Localization of myocardial FDG uptake for prognostic risk stratification in corticosteroid-naïve cardiac sarcoidosis

Munehisa Bekki, MD,[a] Nobuhiro Tahara, MD, PhD,[a] Atsuko Tahara, MD,[a] Yoichi Sugiyama, MD, PhD,[a] Shoko Maeda-Ogata, MD,[a] Akihiro Honda, MD, PhD,[a] Sachiyo Igata, MD,[a] Mika Enomoto, MD, PhD,[a] Tatsuyuki Kakuma, MPH, PhD,[b] Hayato Kaida, MD, PhD,[c] Toshi Abe, MD, PhD,[d] and Yoshihiro Fukumoto, MD, PhD[a]

[a] Division of Cardiovascular Medicine, Department of Medicine, Kurume University School of Medicine, Kurume, Japan
[b] Biostatics Center, Kurume University, Kurume, Japan
[c] Department of Radiology, Faculty of Medicine, Kindai University, Osakasayama, Osaka, Japan
[d] Department of Radiology, Kurume University School of Medicine, Kurume, Japan

Received Jun 5, 2020; accepted May 12, 2021
doi:10.1007/s12350-021-02684-w

Background. **The localization of myocardial 18F-fluorodeoxyglucose (FDG) uptake affecting long-term clinical outcomes has not been elucidated in patients with corticosteroid-naïve cardiac sarcoidosis (CS).**

Objectives. **This study sought to investigate the localization of myocardial FDG uptake on positron emission tomography (PET) and myocardial perfusion abnormality to predict adverse events (AEs) for a long-term follow-up in patients with corticosteroid-naïve CS.**

Methods. **Consecutive 90 patients with clinical suspicion of CS who underwent FDG-PET imaging to assess for inflammation were enrolled. AEs were defined as a composite of sustained ventricular tachycardia (VT), heart transplantation, and all-cause death, which were ascertained by medical records, defibrillator interrogation, and telephone interviews.**

Results. **Of 90 patients, 42 patients (mean age 62.9 ± 12.0 years; 76.2% females) were confirmed active cardiac involvement. Over a median follow-up of 4.9 years, 15 patients with CS experienced AEs including 6 sustained ventricular tachycardias (VT) and 9 deaths. Cox proportional-hazards model after adjustment for left ventricular systolic dysfunction revealed that FDG uptake in the right ventricle (RV) or basal anterolateral area of the left ventricle (LV) with myocardial perfusion abnormality was predictive of AEs.**

Conclusions. **FDG uptake in the RV or basal anterolateral area of the LV with myocardial perfusion abnormality provides long-term prognostic risk stratification in patients with corticosteroid-naïve CS. (J Nucl Cardiol 2022;29:2132–44.)**

Key Words: Cardiac sarcoidosis • myocardial inflammation • FDG-PET • adverse events

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12350-021-02684-w.

Reprint requests: Nobuhiro Tahara, MD, PhD, Division of Cardiovascular Medicine, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume830-0011, Japan; *ntahara@med.kurume-u.ac.jp*

1071-3581/$34.00

Abbreviations	
LV	Left ventricular
FDG	18F-fluorodeoxyglucose
PET	Positron emission tomography
CS	Cardiac sarcoidosis
AE	Adverse event
HbA1c	Glycated hemoglobin
FFA	Free fatty acid
ACE	Angiotensin-converting enzyme
BNP	Brain natriuretic peptide
NT-pro-BNP	N-terminal pro-BNP
SUV	Standardized uptake value
SD	Standard deviation
COV	Coefficient of variation
RV	Right ventricular
Tc-MIBI	^{99m}Technetium-methoxy-isobutylisonitrile
SRS	Summed rest score
JMHW	Japanese Ministry of Health and Welfare
ICD	Implantable cardioverter defibrillator
VT	Ventricular tachycardia

See related editorial, pp. 2145–2148

INTRODUCTION

Sarcoidosis is a granulomatous disorder of unknown etiology that may affect many organs. Although it is not usually life-threatening,[1] granulomatous inflammation in the myocardium can lead to lethal arrhythmias, conduction abnormalities, and left ventricular dysfunction, ultimately resulting in heart failure and death.[2] Systemic corticosteroid therapy, which impedes granuloma inflammation, has been utilized for treatment of active sarcoidosis. Also, it is effective against cardiac manifestations of sarcoidosis such as left ventricular (LV) dysfunction, LV remodeling and cardiac death.[3,4] Therefore, the identification of cardiac involvement has important treatment and prognostic implications.[2]

Recently, positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) has become the mainstay of non-invasive imaging modality for the assessment of inflammatory activity in patients with cardiac sarcoidosis (CS). Prior studies have demonstrated that focal or heterogeneous myocardial FDG uptake provides not only diagnostic benefit but also prognostic risk stratification in patients with CS.[5-8] However, approximately 30% of the CS patients received corticosteroid or immunosuppression therapy and a mean follow-up term was less than 3 years in the studies.[6-8] Despite the ability of FDG-PET to contribute for the prognostic risk stratification of CS patients, the association between myocardial FDG uptake findings and clinical outcomes has not been elucidated in patients with corticosteroid-naïve CS. Moreover, these studies have not elucidated the localization of myocardial FDG uptake to contribute a long-term prognostic impact in patients with CS. Therefore, this study sought to investigate the localization of myocardial FDG uptake to predict adverse events (AEs) for a long-term follow-up in patients with corticosteroid-naïve CS.

METHODS

Study Population

This was a prospective, single-center, observational study. Clinical, laboratory, electrocardiographic, echocardiographic, and angiographic evaluations were assessed for diagnosing CS. FDG-PET imaging was performed to confirm the activity of CS. Patients were excluded if they had an incomplete clinical assessment, fasting plasma glucose $\geq$ 200 mg·dL, HbA1c $\geq$ 8%, insulin therapy, corticosteroid and immunosuppressant therapy prior to FDG-PET scan, malignancies, acute infections, obstructive coronary artery disease ($\geq$ 50% stenosis), and history of coronary revascularization and myocardial infarction. AEs were defined as a composite of lethal arrhythmia, heart transplantation, and all-cause death which were ascertained by medical records, defibrillator interrogation, and telephone interviews. Any ventricular arrythmias requiring cardioversion or anti-tachycardia pacing or were defined as lethal arrythmias. Data were adjudicated based on the date of FDG-PET scan. All participants gave informed consent. The Ethical Committee for the Clinical Research of Kurume University approved this study. This trial was registered with the ClinicalTrials.gov clinical trials database (NCT00958087).

