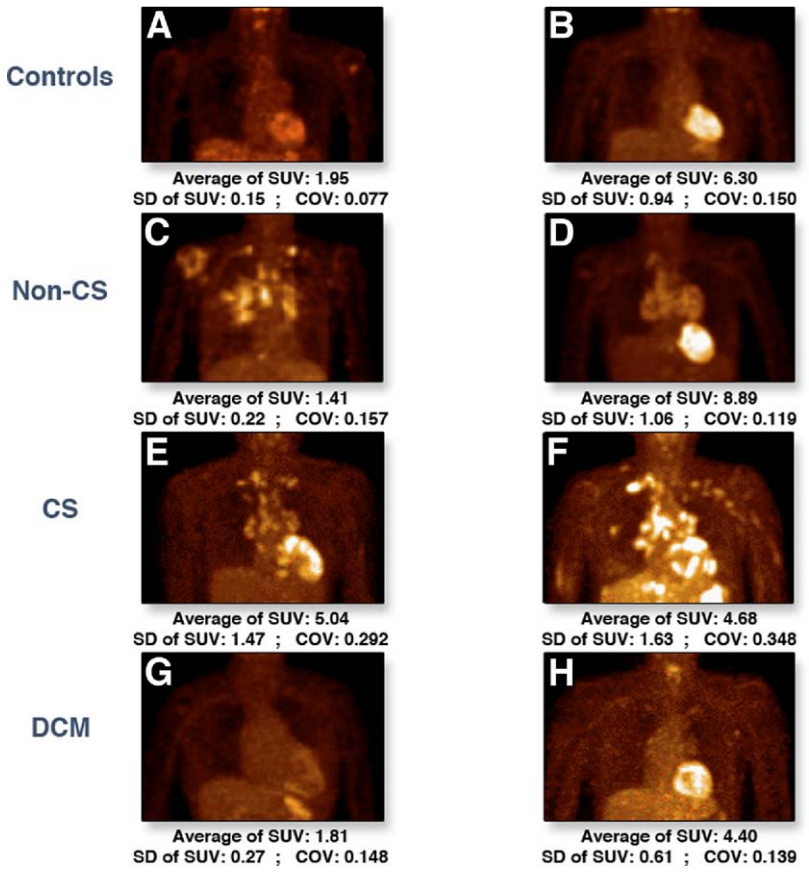

Figure 1. Representative FDG-PET Anterior Views

The myocardial uptake of FDG in healthy control subjects **(A,B)**, noncardiac sarcoidosis **(C,D)**, cardiac sarcoidosis **(E,F)**, and dilated cardiomyopathy **(G,H)** patients. COV = coefficient of variation; CS = cardiac sarcoidosis; DCM = dilated cardiomyopathy; FDG = ^{18}F-fluorodeoxyglucose; PET = positron emission tomography; SUV = standardized uptake value.

wall thinning, a characteristic feature of CS, was more frequent in CS ($p < 0.01$ for trend).

FDG-PET image. The FDG uptake in the heart was highly variable in all subjects. Representative FDG-PET anterior views of maximum intensity projection are demonstrated in Figure 1: panels A, C, E, G show low myocardial uptake and panels B, D, F, H demonstrate high myocardial uptake. In control subjects, non-CS patients, and DCM patients, the uptake was predominantly homogeneous; minor heterogeneity, if seen, did not contribute to significant COV. On the other hand, the uptake appeared distinctly heterogeneous in CS patients with high COV, regardless of the magnitude of FDG uptake (SUV). In addition, distinct FDG uptake was observed in hilar and mediastinal lymph in sarcoidosis patients regardless of cardiac involvement. The result obtained from coregistration of PET and Ga images clearly demonstrated that the regions of FDG uptake closely correlated with almost all sites of Ga uptake in the heart (Fig. 2). As previously reported (14), all CS patients showed myocardial FDG uptake. Also, the diffuse FDG uptake on PET images was not seen. Among the 15 controls, 1 (7%), 4 (27%), 1 (7%), and 9 (60%) individuals exhibited none, diffuse, focal, and focal on diffuse patterns, respectively. Also, there were 5 (42%) non-CS patients and 4 (50%) DCM patients showing the focal on diffuse uptake. When we utilized the presence of "focal" and "focal on diffuse" uptakes for diagnosis of CS using FDG-PET images as described previously, the sensitivity and specificity of the feature for diagnosing CS were 100% and 34%, respectively. It is noteworthy that there were many false positive results confirmed to be CS by "focal on diffuse" finding on FDG-PET.

