Detection of Active Inflammation Status Around Ventricular Aneurysms in Patients With Cardiac Sarcoidosis

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Background: Little is known about the pattern of isotope accumulation in the heart on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography in patients with cardiac sarcoidosis (CS) complicated by ventricular aneurysm (VA).

Methods and Results: We prospectively enrolled 82 consecutive patients with CS; 54 patients with active CS (presence of abnormal 18F-FDG accumulation in the heart) were subdivided into VA (n=17) and non-VA groups (n=37). Strong 18F-FDG accumulation surrounding the VA and its disappearance in the VA center was observed in all patients with VA, probably because of scar formation at the VA. Peak standardized uptake value was higher around the VA than in the VA center (5.1±2.1 vs. 2.2±0.6, P=0.0003) and the VA center had no 18F-FDG accumulation (VA center: 2.2±0.6 vs. control area: 2.1±0.6, P=0.37). On the other hand, in non-VA patients with LV wall thinning (n=28), 18F-FDG accumulation was significantly high, even in the area of LV wall thinning (LV wall thinning area: 3.1±0.8 vs. control area: 2.0±0.6, P=0.00002).

Conclusions: A pattern of strong 18F-FDG accumulation surrounding the VA and its disappearance in the VA center might be characteristic in patients with CS complicated by VA. Careful attention to FDG uptake would further elucidate CS pathophysiology and aid in the early treatment of VA.

Key Words: 18F-fluorodeoxyglucose positron emission tomography; Cardiac sarcoidosis; Ventricular aneurysm

Sarcoidosis is a multisystem disorder of unknown etiology and pathophysiology.1–3 Cardiac sarcoidosis (CS) can cause atrioventricular block, lethal ventricular tachycardia, congestive heart failure, and sudden cardiac death, leading to a poor prognosis.4 In addition, ventricular aneurysms (VAs) are a well-known manifestation in CS.5–8 However, little is known about the mechanism of VA formation in patients with CS. Using data from 42 autopsy cases of fatal CS, Matsui et al described macroscopic and histological classifications of myocardial lesions in patients with advanced CS; the macroscopic categories comprised spotty, conglomerate-band-like, and dendrite patterns, and the histological categories comprised exudative, granuloma, combined, and fibrotic types. Lesions with inflammatory damage and fibrotic change in the heart vary from focal to multifocal or extensive lesions with severe fibrotic change, leading to left ventricular (LV) and right ventricular (RV) remodeling. VA is a characteristic complication in patients with CS and is accompanied by scar formation.14 Thus, we hypothesized that, with regard to the mechanism of VA formation in CS, inflammatory damage and replacement fibrosis occur in the center of strong inflammatory lesions and cause bulging of the local ventricular wall.

In recent years, advancements in diagnostic imaging modalities, such as cardiac magnetic resonance (CMR), 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT), and echocardiography, have improved the accuracy of the diagnosis of CS.10,11 The presence of late gadolinium enhancement (LGE) on CMR suggests the presence of fibrosis and scar formation in the heart of patients with CS.12,13 18F-FDG-PET is a glucose analog that is useful in differentiating between normal and active inflammatory macrophages and is essential to diagnose active CS.13,14 However, the pattern of isotope accumulation in the heart of patients with CS complicated by VA is unknown. Here, to test our hypothesis regarding the mechanism of VA formation, we examined the accumulation of 18F-FDG in the VA and other areas in the heart of patients with CS using 18F-FDG-PET/CT imaging.

Received April 17, 2019; revised manuscript received August 27, 2019; accepted August 29, 2019; J-STAGE Advance Publication released online October 19, 2019

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imaging in combination with other imaging modalities.

Methods

Patients and Study Design

The study protocol is shown in Figure 1: 82 consecutive patients diagnosed with CS (New York Heart Association [NYHA] class I or II) between June 2008 and October 2018 were enrolled in this prospective study. CS was diagnosed according to the criteria of the Japanese Ministry of Health and Welfare (JMHW) guidelines, revised in 2006. Additionally, CS was defined as active (n=54) or non-active (n=28) according to the presence or absence of abnormal 18F-FDG accumulation in the heart on 18F-FDG-PET/CT. Patients with active CS were categorized into VA (n=17) and non-VA (n=37) groups. The non-VA group was composed of subgroups with LV wall thinning (n=28) and without LV wall thinning (n=9).

The Institutional Review Board of Yamaguchi University Hospital approved this study (no. H19-87) on April 16, 2008, and all patients provided written informed consent before participating in the study.