Data Collection

Blood was drawn under a fasting condition for evaluating biochemical variables, including serum levels of calcium and phosphate, C-reactive protein, fasting plasma glucose, fasting plasma insulin, glycated hemoglobin (HbA1c), free fatty acid (FFA), creatinine, angiotensin converting enzyme (ACE), and brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP). The value for HbA1c is estimated as a National Glycohemoglobin Standardization Program.[9] Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease study equation modified with a Japanese coefficient.[10] Plasma BNP $>$ 100 pg·mL or serum N-terminal pro-BNP $>$ 400 pg·mL

were classified as an elevated BNP level. Chest X-ray, resting 12-lead electrocardiography, transthoracic echocardiography, myocardial perfusion scan, and FDG-PET were performed in all patients. Left atrial diameter $>$ 40 mm was defined as enlargement. LV ejection fraction $<$ 40% was categorized as a decreased systolic performance. In 31 of the 42 CS patients, right heart catheterizations were performed with a Swan-Ganz catheter in recumbent position. All these evaluations were carried out within 1 month.

FDG-PET Imaging Procedure

FDG-PET scan was performed as described previously.[5] Following a high-fat/low-carbohydrate diet and after at least 18 hour fasting prior to PET scanning to minimize non-inflammatory myocardial FDG uptake, patients received a single intravenous bolus injection of FDG {4.2 MBq (0.12 mCi)·kg body weight} via the antecubital vein. The patients were conveyed to the scanning suite after resting with a comfortable position in a quiet room. 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). An attenuation correction for the PET imaging was performed by a rotating rod of activity in the PET scanner.

FDG-PET Imaging Analysis

PET imaging was scanned for review on a workstation (Sun Blade 2000, Sun Microsystems, Inc., Santa Clara, California). FDG-PET images were evaluated as previously described.[5] In brief, 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 of each patient. We classified the myocardial FDG uptake into 4 quantitative patterns such as none, diffuse, focal, or focal on diffuse, as previously described.[11] Next, reorientation of the axial images to a standard cardiac orientation was approached and then the standardized uptake value (SUV) was determined. The intensity of myocardial FDG uptake was measured as the standardized uptake value (SUV) in 17 LV segments following a scientific statement from the American Heart Association. Analysis of myocardial FDG uptake was performed by recognition of endo- and epi-myocardial borders and subdividing the LV in each segment. We determined SUV of each segment in all 17 segments for each subject and then calculated average of SUV and standard deviation (SD) of SUV for each patient. The coefficient of variation (COV) of SUV among 17 segments in each patient were calculated by dividing SD of SUV by average of SUV as an index of heterogeneity of the FDG uptake in the LV.[5] Also, the SUV values in each segment were divided by average of SUV as a segmental FDG intensity index. A segmental FDG intensity index $>$ 1 was defined as FDG uptake in the LV. In addition, the presence of FDG uptake in the right ventricular (RV) was assessed in each patient.

Myocardial Perfusion Imaging

All patients underwent myocardial perfusion imaging with ^{99m}Technetium-methoxy-isobutylisonitrile (Tc-MIBI). Single photon emission computed tomography image of myocardial perfusion scan at rest was acquired 45 minutes after intravenous injection of Tc-MIBI (740 MBq) following overnight fasting. Regional myocardial perfusion was assessed by quantitative scoring with a 17-segment 5-point model (0-4: 0, normal; 4, absent) using a cardioREPO program (FUJIFILM Toyama Chemical Co., Ltd.). A summed rest score (SRS) was calculated by adding the perfusion scores in each of the 17 segments. Myocardial perfusion and FDG-PET imaging in each segment were subcategorized as follows: normal perfusion and absence of FDG uptake, abnormal perfusion without FDG uptake (matched pattern), abnormal perfusion with FDG uptake (mismatched pattern), and normal perfusion with FDG uptake. An SRS in the segments without FDG uptake (matched segments) and with FDG uptake (mismatched segments) was also evaluated.

Corticosteroid Therapy

After FDG-PET scan, 30 (71.4%) patients were treated with corticosteroid according to the guidelines for sarcoidosis treatment.[12] In brief, the patients were initially treated with 30 mg·day of prednisolone orally. The prednisolone dose was subsequently decreased by 10 mg every 4 weeks until 10 mg·day, and the maintenance dose of 5 to 10 mg·day was achieved according to each physician's decision thereafter. No patients showed reactivation of myocardial granuloma inflammatory activity. Therefore, an increase of corticosteroid dose was not performed, and no patient received immunosuppressive therapy. Although corticosteroid is regarded as the first-line drug for CS, 12 patients with CS did not received corticosteroid therapy because of rejection of the treatment (N = 9), chronic hepatitis C (N = 1), history of uncontrolled diabetes (N = 1), and presence of diabetic cataract and glaucoma (N = 1). One patient discontinued the corticosteroid therapy due to worsening mental status during the follow-up period.

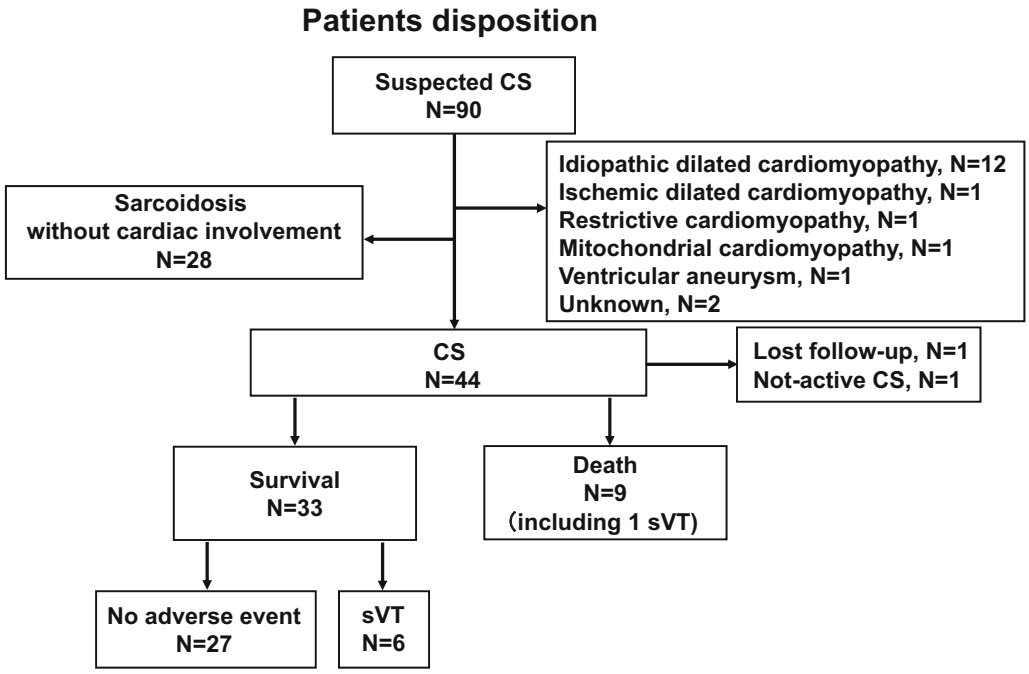

Figure 1. Patients disposition. *CS*, cardiac sarcoidosis; *sVT*, sustained ventricular tachycardia.