The quantitative analysis of FDG uptake in myocardium revealed that the average of SUV was similar among all subject groups (Fig. 3A). Al-

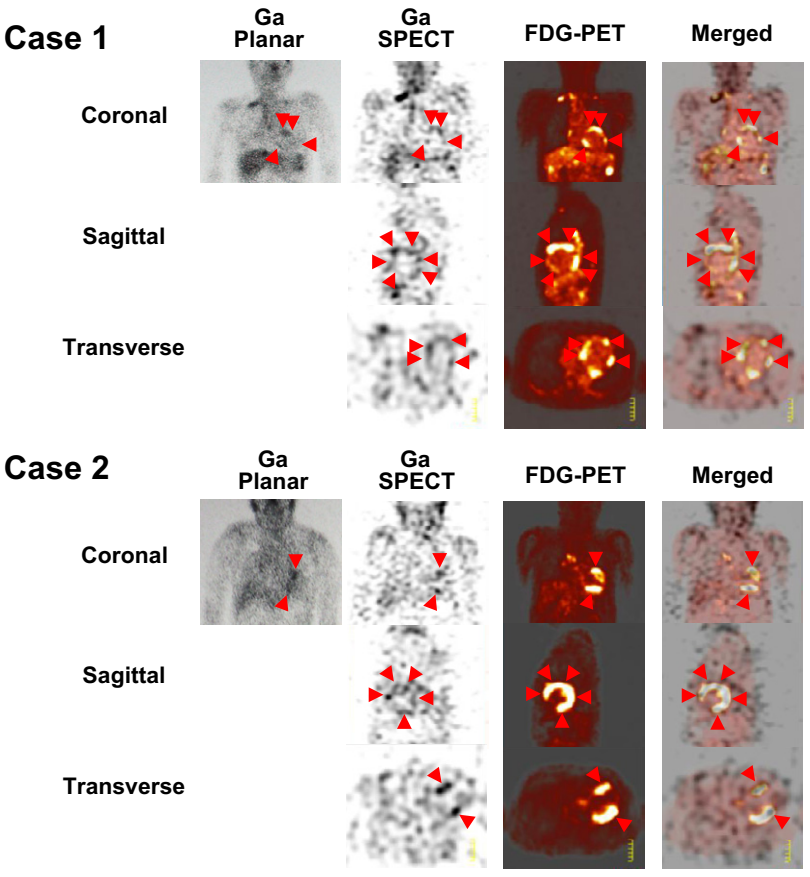

Figure 2. Representative Images of Ga, FDG-PET, and Coregistration of PET and Ga in 2 CS Patients With Cardiac Ga Accumulation

The images of coregistration of positron emission tomography and ^{67}gallium demonstrate that the regions of FDG uptake correlated with almost all sites of ^{67}gallium uptake in the heart (**arrowheads**). Ga = ^{67}gallium; SPECT = single-photon emission computed tomography; other abbreviations as in Figure 1.

though SD of SUV was greater in CS than that of the other subject groups, it was not statistically significant between CS and DCM (Fig. 3B). We calculated COV (SD/average), as another index of heterogeneity independent of basal uptake in the heart (Fig. 3C). The COV value was significantly

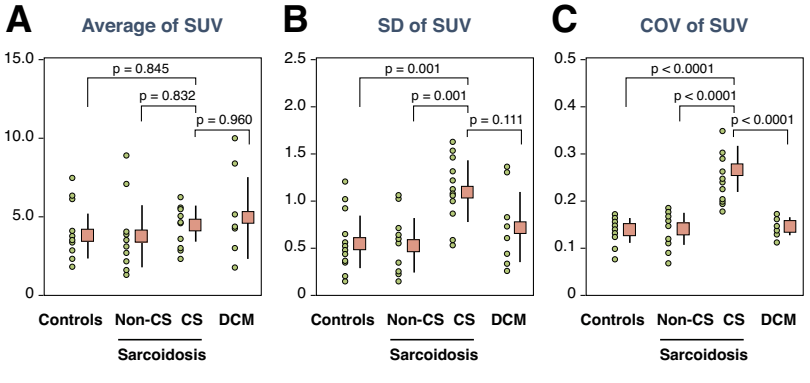

Figure 3. The Quantitative Analysis of FDG Uptake in Myocardium

Average of standardized uptake value (**A**), SD of standardized uptake value (**B**), and coefficient of variation of standardized uptake value (**C**) for myocardial FDG uptake. **Shaded squares** indicate mean ± SD within groups. Abbreviations as in Figure 1.