Standard Clinical Evaluations

All patients underwent 12-lead ECG, echocardiography, and 18F-FDG-PET/CT (and/or 67Ga scintigraphy). All patients were monitored by Holter ECG and/or by an ECG monitor (Nihon Kohden, Tokyo) or an implantable device (implantable cardioverter-defibrillator, cardiac resynchronization therapy defibrillator, or dual-chamber pacemaker). Of the 54 patients with active CS, 40 underwent endomyocardial biopsy.

Evaluation of VA and LV Wall Thinning in Patients With Active CS

VA was defined as a bulging of the ventricular wall at end-diastole on one of the following imaging tests: transthoracic echocardiography, contrast left ventriculography, and magnetic resonance imaging. All patients underwent 2D transthoracic echocardiography. Echocardiographic images (2D standard views) were acquired and interpreted by 2 independent blinded observers. The regional wall motion abnormality (R WMA) score on echocardiography was assessed as the wall motion score, based on a standard 17-segment model, with numerical scores for contractile function as follows: 1, normal contraction; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis.
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The quantitative analysis of 18F-FDG uptake in the lesion was based on the maximum standardized uptake value (SUVmax) per focus, as described previously.19–21 The intensity of myocardial FDG uptake was quantified by measuring the SUV in all 17 segments, in accordance with the Scientific Statement from American Heart Association. Analysis of myocardial FDG uptake was performed by recognizing the endomyocardial and epicardial borders and by subdividing the LV in each segment. We determined the SUV of all 17 segments for scar formation.

Evaluation of Inflammatory Activity Using 18F-FDG-PET/CT

All patients underwent 18F-FDG-PET/CT scanning using a 16-slice hybrid PET/CT scanner (Gemini GXL16, Philips Medical System), with whole-body and cardiac acquisitions as described previously.19–21 The quantitative analysis of 18F-FDG uptake in the lesion was based on the maximum standardized uptake value (SUVmax) per focus, as described previously.19–21 The intensity of myocardial FDG uptake was quantified by measuring the SUV in all 17 segments, in accordance with the Scientific Statement from American Heart Association. Analysis of myocardial FDG uptake was performed by recognizing the endomyocardial and epicardial borders and by subdividing the LV in each segment. We determined the SUV of all 17 segments for scar formation.

Table 1. Characteristics of Patients With Active Cardiac Sarcoidosis in the Non-VA and VA Groups

| Characteristic                          | Total (n=54) | non-VA (n=37) | VA (n=17) | P value |
|----------------------------------------|-------------|---------------|-----------|---------|
| Age (years)                            | 63.6±13.0   | 63.1±13.4     | 64.8±12.3 | 0.668   |
| BSA (kg/m²)                            | 1.53±0.17   | 1.56±0.19     | 1.47±0.12 | 0.061   |
| Sex (F/M)                              | 36/18       | 23/14         | 13/4      | 0.300   |
| NYHA class                             | 1.57±0.50   | 1.49±0.51     | 1.76±0.44 | 0.057   |
| LVDd (mm)                              | 55.4±7.7    | 54.0±7.8      | 58.6±6.4  | 0.022   |
| LVEF (%)                               | 41.7±12.5   | 44.1±12.9     | 36.6±10.0 | 0.032   |
| RWMA score                             | 2.22±0.69   | 2.05±0.71     | 2.59±0.50 | 0.005   |
| SBP (mmHg)                             | 109.6±17.9  | 111.6±18.0    | 105.2±17.3| 0.439   |
| HR (bpm)                               | 69.3±8.3    | 69.3±8.2      | 69.1±8.7  | 0.940   |
| BNP (pg/mL)                            | 151.8±161.1 | 128.3±148.5   | 202.8±179.6| 0.099   |
| U-8O-HdG (mg/mg-Cr)                    | 15.1±7.0    | 15.5±7.8      | 14.1±5.0  | 0.661   |
| UA (mg/dL)                             | 5.42±2.20   | 5.28±1.88     | 5.77±2.85 | 0.510   |
| CRP (mg/dL)                            | 0.15±0.18   | 0.15±0.18     | 0.16±0.18 | 0.955   |
| TNF-α (pg/mL)                          | 1.81±1.21   | 1.77±1.16     | 1.89±1.38 | 0.866   |
| IL-6 (pg/mL)                           | 3.09±2.03   | 3.18±2.25     | 2.88±1.54 | 0.953   |
| ACE (U/L)                              | 13.07±6.54  | 13.38±7.01    | 12.37±5.49| 0.795   |
| T-bil (mg/dL)                          | 0.58±0.20   | 0.60±0.21     | 0.52±0.16 | 0.090   |
| BUN (mg/dL)                            | 18.15±6.11  | 17.59±5.71    | 19.35±6.94| 0.318   |
| eGFR (mL/min/1.73 m²)                  | 62.66±23.53 | 64.87±22.54   | 57.85±25.58| 0.230   |
| TnT (ng/mL)                            | 0.018±0.013 | 0.016±0.011   | 0.021±0.016| 0.404   |
| SUVmax                                 | 5.87±2.21   | 6.12±2.16     | 5.39±2.28 | 0.193   |
| Comorbidity                            |             |               |           |         |
| HT                                     | 22/54       | 16/37         | 6/17      | 0.581   |
| DL                                     | 21/54       | 14/37         | 7/17      | 0.815   |
| DM                                     | 10/54       | 7/37          | 3/17      | 0.615   |
| Advanced AVB                           | 14/54       | 11/37         | 3/17      | 0.277   |
| Sustained VT                           | 12/54       | 8/37          | 4/17      | 0.567   |
| Coronary artery disease                | 2/54        | 2/37          | 0/17      | 0.841   |
| Treatment                              |             |               |           |         |
| ACEI/ARB                               | 38/54       | 24/37         | 14/17     | 0.191   |
| β-blocker                              | 38/54       | 25/37         | 13/17     | 0.506   |
| Amiodarone                             | 16/54       | 12/37         | 4/17      | 0.506   |
| Loop diuretics                         | 20/54       | 11/37         | 9/17      | 0.101   |
| Aldosterone antagonist                 | 14/54       | 8/37          | 6/17      | 0.230   |
| Statin                                 | 12/54       | 8/37          | 4/17      | 0.567   |
| Steroid                                | 12/54       | 7/37          | 5/17      | 0.300   |
| ICD/CRT-D                              | 26/54       | 17/37         | 9/17      | 0.633   |