Statistical Analysis

Data were presented as mean ± standard deviation or medians with the interquartile range. The Shapiro-Wilk test was performed to evaluate the assumption of normality. Statistical analysis was performed by means of appropriate parametric and non-parametric methods. Categorical variables were compared between groups by the use of χ^2-analysis. Clinical outcomes according to the localization of myocardial FDG uptake are illustrated using Kaplan-Meier survival curves and compared using the log-rank test. Cox proportional-hazards regression analysis was performed after adjustment for LV systolic dysfunction to obtain hazard ratios for AEs. Effect of corticosteroid therapy was estimated as time-dependent covariate. Values of less than 0.05 were considered to be statistically significant. Statistical analyses were performed with the use of the SPSS system (SPSS Inc., Chicago, IL, USA) and SAS software (Release 9.4, SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

Consecutive 90 patients with clinical suspicion of CS were enrolled. Seventy-two of the 90 patients were clinically and/or histologically diagnosed systemic sarcoidosis. The remaining 18 patients without evidence of CS were diagnosed as other cardiomyopathies including idiopathic dilated cardiomyopathy, mitochondrial cardiomyopathy, restrictive cardiomyopathy, or unknown cardiomyopathy with LV aneurysm. Forty-four of the 72 patients with systemic sarcoidosis were confirmed cardiac involvement based on guidelines established by the Japanese Ministry of Health and Welfare (JMHW).[5] One patient was lost follow-up and one was determined an inactive CS by FDG-PET imaging (Figure 1). There were 25 biopsy-proven patients with sarcoidosis, and the remaining 17 patients were clinically diagnosed as extracardiac sarcoidosis with cardiac abnormalities compatible with cardiac sarcoidosis based on JMHW criteria, satisfying 2 or more of 4 the major criteria (N = 13) or 1 in 4 the major criteria and 2 or more of the 5 minor criteria (N = 4). Characteristics of CS patients are presented in Table 1. Advanced atrioventricular block requiring a permanent pacemaker and echocardiographic LV wall asynergy/thinning/aneurysm were frequently noted. A total of 22 patients received a permanent pacemaker or implantable cardioverter defibrillator (ICD) at baseline; pacemaker for atrioventricular block in 19 and ICD for sustained ventricular arrhythmia in 9.

Table 1. Baseline characteristics

Variables [normal value]	Overall	Patients without AEs	Patients with AEs	*P* value
Number	42	27	15	
Age, year	62.9 ± 12.0	61.3 ± 12.8	65.7 ± 9.7	0.268
Female, N (%)	32 (76.2)	20 (74.1)	12 (80.0)	0.957
Body mass index, $kg{\cdot}m^2$	22.2 ± 4.2	22.2 ± 3.4	22.4 ± 5.3	0.866
Cardiothoracic ratio, %	52.1 ± 5.9	51.6 ± 6.6	53.0 ± 4.3	0.483
Serum calcium, [8.8–10.1] mg·dL	9.42 [9.17–9.77]	9.33 [9.10–9.66]	9.58 [9.29–9.83]	0.725
Serum phosphate, [2.7–4.6] mg·dL	3.75 ± 0.39	3.69 ± 0.40	3.85 ± 0.33	0.235
C-reactive protein, [< 0.14] mg·dL	0.08 [0.04–0.21]	0.06 [0.04–0.15]	0.18 [0.04–0.33]	**0.015**
Fasting plasma glucose, mg·dL	95.5 [89.0–102.0]	96.0 [89.5–101.0]	95.0 [88.0–107.0]	0.538
Fating insulin, μU·mL	5.10 [3.60–7.90]	5.10 [3.60–7.40]	6.95 [3.78–10.65]	0.259
Free fatty acid, [140–850] μEq·L	576.5 [368.8–691.0]	524.0 [302.0–794.8]	612.5 [568.3–634.3]	0.900
Hemoglobin A1c, %	5.95 ± 0.62	5.94 ± 0.62	5.96 ± 0.60	0.925
Estimated GFR, $mL{\cdot}min{\cdot}1.73\ m^2$	67.7 ± 22.5	73.9 ± 23.3	58.0 ± 16.7	**0.028**
Uric acid, [3.7–7.0] mg·dL	6.07 ± 1.67	5.58 ± 1.53	6.90 ± 1.55	**0.012**
ACE, [8.3–21.4] IU·L·37°C	19.44 ± 10.13	20.63 ± 11.32	17.29 ± 7.03	0.317
Elevated BNP, N (%)	28 (66.7)	16 (59.3)	12 (80.0)	0.306
Pulmonary involvement, N (%)	25 (59.5)	18 (66.7)	7 (46.7)	0.349
Bilateral hilar lymphadenopathy, N (%)	22 (52.4)	16 (59.3)	6 (40.0)	0.382
Ophthalmic involvement, N (%)	15 (35.7)	11 (40.7)	4 (26.7)	0.565
Cutaneous involvement, N (%)	11 (26.2)	8 (29.6)	3 (20.0)	0.754
Positive biopsy results	25 (59.5)	20 (74.1)	5 (33.3)	< 0.01
Atrial fibrillation, n (%)	5 (11.9)	1 (3.7)	4 (26.7)	0.088
Right bundle branch block, N (%)	12 (28.6)	8 (29.6)	4 (26.7)	0.879
Left bundle branch block, N (%)	4 (9.5)	3 (11.1)	1 (6.7)	0.938
Advanced atrioventricular block, N (%)	25 (59.5)	16 (59.3)	9 (60.0)	0.442
Sustained ventricular tachycardia, N (%)	8 (19.0)	3 (11.1)	5 (33.3)	0.178
Devices implanted prior to initial FDG-PET scan				
Pacemaker, N (%)	19 (45.2)	13 (48.1)	6 (40.0)	0.853
Implantable cardioverter defibrillator, N (%)	9 (21.4)	3 (11.1)	6 (40.0)	0.073
Cardiac resynchronization therapy, N (%)	6 (14.3)	2 (7.4)	4 (26.7)	0.212
Echocardiographic data				
LV local asynergy, N (%)	34 (81.0)	21 (77.8)	13 (86.7)	0.770
LV wall thinning, N (%)	33 (78.6)	20 (74.1)	13 (86.7)	**0.023**
Left atrial diameter, mm	38.5±6.7	36.5±5.7	42.2±7.0	**0.008**
LV end-diastolic diameter, mm	54.3 ± 8.8	52.6 ± 9.0	57.5 ± 7.5	0.090
LV end-systolic diameter, mm	41.8 ± 11.6	39.9 ± 12.1	45.1 ± 9.8	0.170
LV ejection fraction, %	46.5 ± 16.6	48.5 ± 17.1	42.9 ± 15.1	0.303
LV aneurysm	11 (26.2)	6 (22.2)	5 (33.3)	0.676
Anteroseptal wall, N (%)	1 (2.4)	0 (0)	1 (6.7)	0.763
Anterolateral wall, N (%)	5 (11.9)	2 (7.4)	3 (20.0)	0.478
Inferior wall, N (%)	2 (4.8)	1 (3.7)	1 (6.7)	0.746
Posterior wall, N (%)	4 (9.5)	3 (11.1)	1 (6.7)	0.938
Apex wall, N (%)	2 (4.8)	2 (7.4)	0 (0)	0.746