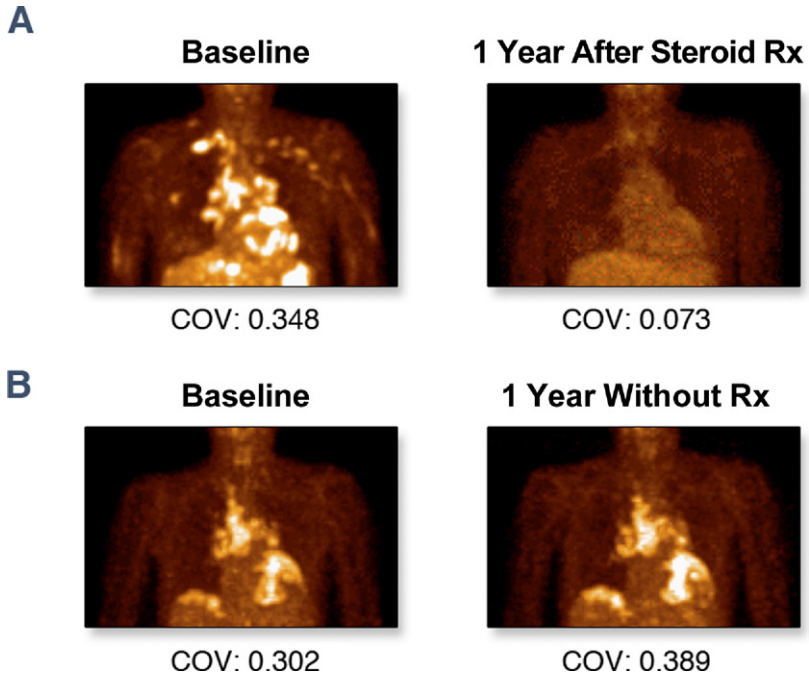

Figure 4. Follow-Up FDG-PET Scans at 1 Year in CS Patients

Serial FDG–positron emission tomography scan after corticosteroid therapy revealed complete resolution of the heterogeneity of myocardial FDG uptake **(A)**, whereas more heterogeneous myocardial FDG uptake was seen in an untreated patient after 1 year **(B)**. Rx = corticosteroids; other abbreviations as in Figure 1.

greater in CS patients (0.25 ± 0.05) than in control subjects (0.14 ± 0.03, $p < 0.01$), non-CS patients (0.14 ± 0.03, $p < 0.01$), or DCM patients (0.15 ± 0.02, $p < 0.01$). The cutoff COV value for the diagnosis of CS was computed as 0.18 with sensitivity of 100% and specificity of 97% by the receiver-operator characteristic curve.

Corticosteroid treatment. Corticosteroid treatment was initiated in 9 of 12 patients with CS; the remaining 3 CS patients had not received corticosteroid treatment. One-year corticosteroid treatment prevented deteriorations of LV remodeling (LV end-diastolic diameter from 53.4 ± 7.8 mm to 56.8 ± 6.8 mm, $p = 0.33$) and LV systolic function (LV ejection fraction from 53.0 ± 12.6% to 55.6 ± 13.7%, $p = 0.90$). Representative FDG-PET images are shown in Figure 4 from a patient who took corticosteroid and 1 who did not. There was almost a complete resolution of heterogeneity after corticosteroid therapy. On the other hand, heterogeneity further increased without corticosteroid treatment. The pooled data of COV in 9 CS patients 1 month after corticosteroid therapy showed a significant decrease in FDG uptake from 0.24 ± 0.05 to 0.14 ± 0.06 ($p < 0.05$); FDG uptake remained low throughout the 12-month follow-up (Fig. 5). There were 3 patients, 2 non-CS and 1 CS, without corticosteroid treatment who underwent repeated FDG-PET scans 1 year after. The COV value of 1 CS patient without steroid therapy increased from

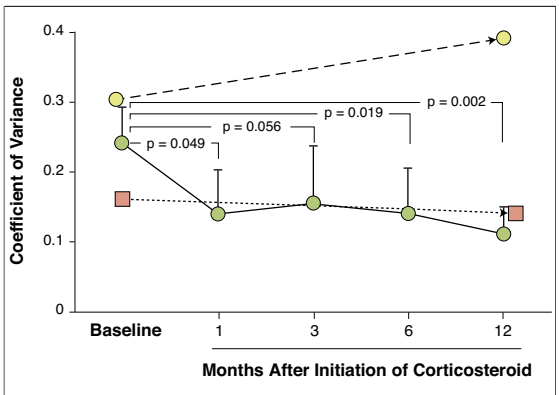

Figure 5. The Time Course of COV

Dark green circles indicate mean ± SD changes in COV of maximum SUV in 9 cardiac sarcoidosis patients from baseline to 12 months after corticosteroid therapy. The **orange squares** indicate the COV value in 2 noncardiac sarcoidosis in baseline and 12-month follow-up FDG–PET. The **light green circles** indicate the COV value in a cardiac sarcoidosis patient not treated with corticosteroid in baseline and 12-month follow-up FDG–positron emission tomography. Abbreviations as in Figure 1.