The normal range of U-8-OHdG was defined as <10 ng/mg-Cr, in accordance with a previous study.21 ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; AVB, atriocentric block; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy defibrillator; CS, cardiac sarcoidosis; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IL-6, interleukin-6; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RWMA, regional wall motion abnormality; SBP, systolic blood pressure; SUVmax, maximum standardized uptake value; T-bil, total bilirubin; TNF-α, tumor necrosis factor-α; TnT, troponin T; U-8-OHdG, urinary 8-hydroxy-2’-deoxyguanosine; UA, uric acid; VA, ventricular aneurysm; VT, ventricular tachycardia.
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18F-FDG accumulation around the VA in the heart (Figure 2). Specifically, we first reconstituted the 18F-FDG-PET/CT image corresponding to the CMR image and/or echocardiogram and/or left ventriculogram that showed the VA (Figure 2A, B). We then drew the vertical axis from each subject and then calculated the peak SUV for each patient as a polar map.

In patients with active CS and VA, 18F-FDG-PET/CT scans were reconstituted using a workstation (syngo MBF, Siemens, Germany) in order to examine the pattern of 18F-FDG accumulation around the VA in the heart (Figure 2). Specifically, we first reconstituted the 18F-FDG-PET/CT image corresponding to the CMR image and/or echocardiogram and/or left ventriculogram that showed the VA (Figure 2A, B). We then drew the vertical axis from each subject and then calculated the peak SUV for each patient as a polar map.