Table 1 continued

Variables [normal value]	Overall	Patients without AEs	Patients with AEs	*P* value
Myocardial perfusion data				
SRS in the entire LV	18.0 (10.5-27.3)	16.0 (5.0-25.0)	23.0 (14.0-29.0)	0.118
SRS in segments without FDG uptake (matched segments)	9.0 (4.0-13.0)	8.0 (3.0-12.0)	9.0 (7.0-13.0)	0.163
SRS in segments with FDG uptake (mismatched segments)	7.5 (3.0-17.0)	6.0 (1.0-17.0)	10.0 (5.0-14.0)	0.081
FDG-PET data				
Coefficient of variation	0.188 ± 0.064	0.181 ± 0.067	0.200 ± 0.056	0.369
Right ventricular uptake, N (%)	15 (35.7)	6 (22.2)	9 (60.0)	**0.014**
Medication use, N (%)				
Digitalis, N (%)	2 (4.8)	0 (0)	2 (13.3)	0.235
Diuretics, N (%)	17 (40.5)	9 (33.3)	8 (53.3)	0.492
β blockers, N (%)	15 (35.7)	10 (37.0)	5 (33.3)	0.924
Calcium channel blockers, N (%)	6 (14.3)	4 (14.8)	2 (13.3)	0.742
ACE inhibitors, N (%)	9 (21.4)	5 (18.5)	4 (26.7)	0.823
Angiotensin receptor blockers, N (%)	16 (38.1)	11 (40.7)	5 (33.3)	0.887
Anti-arrhythmic agents, N (%)	5 (11.9)	2 (7.4)	3 (20.0)	0.478
Anti-coagulant agents, N (%)	10 (23.8)	3 (11.1)	7 (46.7)	**0.027**
Ongoing corticosteroid therapy after FDG-PET scan, N (%)	30 (71.4)	21 (77.8)	9 (60.0)	0.222

Continuous variables are summarized by mean ± SD or median (interquartile range). Categorical variables are summarized by frequency and percentage.
Plasma values of BNP > 100 pg·mL or N-terminal pro-BNP > 400 pg·mL were classified as an elevated BNP level. P values in bold are statistically significant.
AEs, adverse events; *GFR*, glomerular filtration rate; *ACE*, angiotensin-converting enzyme; *BNP*, brain natriuretic peptide; *FDG*, 18F-fluorodeoxyglucose; *PET*, positron emission tomography; *LV*, left ventricular; *SRS*, summed rest score

FDG-PET Imaging and Myocardial Perfusion Imaging

Myocardial FDG uptake was varied in each individual. Thirty-two (76.2%) and 10 (23.8%) patients exhibited the focal and focal on diffuse patterns, respectively. FDG uptake in the LV indicated predominantly heterogeneous with high COV (0.188 ± 0.064), as previously described (5). The intra- and inter-observer variability of SUV measurements were less than 5%. FDG uptake in the RV was seen in 15 patients (35.7 %) (Table 1). Thirty-five (83.3%) patients had significant FDG uptake on whole-body FDG-PET, suggestive of active extracardiac sarcoidosis. An SRS in the entire LV was 18.0 (10.5-27.3). The SRS in the segments without FDG uptake (matched) and with FDG uptake (mismatched) was 9.0 (4.0-13.0) and 7.5 (3.0-17.0), respectively.

Outcomes

During a mean follow-up period of 4.9 years, 15 of 42 patients (35.7%) with CS experienced lethal ventricular tachycardia (VT) and/or all-cause death as the primary endpoint. There were 9 deaths including 1 patient who had a sustained VT event and 6 patients with sustained VTs, but no heart transplantation, during the follow-up period (Figure 1). As shown in Table 1, serum levels of CRP and uric acid in patients with AEs were significantly higher than those without AEs. Age, gender, glycemic state, circulating levels of ACE, cardio-thoracic ratio, LV ejection fraction, LVEF, and the percentage of elevated BNP, advanced AV block, LV wall asynergy/aneurysm, and ongoing corticosteroid therapy after FDG-PET scan were comparable between the 2 groups. The heterogeneity of FDG uptake (COV values) in a 17-segmental model was similar in both

groups. FDG uptake in the RV was more frequent in patients with AEs than those without AEs (Table 1). The survival rate free from AEs was significantly lower in patients with FDG uptake in the RV than those without it (Figure 2). In patients with AEs, segmental FDG intensity indices in the basal inferoseptal (segment 3), basal inferior (segment 4), and mid inferoseptal (segment 9) areas were significantly lower and those in the basal anterolateral (segment 6) area were significantly higher than patients without AEs (Table 2). The survival rate free from AEs was significantly lower in patients with FDG uptake in the basal anterolateral area of the LV than those without it (Figure 3A).

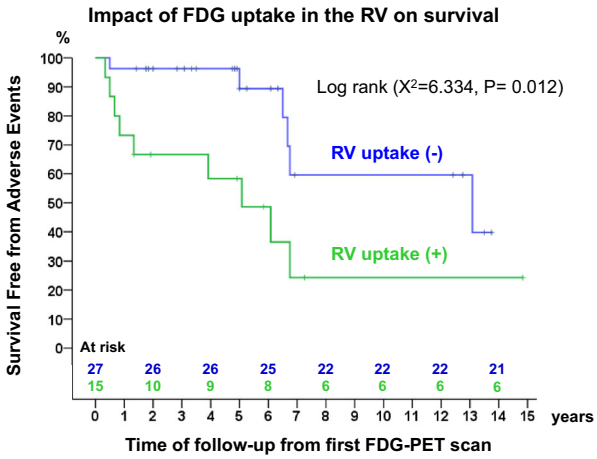

Figure 2. Impact of FDG uptake in the RV on survival. Kaplan-Meier survival curve showing survival free from adverse events stratified by FDG uptake in the RV. *FDG*, 18F-fluorodeoxyglucose; *RV*, right ventricle..