0.30 to 0.39, indicating worsening of disease activity (Fig. 5). In 2 non-CS patients, it appeared to be reproducible from 0.16 to 0.14, suggesting a potential role for serial testing (Fig. 5).

DISCUSSION

The FDG uptake was distinctly heterogeneous in CS patients. Coefficient of variation, an index of heterogeneity of FDG uptake, emerged as a useful marker of CS and active myocardial inflammation. In DCM, the COV was comparable to non-CS and healthy control subjects.

FDG is a synthetic tracer that mimics the biochemical behavior of the natural glucose molecule. Because normal myocardium uses free fatty acids as the energy source under resting physiologic conditions in the fasting state, FDG uptake into the normal heart is expected to be low. However, some healthy subjects demonstrate higher FDG uptake based on various factors, such as dietary habits, old age, obesity, and glycemic state. In this study, we did not find a significant correlation between FDG uptake and age, body mass index, or blood glucose levels in control subjects. In fact, we excluded subjects with blood glucose >120 mg/dl. The wide disparity of FDG uptake in the normal heart has also been reported previously (17,18). The FDG uptake in DCM was similar to that in healthy control subjects, suggesting no diagnostic usefulness of the average of FDG uptake for DCM. Whenever present, myocardial glucose utilization was normally expected to be homogeneous in the normal controls. However, SD of SUV slightly varied in control subjects (Fig. 3B), a large spatial and temporal heterogeneity of the myocardial metabolic pattern has been previously reported in subjects without heart disease (17), and FDG uptake in the lateral LV wall has been shown to be high (19,20). The heterogeneity of myocardial glucose metabolism in the normal human heart may be related to regional substrate availability. Caution should be exercised in the interpretation of SD of SUV because it is dependent on total FDG uptake. As such, we calculated COV of SUV in each patient by dividing SD of SUV by average of SUV as an index of heterogeneity of the FDG uptake. The COV in control subjects was low and relatively constant, which is indicative of homogenous uptake of FDG in the normal heart.

In CS patients, the COV was significantly high compared to that of control subjects, indicating heterogeneous uptake of FDG. In CS, FDG uptake in some regions of the heart may be decreased due to myocardial fibrosis, whereas it may be increased in other regions due to inflammatory granulomas. Coefficient of variation in CS patients was not only high but also distinctly different from that of control subjects and non-CS patients. The high COV in CS patients indicates the presence of active inflammation because the high COV prior to steroid treatment decreased to the level of healthy control subjects after treatment; FDG uptake also resolved in the hilar and mediastinal lymph nodes after steroid treatment. A high heterogeneous FDG uptake in DCM should also be possible due to myocardial cell loss or regional fibrosis. In fact, occasionally images did appear to demonstrate some heterogeneity in FDG uptake (Fig. 1H). However, COV in DCM was not high and comparable to that in controls, which suggests that interstitial fibrosis alone without active inflammation may not suffice for distinct FDG heterogeneity. Beta-blockers may also affect regional FDG uptake (21,22), but the COV in DCM patients receiving beta-blockers (0.15 ± 0.01) was similar to that of patients not receiving beta-blockers (0.14 ± 0.02, $p = 0.49$). Visual inspection gave us an impression of heterogeneous uptake of FDG infrequently in DCM, but the COV was always below 0.18 and comparable to control subjects. The visual impression of heterogeneity in DCM is reflected by SD (Fig. 3B), which was high in some cases.

Heterogeneous uptake of FDG into the heart, therefore, is diagnostic of CS. However, because heterogeneity is dependent on the total myocardial FDG uptake, the heterogeneity index, COV >0.18, provides a high sensitivity and specificity for diagnosis of CS. Also, COV is useful for monitoring the response to corticosteroid treatment.

Study limitations. There are some obvious limitations in the present study. First, the small study size limits our interpretation and discussion. In addition, single-center data limits the generalizability of our findings by its selection bias. With regard to selection bias, we cannot exclude the possibility of unknown confounders. Second, we did not randomize patients with or without the use of corticosteroids and were not able to judge clinical benefits of corticosteroids from this study. Although atrial fibrillation and left bundle branch block are reported to affect the regional glucose utilization (23,24), the small sample size does not allow such analysis. Future investigations with a larger study size are needed to address these issues.