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| No. | Age (years) | Sex | NYHA | ECG/Holter findings | LVEF | Basal wall thinning | Location of VA | 18F-FDG PET/CT | CMR | Perfusion defect on scintigraphy or PET | CAG | Diagnosis |
|-----|-------------|-----|------|---------------------|------|---------------------|---------------|----------------|-----|----------------------------------------|-----|-----------|
| 1   | 56          | F   | 1    | SVT                 | 37   | +                   | Pos wall      | Ant, Pos, Inf wall, IVS, RV | Skin, liver, bone, lymph node | LGE: IVS, apex, Inf, Pos*, Lat wall | ND | Intact 1 3 |
| 2   | 80          | F   | 2    | CLBBB, PVC          | 25   | +                   | Inf wall      | IVS, Lat, Ant, Inf wall | Lymph node | LGE: Inf* wall | ND | Intact 2 2 |
| 3   | 63          | F   | 2    | NSVT                | 38   | +                   | IVS           | Lymph node | ND | ND | Intact 2 2 |
| 4   | 36          | M   | 1    | SVT                 | 22   | –                   | IVS, Inf wall | – | LGE: IVS*, Inf wall | ND | Intact 1 4 |
| 5   | 67          | F   | 2    | NSVT                | 40   | +                   | IVS           | Ant, Pos wall, IVS, RV, RA, LA | Lymph node | LGE: IVS*, Inf wall, apex | IVS*, Ant wall | Intact 3 4 |
| 6   | 48          | F   | 2    | NSVT, cAVB          | 43   | –                   | Pos wall      | IVS, Apex, Lat, Pos wall | – | LGE: Pos* wall | Pos* wall | Intact 1 3 |
| 7   | 67          | F   | 2    | NSVT, cAVB          | 45   | +                   | IVS           | Liver, lymph node | ND | ND | Intact 3 1 |
| 8   | 67          | F   | 2    | PVC                 | 35   | –                   | IVS           | Lymph node | ND | IVS | Intact 1 3 |
| 9   | 77          | M   | 2    | SVT                 | 32   | +                   | Lat wall      | IVS, Inf wall | – | ND | Pos, Lat* wall | Intact 1 3 |
| 10  | 48          | F   | 1    | PVC, abnormal O wave| 40   | –                   | Apex          | IVS, Inf, Pos, Lat, Ant wall | – | LGE: Ant wall, apex | ND | Intact 1 4 |
| 11  | 71          | M   | 2    | PVC                 | 28   | –                   | Inf wall      | IVS, Inf, Ant wall | Lymph node | LGE: Inf*, Pos wall | Inf* wall | Intact 1 4 |
| 12  | 68          | F   | 2    | SVT                 | 52   | +                   | Ant wall      | IVS, Lat, Pos, Ant wall | – | LGE: IVS, Ant*, Inf wall | Ant* wall | Intact 1 4 |
| 13  | 73          | F   | 2    | NSVT, cAVB          | 30   | –                   | Apex          | IVS, Pos wall | – | ND | ND | Intact 1 3 |
| 14  | 69          | M   | 2    | SVT, cAVB           | 40   | +                   | Inf wall      | IVS, Lat, Ant wall | Lymph node | LGE: Inf*, Pos, Lat wall, IVS | ND | Intact 2 4 |
| 15  | 57          | F   | 1    | NSVT, cAVB          | 60   | +                   | IVS           | Lymph node | LGE: IVS*, Ant wall, RV | IVS* | Intact 2 3 |
| 16  | 73          | F   | 2    | SVT, cAVB           | 30   | –                   | Apex          | IVS, Ant, Lat, Inf wall | – | ND | Apex*, Lat wall | Intact 2 3 |
| 17  | 82          | F   | 2    | SVT                 | 25   | –                   | IVS           | ND | ND | ND | Intact 1 3 |

*The location of the VA. Ant, anterior; CAG, coronary angiography; cAVB, complete atioventricular block; CLBBB, complete left bundle branch block; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; CT, computed tomography; ECG, electrocardiogram; 18F-FDG, 18F-fluorodeoxyglucose; Inf, inferior; IVS, interventricular septum; Lat, lateral; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; ND, not determined; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PET, positron emission tomography; Pos, posterior; PVC, premature ventricular contraction; RV, right ventricle; SVT, sustained ventricular tachycardia; VA, ventricular aneurysm.
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of 2 cardiologists and 1 radiologist blinded to the subject’s treatment assignment and other clinical information. We classified the 18F-FDG-PET/CT images into 4 patterns according to the uptake, as previously described: none, diffuse, focal, and focal on diffuse. We defined the focal and focal on diffuse patterns as active CS.

We performed CMR imaging to confirm the presence of the VA. We then performed 18F-FDG-PET/CT imaging and compared the results with those of the CMR and echocardiography. We reconstructed the 18F-FDG-PET/CT images and made short-axis views at the center of the VA (Figure 2C), and made short-axis views at the top, mid, and base of the VA (Figure 2D). In non-VA patients with active CS and LV wall thinning, we first reconstituted the 18F-FDG-PET/CT image corresponding to the LV long-axis image of the echocardiogram or CMR image and then made LV short-axis images.

18F-FDG-PET/CT images were visually evaluated for the presence of FDG uptake in the heart, with the agreement of 2 cardiologists and 1 radiologist blinded to the subject’s treatment assignment and other clinical information. We classified the 18F-FDG-PET/CT images into 4 patterns according to the uptake, as previously described: none, diffuse, focal, and focal on diffuse. We defined the “focal” and “focal on diffuse” patterns as active CS.