The SRS in segments without FDG uptake (matched segments) was comparable among patients with and without AEs (P = 0.134). Statistically significant difference of the SRS in segments with FDG uptake (mismatched segments) between the 2 groups was not achieved (P = 0.081). There were 14 of 42 (33.3%) patients with CS showing abnormal myocardial perfusion in the basal anterolateral area (segment 6). Focus on the basal anterolateral area, there were 18 patients having normal perfusion without FDG uptake, 16 patients with abnormal perfusion or FDG uptake, and 8 patients having abnormal perfusion with FDG uptake. The presence of both perfusion abnormality and FDG uptake had the strongest association with adverse events (Figures 3B). Tc-MIBI, FDG-PET, and co-registered FDG-PET with Tc-MIBI images distinctly indicated perfusion-metabolism mismatch in the anterolateral area in a cardiac sarcoidosis patient with adverse event (Figure 4). Also, FDG-PET, CT, and co-registered FDG-PET with CT images clearly demonstrated that FDG

Table 2. Segmental FDG intensity index

17 segments	Patients without AEs	Patients with AEs	*P* value
1. Basal anterior area	0.99 ± 0.19	1.07 ± 0.14	0.183
2. Basal anteroseptal area	0.92 ± 0.19	0.86 ± 0.13	0.293
3. Basal inferoseptal area	0.91 ± 0.20	0.73 ± 0.20	**0.006**
4. Basal inferior area	0.93 ± 0.16	0.74 ± 0.18	**0.001**
5. Basal inferolateral area	0.90 ± 0.17	0.93 ± 0.13	0.580
6. Basal anterolateral area	0.96 ± 0.14	1.09 ± 0.17	**0.014**
7. Mid anterior area	1.08 ± 0.18	1.19 ± 0.16	0.068
8. Mid anteroseptal area	1.12 ± 0.21	1.06 ± 0.19	0.360
9. Mid inferoseptal area	1.08 ± 0.18	0.95 ± 0.14	**0.029**
10. Mid inferior area	0.99 ± 0.14	0.96 ± 0.17	0.490
11. Mid inferolateral area	0.99 ± 0.16	0.97 ± 0.15	0.815
12. Mid anterolateral area	1.05 ± 0.17	1.15 ± 0.17	0.089
13. Apical anterior area	1.06 ± 0.26	1.21 ± 0.14	0.053
14. Apical septal area	1.06 ± 0.19	1.04 ± 0.14	0.680
15. Apical inferior area	1.02 ± 0.13	1.07 ± 0.15	0.299
16. Apical lateral area	1.03 ± 0.18	1.08 ± 0.15	0.406
17. Apex area	0.90 ± 0.18	0.92 ± 0.16	0.753

AEs, adverse events; *GFR*, glomerular filtration rate; *ACE*, angiotensin-converting enzyme; *BNP*, brain natriuretic peptide; *FDG*, 18F-fluorodeoxyglucose; *PET*, positron emission tomography; *LV*, left ventricular; *SRS*, summed rest score
P values in bold are statistically significant.

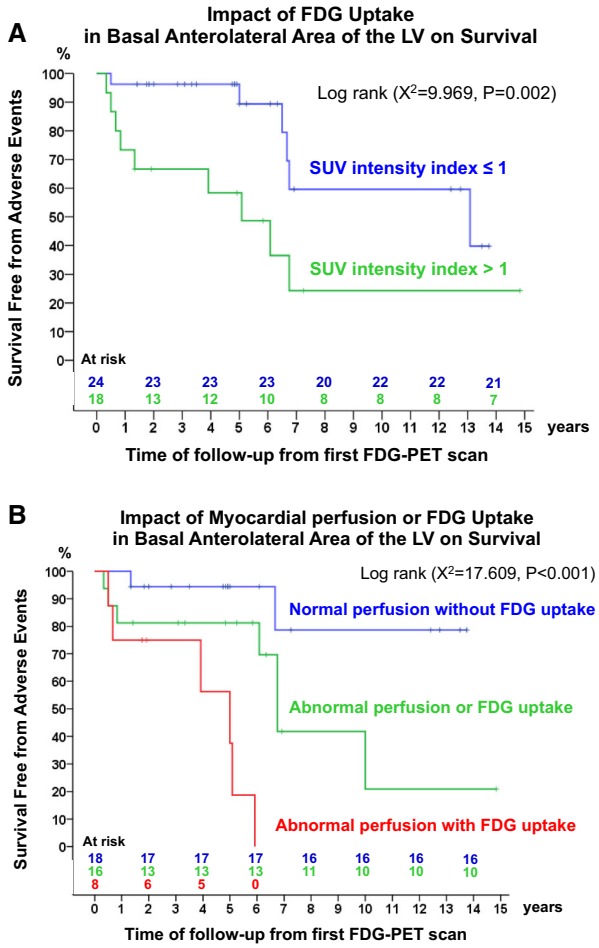

Figure 3. **A** Impact of FDG uptake in basal anterolateral area of the LV on survival. Kaplan-Meier survival curve showing survival free from adverse events stratified by FDG uptake in basal anterolateral area of the LV. **B** Impact of FDG uptake in basal anterolateral area of the LV with myocardial perfusion abnormality on survival. Kaplan-Meier survival curve showing survival free from adverse events stratified by FDG uptake in basal anterolateral area of the LV and/or myocardial perfusion abnormality. *FDG*, 18F-fluorodeoxyglucose; *LV*, left ventricle..

uptake located in the RV and the anterolateral area of the LV in the same patient (Figure 4).

Predictors of AEs

As shown in Table 3, univariate analysis revealed that left atrial enlargement, LV systolic dysfunction, tricuspid regurgitation pressure gradient, use of anti-arrhythmic agents, LV aneurysm in anterolateral and inferior areas, abnormal perfusion in the basal antero-lateral area, and FDG uptake in the RV and basal anterolateral area of the LV (segment 6) were predictive of AEs. Glycemic state, renal function, and steroid therapy after FDG-PET scan were not associated with AEs. COV values and the presence of extracardiac FDG uptake had no significant association with AEs. Cox proportional-hazards regression analysis was performed using robust multivariable adjustments for survival. LV systolic dysfunction was employed as a covariate factor, because LV systolic performance was a potent prognostic factor in CS patients treated with corticosteroid.[3] Multivariate analysis demonstrated that FDG uptake in the RV or basal anterolateral area of the LV with perfusion abnormality were associated with AEs (Table 4).