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CONCLUSIONS

Heterogeneous uptake in the heart on FDG-PET is highly suggestive of CS, but a quantitative evaluation is necessary, especially for differential diagnosis from DCM. The heterogeneous uptake in the heart in CS may disappear as early as 1 month after the corticosteroid therapy.

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REFERENCES

1. Reich JM. Mortality of intrathoracic sarcoidosis in referral vs population-based settings: influence of stage, ethnicity, and corticosteroid therapy. Chest 2002;121:32–9.
2. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, Kawabata Y. Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. Acta Pathol Jpn 1993;43:372–6.
3. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. Am Heart J 1999;138:299–302.
4. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M. Cardiac sarcoidosis: diagnostic, prognostic, and therapeutic considerations. Cardiovasc Drugs Ther 1996;10:495–510.
5. Perry A, Vuitch F. Causes of death in patients with sarcoidosis. A morphologic study of 38 autopsies with clinicopathologic correlations. Arch Pathol Lab Med 1995;119:167–72.
6. Terasaki F, Ukimura A, Tsukada B, et al. Enhanced expression of type 1 helper T-cell cytokines in the myocardium of active cardiac sarcoidosis. Circ J 2008;72:1303–7.
7. Roberts WC, Vowels TJ, Ko JM, Capehart JE, Hall SA. Cardiac transplantation for cardiac sarcoidosis with initial diagnosis by examination of the left ventricular apical "core" excised for insertion of a left ventricular assist device for severe chronic heart failure. Am J Cardiol 2009;103:110–4.
8. Yazaki Y, Isobe M, Hiroe M, et al., on behalf of Central Japan Heart Study Group. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol 2001;88:1006–10.
9. Chiu CZ, Nakatani S, Zhang G, et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. Am J Cardiol 2005;95:143–6.
10. Brudin LH, Valind SO, Rhodes CG, et al. Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography. Eur J Nucl Med 1994;21:297–305.
11. Chen CJ, Lee BF, Yao WJ, et al. Dual-phase 18F-FDG PET in the diagnosis of pulmonary nodules with an initial standard uptake value less than 2.5. AJR Am J Roentgenol 2008;191:475–9.
12. Yamagishi H, Shirai N, Takagi M, et al. Identification of cardiac sarcoidosis with (13)N-NH(3)/(18)F-FDG PET. J Nucl Med 2003;44:1030–6.
13. Okumura W, Iwasaki T, Toyama T, et al. Usefulness of fasting 18F-FDG PET in identification of cardiac sarcoidosis. J Nucl Med 2004;45:1989–98.
14. Ishimaru S, Tsujino I, Takei T, et al. Focal uptake on 18F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 2005;26:1538–43.
15. Diagnostic standard and guidelines for sarcoidosis. Jpn J Sarcoidosis and Granulomatous Disorders [in Japanese] 2007;27:89–102.
16. Cerqueira MD, Weissman NJ, Dilsizian V, et al. , on behalf of American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. Circulation 2002;105:539–42.
17. Inglese E, Leva L, Matheoud R, et al. Spatial and temporal heterogeneity of regional myocardial uptake in patients without heart disease under fasting conditions on repeated whole-body 18F-FDG PET/CT. J Nucl Med 2007;48:1662–9.
18. Khandani AH, Isasi CR, Donald Blaufox M. Intra-individual variability of cardiac uptake on serial whole-body 18F-FDG PET. Nucl Med Commun 2005;26:787–91.
19. Gropler RJ, Siegel BA, Lee KJ, et al. Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. J Nucl Med 1990;31:1749–56.
20. Bartlett ML, Bacharach SL, Voipio-Pulkki LM, Dilsizian V. Artifactual inhomogeneities in myocardial PET and SPECT scans in normal subjects. J Nucl Med 1995;36:188–95.
21. Wallhaus TR, Taylor M, DeGrado TR, et al. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. Circulation 2001;103:2441–6.
22. Tokita N, Zanzonico P, Dunphy M, et al. Suppression of physiological myocardial fluorodeoxyglucose uptake. J Am Coll Cardiol 2004;43 Suppl A:337A
23. Wu YW, Naya M, Tsukamoto T, et al. Heterogeneous reduction of myocardial oxidative metabolism in patients with ischemic and dilated cardiomyopathy using C-11 acetate PET. Circ J 2008;72:786–92.
24. Lindner O, Vogt J, Baller D, et al. Global and regional myocardial oxygen consumption and blood flow in severe cardiomyopathy with left bundle branch block. Eur J Heart Fail 2005;7:225–30.

Key Words: cardiac sarcoidosis ■ dilated cardiomyopathy ■ ^{18}F-fluorodeoxyglucose–positron emission tomography ■ heterogeneity.