Figure 3. Reconstructed 18F-FDG-PET/CT images of the VA. Case 1: CMR shows the VA at the posterobasal LV wall. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 2: Echocardiography shows the VA at the inferobasal LV wall. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 3: Echocardiography shows the VA at the mid-IVS. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 4: Echocardiography shows the VA at the buetal IVS. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 5: Echocardiography shows the VA at the mid-IVS. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 6: Contrast left ventriculography shows the VA at the posterobasal LV wall. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 7: Echocardiography shows the VA at the LV apex. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 8: Contrast left ventriculography shows the VA at the mid-inferior LV wall. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 9: CMR shows the VA at the anterobasal LV wall. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 10: Echocardiography shows the VA at the apex. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 11: Echocardiography shows the VA at the inferobasal LV wall. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 12: Echocardiography shows the VA at the LV apex. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 13: Echocardiography shows the VA at the LV apex. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 14: Echocardiography shows the VA at the LV apex. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Case 15: Echocardiography shows the VA at the LV apex. The reconstructed PET/CT image shows incomplete-donut-shaped accumulation around the VA. Red arrows indicate the VA. IVS, interventricular septum. Other abbreviations as in Figures 1, 2.
Measurement of Urinary 8-Hydroxy-2'-Deoxyguanosine (U-8-OHdG) and Other Neurohumoral/Inflammatory Factors

U-8-OHdG concentrations, a marker of oxidative stress, were measured using an enzyme-linked immunosorbent assay kit (Japan Institute for the Control of Aging, Fukuroi, Japan) with anti-8-OHdG antibody (N45.1), as described previously.19–22 Other neurohormonal and inflammatory factors were measured as described previously.19–22

Steroid Therapy for Active CS

Corticosteroid treatment (prednisolone) was initiated according to existing Japanese protocols as follows: 30 mg/day for 4 weeks with gradual tapering of the dose to 5–10 mg every other day over 6 months to establish the minimal effective dose.

Statistical Analysis

Data are expressed as mean±standard deviation, or as frequency counts. For continuous variables, intergroup differences were evaluated using the Mann-Whitney U and Wilcoxon signed-rank tests. Wilcoxon signed-rank test with Bonferroni correction was used for comparison among 4 groups. For categorical variables, such as sex and treatment, intergroup differences were evaluated using the χ² test. All analyses were performed using SPSS version 19 (SPSS, Inc., Chicago, IL, USA). P<0.05 or P<0.0083 after Bonferroni correction was considered to indicate statistical significance.
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Figure 5. Inflammation and scar formation in the VA formation process. (A) The course of VA formation in a patient with CS (Case 5). A 67-year-old female presented with palpitation (non-sustained ventricular tachycardia) and systolic heart failure of unknown etiology. She was diagnosed with active CS by the presence of focal $^{18}$F-FDG accumulation in the heart and LGE on CMR, and corticosteroid treatment was started. In this case, $^{18}$F-FDG-PET/CT and echocardiography were followed up. At baseline, there is no VA in the LV on echocardiography, but strong $^{18}$F-FDG accumulation is observed at the IVS. Five months later, thinning and bulging of the IVS wall are observed (Supplementary Movie) with a sustained increase of $^{18}$F-FDG accumulation around the VA and a decrease of $^{18}$F-FDG accumulation at the central core. As Case 5 was refractory to steroid therapy, high-dose prednisolone (0.5 mg/kg/day) was re-administered and a maintenance dose was prescribed. At both 17 months later and 5 years later, after the steroid therapy, $^{18}$F-FDG accumulation is weaker at the VA lesion. Additionally, $^{13}$N-NH$_3$-PET shows a myocardial perfusion defect at the VA, suggesting scar formation at the VA. (B) Autopsy case of CS complicated by VA (Case 9). A 77-year-old male presented with sustained ventricular tachycardia. He was diagnosed with CS from echocardiography, $^{18}$F-FDG PET/CT, and $^{201}$Tl scintigraphy findings. He subsequently died from an exacerbation of heart failure. Echocardiography (long-axis view) shows the VA at the LV lateral wall (arrow). $^{18}$F-FDG-PET/CT (short-axis view) shows accumulation at the anterior and lateral LV walls. At autopsy the VA was visible at the LV lateral wall (arrow). Histological images show severe fibrosis, especially at the VA in the LV lateral wall. (C) Proposed mechanism of VA formation. First, strong focal inflammation occurs in the heart, scar formation and aneurysmal changes then occur, finally resulting in extensive fibrosis and remodeling. LGE, late gadolinium enhancement. Other abbreviations as in Figures 1–3.
Evaluation of Inflammation Using 18F-FDG-PET/CT