Effect of Corticosteroid Therapy on FDG-PET

There were 30 patients treated with corticosteroid according to the guidelines for sarcoidosis treatment.[12] In 24 of the 30 patients, serial FDG-PET scans were performed within 1 year after corticosteroid therapy. In a group with AEs, segmental FDG intensity index in the basal anterolateral area was significantly reduced after corticosteroid therapy (1.14 ± 0.10 to 0.94 ± 0.15, P <0.001). On the other hand, corticosteroid therapy for a group without AEs did not alter FDG activity in the basal inferior (0.78 ± 0.13 to 0.84 ± 0.18, P =0.187)/ basal inferoseptal (0.79 ± 0.17 to 0.91 ± 0.28, P =0.259)/ mid inferoseptal (0.89 ± 0.07 to 0.99 ± 0.17, P =0.138) areas.

DISCUSSION

The molecular targeting approach using FDG-PET has been widely utilized for assessment of inflammatory localization and activity in patients with CS. Meta-analysis revealed that the diagnostic accuracy of CS by FDG-PET was approximately 90% sensitivity and 80% specificity.[13] Furthermore, FDG-PET provides a prognostic benefit exceeding diagnostic image analysis in patients with CS.[6-8] However, it has not been elucidated the localization of FDG uptake to contribute a long-term prognostic impact in patients with corticosteroid-naïve CS.

A novel finding from our study is that focal FDG uptake in the RV or basal anterolateral area of the LV with myocardial perfusion abnormality was independently associated with AEs, which provides long-term prognostic risk stratification in patients with corticosteroid-naïve CS.

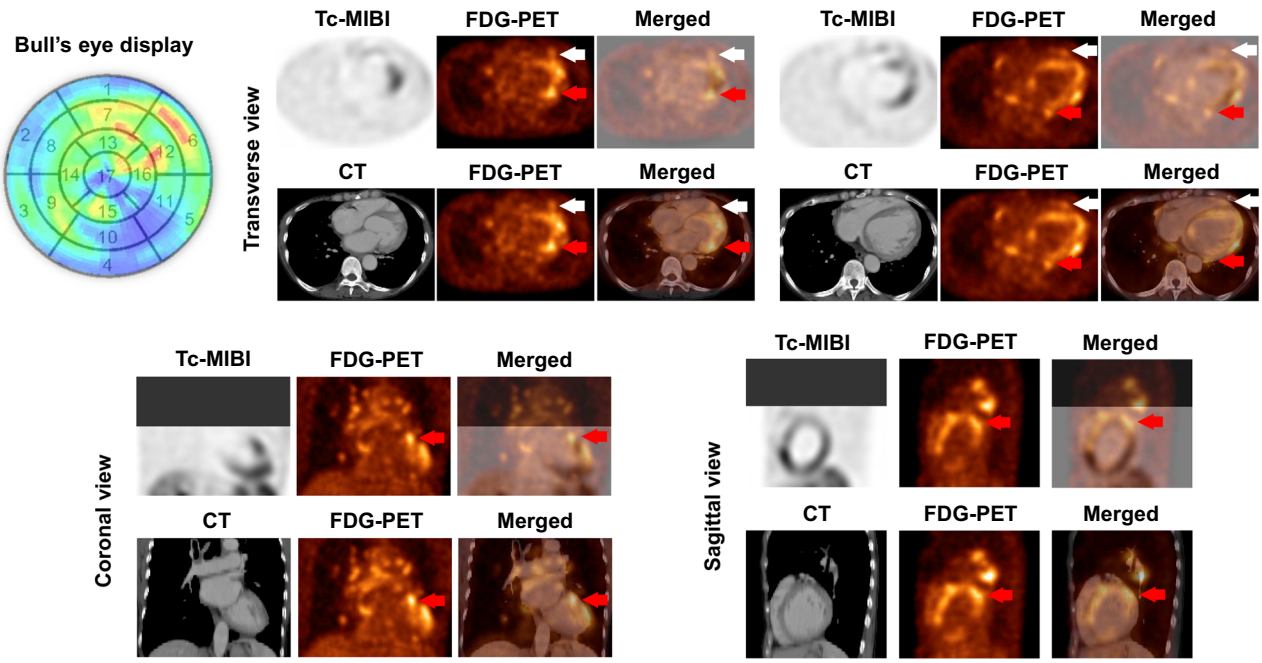

Figure 4. A representative cardiac sarcoidosis case with adverse event. Tc-MIBI, FDG-PET, and co-registered FDG-PET with Tc-MIBI images distinctly indicated perfusion metabolism mismatch in the anterolateral area. Also, FDG-PET, CT, and co-registered FDG-PET with CT images clearly demonstrated that FDG uptake located in the right ventricle (white arrows) and anterolateral area of the left ventricle (red arrows). *Tc-MIBI* ^{99m}Technetium-methoxy-isobutylisonitrile; *FDG* 18F-fluorodeoxyglucose; *PET* positron emission tomography; *CT* computed tomography; *LV* left ventricle.

Evaluation of Myocardial FDG Activity

Active myocardial inflammation is crucial for disease progression in patients with CS. Blankstein et al. have reported that focal FDG uptake along with abnormal myocardial perfusion was associated with AEs in suspected CS patients.[6] The study is limited to categorical results of PET imaging with 82rubidium and FDG. Quantitative analysis of FDG uptake would be more specific than visual interpretations in the assessment of the disease activity. Sperry et al. have demonstrated that quantitative measures of perfusion-metabolism mismatch and heterogeneity of myocardial FDG uptake (COV values) were significantly associated with the composite outcome in patients with suspected CS.[7] The measure of heterogeneity in myocardial glucose uptake may be a pivotal metric signifying a diagnostic and prognostic advantage in this disease process.[7] However, these studies have not elucidated the localization of myocardial FDG uptake to contribute a long-term prognostic impact in patients with corticosteroid-naïve CS. In the present study, the COV values did not indicate the predicts of AEs. The reason could be a different ethnicity and population of patients among the studies. Very recently, Flores et al. have demonstrated that patients with high SUV of FDG in basal segments are at increased risk of cardiac events.[8] However, the localization of myocardial FDG uptake predicting AEs was not shown in detail. Although SUV is the most common parameter widely utilized to measure tracer accumulation in PET imaging, the measurements can be influenced by a variety of biologic and technologic factors.[14,15] Especially in the myocardium, the assessment of FDG activity needs to be further standardized.

