Heterogeneous Myocardial FDG Uptake and the Disease Activity in Cardiac Sarcoidosis

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OBJECTIVES This study evaluated the usefulness of fasting 18F-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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Cardiac 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. 

\[ ^{18} \text{F-fluorodeoxyglucose} \] (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

**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.
- e. Endomyocardial biopsy: interstitial fibrosis or monocytic infiltration over moderate grade.

CMR = cardiac magnetic resonance, CRBBB = complete right bundle branch block, CS = cardiac sarcoidosis, ECG = electrocardiogram, PVC = premature ventricular contraction.
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 radionuclide imaging using 99m-technetium sestamibi (Tc-MIBI) for myocardial perfusion, 67gallium (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. $^{67}$Ga accumulation in the gallbladder, all patients drank after at least 12 h of fasting. To remove Tc-MIBI after intravenous injection of Tc-MIBI (740 MBq) for myocardial perfusion scan at rest was acquired 3 h. Photon emission computed tomography images of Ga scintigraphy for whole-body imaging. Single-myocardial perfusion imaging with Tc-MIBI and Ga scintigraphy 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. 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. LV in each segment. We determined SUV of 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.
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 A1C, 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.

Table 3. Summary of Clinical Variables

<table>
<thead>
<tr>
<th>Variables (Normal Value)</th>
<th>Non-CS (n = 12)</th>
<th>CS (n = 12)</th>
<th>DCM (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56.8 ± 17.6</td>
<td>63.0 ± 10.6</td>
<td>58.3 ± 7.9</td>
</tr>
<tr>
<td>Age (range), yrs</td>
<td>27–80</td>
<td>44–80</td>
<td>44–66</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>8 (67)</td>
<td>9 (75)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Cardiothoracic ratio, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast blood sugar, [80–109] mg/dl</td>
<td>95.9 ± 7.4</td>
<td>99.0 ± 7.6</td>
<td>103.6 ± 7.9</td>
</tr>
<tr>
<td>HbA1C [4.3–5.8] %</td>
<td>5.39 ± 0.17</td>
<td>5.65 ± 0.66</td>
<td>5.46 ± 0.36</td>
</tr>
<tr>
<td>BNP, [&lt;18.4] pg/ml</td>
<td>23.5 ± 1.8</td>
<td>160.2 ± 12.3*</td>
<td>123.5 ± 9.5*</td>
</tr>
<tr>
<td>CRP, (&lt;0.20) mg/dl</td>
<td>0.71 ± 0.95</td>
<td>0.22 ± 0.27</td>
<td>0.12 ± 0.19</td>
</tr>
<tr>
<td>Serum calcium, [8.7–10.3] mg/dl</td>
<td>9.17 ± 0.26</td>
<td>9.83 ± 0.97</td>
<td>9.18 ± 0.30</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>48.1 ± 6.3</td>
<td>53.8 ± 7.3</td>
<td>64.9 ± 9.6*</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>29.9 ± 5.0</td>
<td>40.0 ± 9.9</td>
<td>54.8 ± 10.5*</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>67.8 ± 4.7</td>
<td>50.3 ± 13.6*</td>
<td>33.3 ± 8.5*</td>
</tr>
<tr>
<td>LV wall thinning, n (%)</td>
<td>0 (0)</td>
<td>9 (75)*</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Advanced AVB, n (%)</td>
<td>1 (8)</td>
<td>5 (42)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Ventricular tachycardia, n (%)</td>
<td>1 (8)</td>
<td>8 (67)*</td>
<td>5 (63)*</td>
</tr>
<tr>
<td>Myocardial perfusion defect, n (%)</td>
<td>0 (0)</td>
<td>12 (100)*</td>
<td>5 (63)*</td>
</tr>
<tr>
<td>Cardiac Ga accumulation, n (%)</td>
<td>0 (0)</td>
<td>4 (33)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Medication use, n (%)</th>
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<tbody>
<tr>
<td>Digitalis</td>
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<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>ARB</td>
</tr>
<tr>
<td>Beta blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Antiarrhythmic agents</td>
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<tr>
<td>Warfarin</td>
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</table>

Data in parenthesis are percentages. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; CS = cardiac sarcoidosis; DCM = dilated cardiomyopathy; HbA1C = glycosylated hemoglobin A1C; other abbreviations as in Table 2.
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-
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
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...
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 homogeneous 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.
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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RECOMMENDED READING


Key Words: cardiac sarcoidosis • dilated cardiomyopathy • 18F-fluorodeoxyglucose–positron emission tomography • heterogeneity.