The 18F-FDG-PET/CT image reconstruction process with serial short-axis views of the VA is shown in Figure 2. 18F-FDG-PET/CT images for each patient in the VA group are shown in Figure 3. In all patients, 18F-FDG accumulation was observed around the VA, with low accumulation at the center of the VA; 4 patients showed donut-shaped accumulation (Cases 5, 8, 10 and 14), and 13 patients showed incomplete-donut-shaped accumulation (Cases 1–4, 6, 7, 9, 11–13, 15, 16 and 17). Peak SUV around the VA was higher than in the center of the VA (around VA; 5.1 ± 2.1 vs. center of VA; 2.2 ± 0.6, P=0.0003) and as high as that in the other focal regions (other than VA) with the highest level of 18F-FDG accumulation (around VA; 5.1 ± 2.1 vs. other than VA; 4.9 ± 2.6, P=0.21) (Figure 4A,B). There was no difference in the SUV value between the center of the VA and the minimum SUV in all of the heart (control; 2.1 ± 0.6 vs. center of VA; 2.2 ± 0.6, P=0.37) (Figure 4A,B).

In non-VA patients with LV wall thinning (n=28), 18F-FDG accumulation was significantly high, even in the area of LV thinning (control: 2.0±0.6 vs. LV wall thinning: 3.1±0.8, P=0.00002). However, 18F-FDG accumulation was higher outside of the LV wall thinning area than in the center of the LV wall thinning area (outside of LV wall thinning: 6.3±2.9 vs. LV wall thinning: 3.1±0.8, P=0.000004) (Figure 4C,D). However, there was no difference in the peak SUV value between the non-VA and VA groups (P=0.193).

Results

Baseline Patient Characteristics

Among the 28 patients with non-active CS, 4 had VAs. In contrast, the 54 patients with active CS comprised 17 patients with VAs (VA group) and 37 patients without VAs (non-VA group). Table 1 shows the patients' characteristics in the VA and non-VA groups; including comorbidities and treatments, there were no significant intergroup differences in the evaluated characteristics except for LVDd, LVEF, and the RWMA score. Table 2 shows the clinical data for each patient in the VA group. VAs were detected on echocardiography at the interventricular septum (IVS) in 7 patients (Cases 3–5, 7, 8, 15 and 17), inferior wall in 3 patients (Cases 2, 11 and 14), apex in 3 patients (Cases 10, 13 and 16), posterior wall in 2 patient (Cases 1 and 6), anterior wall in 1 patient (Case 12), and lateral wall in 1 patient (Case 9). Of the 17 patients with VAs, 10 underwent contrast-enhanced cardiac MRI and LGE was observed in the area of the heart corresponding to the VA in all cases. Similarly, 7/17 patients underwent 201TI scintigraphy or 13N-NH3-PET to detect perfusion defects; a perfusion defect was observed in the area of the heart corresponding to the VA in all cases. Coronary angiography showed intact arteries in all patients with VAs, and significant stenosis of the coronary artery in 2/37 non-VA patients.

Figure 6. Representative cases of attenuation of inflammation via steroid therapy. (A) After steroid therapy, 18F-FDG accumulation around the VA is attenuated on 18F-FDG-PET/CT (Cases 1, 5, 8). (B) Comparison of the SUVmax before and after steroid therapy in 7 patients with active CS and VA. The average SUVmax after steroid therapy was significantly reduced compared with before steroid therapy. SUVmax, maximum standardized uptake. Other abbreviations as in Figures 1, 2.
Time Course of VA Formation

In Case 5, 18F-FDG-PET/CT and echocardiography were followed up to evaluate the process of VA formation in CS. At baseline, there was no VA in the left ventricle on echocardiography, but strong 18F-FDG accumulation (SUVmax, 10.41) was observed at the IVS (Figure 5A). At 5 months after baseline, thinning and bulging of the IVS wall were observed, and 18F-FDG accumulation was diminished in the central core (Figure 5A). At 17 months later, and 5 years after, 18F-FDG accumulation (SUVmax, 4.21) had gradually weakened at the VA lesion area (Figure 5A). Additionally, 11N-NH3-PET showed a myocardial perfusion defect at the VA, suggesting scar formation (Figure 5A). In Case 9, echocardiography showed the VA at the lateral LV wall, and 18F-FDG-PET/CT showed 18F-FDG accumulation around the VA (Figure 5B). Furthermore, autopsy cardiac tissue showed replacement fibrosis and scar formation at the site of the VA (Figure 5B).