In consistent with a study,[6] our study demonstrated that FDG uptake in the RV was associated with AEs in CS patients. Moreover, corticosteroid-naïve CS patients with FDG uptake in the RV had a threefold higher event rate than those without FDG uptake in the RV. A necropsy study reported that approximately 50% of CS patients had involvement in the RV,[16] suggesting FDG uptake in the RV contributes myocardial inflammation. In our 31 (73.8%) patients with CS, hemodynamics was examined by right heart catheterization. As shown in supplementary table, mean pulmonary artery pressure in patients with AEs was significantly higher those without AEs (24.0 ± 7.6 mmHg vs 15.9 ± 3.1 mmHg, $P <$

Table 3. Cox proportional-hazards regression analysis

Variables	HR	95% CI	*P* value
Age	1.02	0.97–1.09	0.408
Gender[a]	1.17	0.33–4.19	0.805
Cardiothoracic ratio	1.02	0.93–1.13	0.629
Atrial fibrillation[a]	3.65	1.09–12.22	**0.035**
Advanced atrioventricular block[a]	1.37	0.47–3.99	0.566
Left atrial enlargement[a]	4.17	1.46–11.89	**0.008**
LV systolic dysfunction[a]	3.46	1.21–9.88	**0.020**
Tricuspid regurgitation pressure gradient	1.09	1.02–1.17	**0.012**
C-reactive protein	1.40	0.84–2.34	0.196
Estimated GFR	0.99	0.97–1.01	0.302
Uric acid	1.28	0.90–1.84	0.170
Hemoglobin A1c	0.74	0.31–1.78	0.499
ACE	0.80	0.49–1.30	0.376
Elevated BNP[a]	2.33	0.66–8.28	0.190
Ongoing corticosteroid therapy after initial FDG-PET scan[a]	2.10	0.71–6.21	0.181
ACE inhibitors[a]	1.40	0.44–4.46	0.574
Anti-arrhythmic agents[a]	5.02	1.24–20.42	**0.024**
Anti-coagulant agents[a]	2.22	0.80–6.18	0.126
LV aneurysm in anteroseptal area[a]	4.66	0.57–38.22	0.152
LV aneurysm in anterolateral area[a]	6.16	1.51–25.12	**0.011**
LV aneurysm in inferior area[a]	5.22	0.60–45.31	0.134
LV aneurysm in posterior area[a]	1.09	0.14–8.54	0.937
FDG uptake in basal inferoseptal area	0.43	0.06–3.34	0.422
FDG uptake in basal inferior area	0.27	0.04–2.05	0.205
FDG uptake in mid inferoseptal area	0.36	0.12–1.07	0.066
FDG uptake in basal anterolateral area	5.72	1.79–18.28	**0.003**
FDG uptake in the right ventricle[a]	2.81	1.01–7.79	**0.047**
SRS in the entire LV	1.04	0.99–1.09	0.122
SRS in segments without FDG uptake (matched segments)	1.02	0.95–1.09	0.565
SRS in segments with FDG uptake (mismatched segments)	1.07	1.00–1.15	0.064
Abnormal perfusion in basal inferoseptal area	2.91	0.97–874	0.057
Abnormal perfusion in basal inferior area	2.36	0.65–8.56	0.191
Abnormal perfusion in mid inferoseptal area	1.03	0.37–2.86	0.957
Abnormal perfusion in basal anterolateral area	2.87	1.03–8.04	**0.044**
Abnormal perfusion with FDG uptake in basal anterolateral area	4.64	1.90–11.36	**0.001**

CI, confidence interval; *AEs*, adverse events; *GFR*, glomerular filtration rate; *ACE*, angiotensin-converting enzyme; *BNP*, brain natriuretic peptide; *FDG*, 18F-fluorodeoxyglucose; *PET*, positron emission tomography; *LV*, left ventricular; *SRS*, summed rest score
[a]No = 0, Yes = 1. Left atrial diameter > 40 mm was defined as enlargement. LV ejection fraction < 40% was categorized as a decreased systolic performance. *P* values in bold are statistically significant

0.001). Our findings suggest that RV overload may also contribute to FDG uptake in the RV besides ongoing active inflammation. Also, our study revealed that myocardial perfusion abnormality with FDG uptake in the basal anterolateral area of the LV provides prognostic risk stratification in patients with corticosteroid-naïve CS. It is unclear why perfusion abnormality with FDG uptake in the basal anterolateral area of the LV was useful for risk stratification in corticosteroid-naïve CS. This is intriguing especially because LV wall aneurysm and perfusion abnormality in the anterolateral area were predictive of AEs in Cox proportional-hazards model (Table 3), although the ventricular septum had the largest percentage of cardiac involvement in patients with CS.[16] Myocardial aneurysm with perfusion

Table 4. Cox proportional-hazards regression analysis adjusted by LV systolic dysfunction

Variables	HR	95% CI	*P* value
Model 1			
LV systolic dysfunction[a]	2.91	1.00–8.48	0.050
FDG uptake in the right ventricle[a]	3.00	1.04–8.65	**0.043**
Model 2			
LV systolic dysfunction[a]	2.06	0.67–6.37	0.208
Perfusion abnormality or FDG uptake[b]	3.66	0.75–17.83	0.109
Perfusion abnormality and FDG uptake[b]	15.04	2.36–95.73	**0.004**

CI, confidence interval; *AEs*, adverse events; *GFR*, glomerular filtration rate; *ACE*, angiotensin-converting enzyme; *BNP*, brain natriuretic peptide; *FDG*, 18F-fluorodeoxyglucose; *PET*, positron emission tomography; *LV*, left ventricular; *SRS*, summed rest score
[a]No = 0, Yes = 1
[b]Normal perfusion and absence of FDG uptake = 0, Perfusion abnormality or FDG uptake = 1, Perfusion abnormality and FDG uptake = 2
P values in bold are statistically significant.

abnormality and active inflammation has a chance of being an arrhythmogenic substrate.

Normal Variant Activity

Lateral wall is a common region for normal variant activity of FDG.[17] To be convinced of the importance of myocardial FDG localization, we evaluated myocardial FDG uptake in a cohort of age- and gender-matched healthy control subjects (N = 23, mean age 63.3 ± 4.9 years; 13 females). Segmental FDG intensity index in the basal inferolateral and mid inferolateral areas in control subjects was greater than those in CS patients with AEs (basal inferolateral area: Controls 1.11 ± 0.18 vs CS with AEs 0.93 ± 0.13, $P = 0.002$; mid inferolateral area: Controls 1.23 ± 0.21 vs CS with AEs 0.97 ± 0.15, $P < 0.001$). FDG activity in the mid anterolateral and apical lateral areas was comparable between the 2 groups (mid anterolateral area: Controls 1.19 ± 0.22 vs CS with AEs 1.15 ± 0.17, $P = 0.534$; apical lateral area: Controls 1.07 ± 0.16 vs CS with AEs 1.08 ± 0.15, $P = 0.908$). On the other hand, segmental FDG intensity index in the basal anterolateral area in CS patients with AEs was higher than those in control subjects (CS with AEs 1.09 ± 0.17 vs Controls 0.98 ± 0.11, $P = 0.027$). These findings suggest that FDG activity in the basal anterolateral area of the LV is not associated with the activity in other regions and may be evident to determine the proper prognostic value in the present study.