Effect of Steroid Therapy on VAs

Of 54 active CS patients, 36 underwent steroid therapy. In the VA group (n=17), 12 patients received corticosteroid treatment, at baseline or after assessment of cardiac disease, but 5 patients did not undergo corticosteroid treatment because of advanced age, active hepatitis, poor control of diabetes mellitus, or the patient’s rejection of steroid therapy. A total of 7 patients (Cases 1, 5, 7, 8, 14, 15, 16) underwent 18F-FDG-PET/CT before and after steroid therapy (Figure 6A). Before steroid administration, 18F-FDG accumulation was observed around the VA in all patients. After treatment, 18F-FDG accumulation was attenuated in 5 patients (Cases 7, 8, 14, 15, 16), and had almost disappeared in 2 patients (Cases 1, 5). The average SUVmax after steroid therapy was significantly reduced compared with before steroid therapy (n=7; before treatment: 7.0±2.2 vs. after treatment: 5.0±2.2; P=0.018) (Figure 6B).

Discussion

Importantly, the present study results suggested that a pattern of strong 18F-FDG accumulation around the VA and its disappearance in the VA center might be characteristic of patients with CS and VA, and may indicate progressive scar formation in the center of the VA. This conclusion is supported by the following findings. All 17 patients with CS complicated by VA showed strong 18F-FDG accumulation around the VA on 18F-FDG-PET/CT, accompanied by wall thinning, dyskinesis on echocardiography, and/or LGE on MRI, which suggests the presence of scar formation in the aneurysm. 18F-FDG uptake in the area surrounding the aneurysm was significantly higher than that of the scar tissue in the aneurysm, and it was as high as that for 18F-FDG-positive myocardium in other areas that comprised viable myocardium, judging from the wall motion score, and should be considered as inflammatory regions. These results suggested that 18F-FDG uptake in the area surrounding the aneurysm truly reflects higher 18F-FDG uptake (i.e., very active inflammation status). Interestingly, in one of the 17 patients in the VA group (Case 5), strong 18F-FDG accumulation (SUVmax, 10.41) was observed before aneurysm formation, which then decreased centrally, with progression of the VA and scar formation. In addition, the characteristic 18F-FDG accumulation around the VA was weaker after steroid treatment compared with before steroid treatment, suggesting that the accumulation of 18F-FDG in the heart was caused by inflammation.

There are many case reports of CS complicated by VA,5–9 and the incidence rate is reported as 10–40%.4 Consistent with this, the incidence rate of VAs in the present study was 31% in patients with active CS (defined as the presence of 18F-FDG accumulation in the heart). Furthermore, VAs are commonly observed in the anterolateral and septal walls in patients with CS.8 However, in our 17 cases of CS and VA, the location of the VA was widespread (IVS, anterior, inferior, posterior, and lateral walls; and apex). Therefore, careful attention should be paid to the presence of ventricular wall bulging at end-diastole on imaging tests, including transthoracic echocardiography, contrast left ventriculography, and magnetic resonance imaging. Furthermore, simultaneous 18F-FDG-PET/CT imaging would help further elucidate the characteristic features and pathophysiology of VAs in CS, as well as aid in the early treatment of the VA.

We compared the locations of VA and LV wall thinning, and the distribution and intensity of 18F-FDG accumulation in the heart between patients with VA (n=17) and non-VA with LV wall thinning (n=28) in order to clarify the pathophysiological meaning of the VA (n=17) (Supplementary Methods). The incidental rate of an isolated LV base was significantly greater in non-VA patients with wall thinning than in VA patients (Supplementary Figure 1), suggesting that inflammation expanding over the LV base tends to cause VA formation. Importantly, there was no 18F-FDG accumulation at the center of the VA in the VA group (Figure 4A,B), and 18F-FDG accumulation was significantly elevated at the LV thinning area in non-VA patients with LV wall thinning (Figure 4C,D). Furthermore, the RWMA score, a marker of myocardial fibrosis, was higher in the VA group than in the non-VA patients with LV wall thinning, suggesting that myocardial fibrosis was stronger in the VA group than in the non-VA group (Table 1). Interestingly, multivariate analysis showed that the RWMA score was the only independent determinant factor for VA (Supplementary Table), with a cutoff value of 2.56 to identify patients with VA from the receiver-operating characteristic curve analysis (Supplementary Figure 2). These results suggested that strong myocardial fibrosis as a result of inflammation might contribute to VA formation. The lack of 18F-FDG accumulation in the center of the VA may be a result of transmural fibrosis or severe fibrosis after inflammation, while the 18F-FDG accumulation that still remained in the LV thinning area, despite a decrease in its accumulation, may be attributable to residual myocardium or a small inflammatory area. Taken together, transmural and severe fibrosis caused by inflammation may be important processes in VA formation.

Generally, inflammation in CS initially occurs at the LV base, and then spreads continuously or focally.4 LV wall thinning at locations other than the LV base was significantly associated with VA in the univariate, but not the multivariate analysis (Supplementary Table). Inflammation limited to the LV base may not cause VA formation, whereas the spread of inflammation over or beyond the LV base may cause VA formation because of widespread inflammation and strong fibrosis. Additional studies are needed to clarify the relationship between VA formation and its location.

Based on previous work and the present study results, the following underlying mechanism of VA formation in patients with CS is proposed. Inflammation induces auto-
immune abnormalities, myocardial oxidative stress, and intracellular Ca\(^{2+}\) overload,\(^{23-28}\) which in turn causes apoptosis and necrosis of cardiomyocytes and replacement fibrosis. Furthermore, VA formation occurs with the addition of hemodynamic wall stress. Although it is difficult to quantitatively evaluate the extent of inflammation on \(^{18}\)F-FDG-PET/CT because of its temporal and spatial properties, the portion of the heart where \(^{18}\)F-FDG accumulates may progress to scar formation and/or VA formation, as suggested by the data for Case 5. However, there were no differences between the VA and non-VA groups in measures of inflammatory activity, such as SUVmax, interleukin-6, tumor necrosis factor-\(\alpha\), C-reactive protein, and U-8-OHdG. As the time from CS onset differed among the patients with CS, it may be difficult to compare the inflammatory activity. The process of VA formation can be summarized as follows: first, inflammation occurs; second, replacement fibrosis and scar formation occurs; and ultimately, extensive remodeling occurs, if the inflammation is ongoing.

In the present study, we observed a decrease in inflammatory activity after corticosteroid treatment compared with before treatment (Figure 6). Recently, it was reported that patients with CS complicated by VA have worse clinical outcomes than those with CS uncomplicated by VA.\(^9\) Therefore, corticosteroid intervention is necessary at an early stage of CS.

**Study Limitations**

First, the cohort of CS patients with VA was small. However, this study is the first to report on the pattern of isotope accumulation in the heart on \(^{18}\)F-FDG-PET/CT in patients with active CS and VA, compared with that in patients with active CS without VA, and the present study results aid in elucidating the process and mechanism of VA formation. Second, although patients were diagnosed with CS according to JMHW criteria, those without abnormal isotope accumulation in the heart on \(^{18}\)F-FDG-PET were defined as having non-active CS. As such patients may not truly have CS, their data were excluded from the calculation of the incidence of VA.

**Conclusions**

The present study results suggested that a pattern of strong \(^{18}\)F-FDG accumulation around the VA and its disappearance in the VA center might be characteristic in patients with CS complicated by VA, and may indicate progressive scar formation in the center of the VA. Careful attention to \(^{18}\)F-FDG accumulation around the VA in patients with CS and VA would further elucidate the pathophysiology of CS, as well as aid in the early treatment of VA.

**Acknowledgments**

We thank the patients and families for their participation in this study. We thank all the staff at Yamaguchi University Hospital for their contributions to this study.

**Disclosures**

There are no relationships with industry or conflicts of interest to report.

**Sources of Funding**

This work was funded by grants-in-aid for scientific research from the Ministry of Education in Japan (Grant No. 18K08039 to S.K.) and grants from the Takeda Science Foundation in Japan to S.K. and SENSIN Medical Research Foundation to S.K.

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**Supplementary Files**

**Supplementary Movie.** Case 5 underwent echocardiography in series. Apical 4-chamber-view imaging shows the process of VA formation at the mid IVS and left ventricular remodeling, with hypokinesis of the IVS at baseline, VA formation with wall thinning at the IVS 5 months after baseline, and an extensive decrease in IVS wall motion 17 months and 5 years after baseline. IVS, interventricular septum; VA, ventricular aneurysm.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-19-0248