Corticosteroid Therapy

Corticosteroid is a key treatment for systemic sarcoidosis, if disease activity is high. Especially in CS, corticosteroid can prevent the progression of LV impairment, and improve LV remodeling and prognosis.[3,4] However, some CS patients present fatal ventricular tachyarrhythmias regardless of the corticosteroid therapy. In such patients, specific treatments for the arrhythmias including anti-arrhythmic agents and implantation of ICD are needed. In the present study, effect of corticosteroid therapy was estimated as time-dependent covariate, because the hazard of developing AEs was expected to be different between patients with and without corticosteroid therapy.[3]

In this study, corticosteroid therapy for CS patients with AEs reduced segmental FDG intensity index in the basal anterolateral area with FDG uptake, but did not affect in the basal inferior, basal inferoseptal, and mid inferoseptal areas without FDG uptake for those without AEs. These corticosteroid responses might explain the regional differences of FDG activity in the initial FDG-PET imaging. Segmental FDG intensity index could be utilized to identify high-risk patients with residual FDG uptake after anti-inflammatory treatment. Larger trials are needed to establish whether therapeutic response measurements can predict AEs in patients with CS.

NEW KNOWLEDGE GAINED

In a prospective study of patients with corticosteroid-naïve CS, the presence of myocardial FDG uptake has a potentially important role in evaluating prognostic risk stratification over a mean follow-up of approximately 5 years. Physician awareness of myocardial inflammation for clinical outcomes in patients with CS could be increased.

Limitations

Significant limitations should be considered when interpreting our results. First, our study represents a relatively small number and single-center experience. Single-center data limit the generalizability of our findings by its selection bias. With regard to selection bias, we cannot exclude the possibility of unknown confounders. However, this is a first cohort study to investigate the predicts of AEs in patients with corticosteroid-naïve CS undergoing FDG-PET scan. Additionally, quantitative assessment of myocardial FDG uptake using various PET devices in a multicenter study might provoke a lack of standardized interpretations. Second, we cannot deny that non-inflammatory myocardial uptake might present and interfere with signal quantification of myocardial FDG uptake even with optimal preparations for FDG-PET scan, because a reliable technique for diagnosis of myocardial inflammation does not currently exist. A novel tracer such as a somatostatin receptor subtype-2-binding PET tracer might efficiently detect the myocardial inflammation without concern for non-inflammatory myocardial FDG uptake in patients with CS.[18] Third, misdiagnosis of cardiac sarcoidosis could be occurred without any histologic proof. Meeting both JMHW and Heart Rhythm Society criteria[19] would enhance the robustness of our cohort, but was not associated with increased AEs. Fourth, atrial fibrillation and left bundle branch block could affect the regional glucose utilization.[20,21] Fifth, only cardiac deaths should be included in such survival analysis evaluating myocardial FDG distribution. However, the small sample size does not allow such analyses. Future investigations with a larger study size are needed to address the issues. Sixth, we cannot exclude that cardiac and respiratory motion artifacts can affect myocardial FDG uptake and finally our findings. Although cardiac gating is feasible to overcome the issue, the respiratory motion artifact cannot be resolved by gating approach.

CONCLUSIONS

In conclusion, the localization of myocardial inflammation in the RV or basal anterolateral area of the LV with myocardial perfusion abnormality was associated with the development of AEs. Our study indicates that the presence of myocardial FDG uptake (a biomarker of ongoing inflammation) and perfusion abnormality has a potentially important role in evaluating prognostic risk stratification in patients with corticosteroid-naïve CS.

Acknowledgements

We thank Mami Nakayama, Miho Nakao-Kogure, Katsue Shiramizu, Miyuki Nishikata, Yuri Nishino, Makiko Kiyohiro (Kurume University), and Kouichi Nitta (Hitachi Ltd., Tokyo, Japan) for their technical assistance.

Disclosures

All authors have nothing to disclose regarding the current study.

References

1. Reich JM. Mortality of intrathoracic sarcoidosis in referral vs population-based settings: Influence of stage, ethnicity, and corticosteroid therapy. Chest 2002; 121:32-39
2. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. J Am Coll Cardiol 2016; 68:411-21
3. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, et al; 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
4. Chiu CZ, Nakatani S, Zhang G, Tachibana T, Ohmori F, Yamagishi M et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. Am J Cardiol 2005; 95:143-46
5. Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H et al. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc Imaging 2010; 3:1219-28
6. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol 2014; 63:329-36
7. Sperry BW, Tamarappoo BK, Oldan JD, Javed O, Culver DA, Brunken R et al. Prognostic impact of extent, severity, and heterogeneity of abnormalities on 18F-FDG PET scans for suspected cardiac sarcoidosis. JACC Cardiovasc Imaging 2018; 11:336-45
8. Flores RJ, Flaherty KR, Jin Z, Bokhari S. The prognostic value of quantitating and localizing F-18 FDG uptake in cardiac sarcoidosis. J Nucl Cardiol 2020; 27:2003-10
9. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, et al; IFCC Working Group on HbA1c Standardization. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004;50:166-74
10. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Collaborators developing the Japanese equation for estimated GFR Revised equations for estimated. GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53:982-92
11. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M 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
12. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and

by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160:736-55
13. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: A systematic review and metaanalysis including the Ontario experience. J Nucl Med 2012; 53:241-48
14. Haga Y, Ishii K, Suzuki T. N-glycosylation is critical for the stability and intracellular trafficking of glucose transporter GLUT4. J Biol Chem 2011; 286:31320-27
15. Adams MC, Turkington TG, Wilson JM, Wong TZ. A systematic review of the factors affecting accuracy of SUV measurements. AJR Am J Roentgenol 2010; 195:310-20
16. Tavora F, Cresswell N, Li L, Ripple M, Solomon C, Burke A. Comparison of necropsy findings in patients with sarcoidosis dying suddenly from cardiac sarcoidosis versus dying suddenly from other causes. Am J Cardiol 2009; 104:571-77
17. Gropler RJ, Siegel BA, Lee KJ, Moerlein SM, Perry DJ, Bergmann SR et al. Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. J Nucl Med 1990; 31:1749-56
18. Lapa C, Reiter T, Kircher M, Schirbel A, Werner RA, Pelzer T et al. Somatostatin receptor based PET/CT in patients with the suspicion of cardiac sarcoidosis: An initial comparison to cardiac MRI. Oncotarget 2016; 7:77807-14
19. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014; 11:1305-23
20. Wu YW, Naya M, Tsukamoto T, Komatsu H, Morita K, Yoshinaga K 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
21. Lindner O, Vogt J, Baller D, Kammeier A, Wielepp P, Holzinger J 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