Clinical Value of Patlak Ki Images Extracted From Dynamic ^{18}F -FDG PET/CT For Evaluation of The Relationships Between Disease Activity and Clinical Events in Cardiac Sarcoidosis

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Abstract

Background: Cardiac sarcoidosis (CS) has a poor prognosis because of frequent complication of atrioventricular block, ventricular tachycardia and congestive heart failure. Qualitative or quantitative ^{18}F -FDG PET/CT has been used for diagnosing or assessing the disease activity of CS. However, the association between ^{18}F -FDG myocardial uptake and clinical presentations in CS has not yet been clarified, and it is unknown if Patlak Ki images (Ki images) extracted from dynamic ^{18}F -FDG-PET/CT are useful for evaluating the disease activity or clinical events in CS patients. In this context, this study was performed to investigate the usefulness of SUV and Patlak Ki images extracted from dynamic ^{18}F -FDG-PET/CT for evaluating the risk of severe clinical events (SCEs) in CS.

Methods: The SUV and Ki myocardial images were generated from 30 dynamic ^{18}F -FDG-PET/CT scans of 21 CS patients including those with cardiac dysfunction and arrhythmic events. SUV parameters and Ki parameters (Ki max, Ki mean, Ki volume) were measured for positive myocardial lesions. The Mann–Whitney U-test or Fisher's exact test was used appropriately to assess differences between quantitative variables or compare categorical data. The association between each quantitative parameter and presence of SCEs was analyzed by logistic regression analysis.

Results: The SUV and Ki images both were rated as positive in 19 scans and negative in 11 scans with the same incidence of SCEs which were significantly higher in positive than negative scans [cardiac dysfunction: 78.9% (15/19) vs. 27.2% (3/11), $p=0.009$; arrhythmic events: 65.5% (10/19) vs. 0% (0/11), $p=0.004$].

In 19 positive scans, neither SUV nor Ki parameters were significantly different between scans of patients with cardiac dysfunction ($n=15$) and those without ($n=4$) ($p>0.05$, each), whereas the three Ki parameters were significantly higher in scans for patients with arrhythmic events ($n=10$) than in those without ($n=9$) ($p<0.05$, each). Logistic regression analysis showed that the Ki volume alone was significantly associated with the risk of arrhythmic events (Odds ratio: 1.11, $p=0.047$).

Conclusion: Patlak Ki images may add value to SUV images for evaluating the risk of SCEs in CS patients.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Clinical manifestations of cardiac involvement are estimated to occur in 5% of patients with sarcoidosis, but the prevalence at autopsy has ranged from 25–58% [1, 2]. Cardiac sarcoidosis (CS) has a poor prognosis because of frequent complication of atrioventricular block (AVB), ventricular tachycardia (VT) and congestive heart failure [3–5]. To prevent adverse outcomes, an accurate and early diagnosis is essential so that anti-inflammatory therapy can be initiated [6, 7].

Glucose metabolic activity can be shown by measuring ^{18}F -fluorodeoxyglucose (^{18}F -FDG) uptake during positron emission tomography (PET)/computed tomography (CT) for not only oncological but also inflammatory disorders [8, 9]. Qualitative or quantitative ^{18}F -FDG PET/CT has been used for diagnosing or assessing the disease activity of CS [10, 11]. However, the association between ^{18}F -FDG myocardial uptake and clinical presentations in CS has not yet been clarified.

The Patlak slope, Ki, which represents the rate of ^{18}F -FDG uptake is a quantitative index of ^{18}F -FDG metabolism. Dynamic imaging is required to calculate the Ki, and an arterial input function must be measured and a lesion time-activity curve constructed [12, 13]. Although a good correlation has been reported between the standardized uptake value (SUV) and Ki, they are not equivalent [14]. The SUV measures the total activity in the lesion, and includes both metabolized ^{18}F -FDG and unmetabolized ^{18}F -FDG (unphosphorylated ^{18}F -FDG) in the blood, intercellular spaces, and/or cells. Patlak analysis separates these two components, and the Patlak slope is determined only by metabolized ^{18}F -FDG [15]. Thus, measurements of Ki might contribute to assessments of CS disease activity. However, to our knowledge, only one report has investigated dynamic ^{18}F -FDG-PET/CT images for diagnosis of CS [16], and it is unknown if Patlak Ki images (Ki images) extracted from dynamic ^{18}F -FDG-PET/CT are useful for evaluating the disease activity or clinical events in CS patients.

The study aim was to investigate the usefulness of SUV and Patlak Ki images for evaluating the risk of severe clinical events (SCEs) in CS patients.

Materials And Methods

Study design and patient selection

This retrospective study was approved by institutional review board, which waived the requirement for informed consent. From April 2019 to January 2020, ^{18}F -FDG-PET/CT was performed in 24 consecutive patients for suspected CS or known CS, and their clinical records were reviewed to identify patients for analysis. The inclusion criterion was diagnosis of CS according to the Japanese Society of Sarcoidosis and Other Granulomatous Disorders guidelines [17]. Patients with a history or coexistence of other cardiac disorders were excluded.

Two patients were excluded because of hypertrophic cardiomyopathy and one for insufficient evidence of CS. Finally, 21 CS patients were enrolled (14 women and seven men; mean $\pm$ standard deviation [SD], age 61 years $\pm$ 11; age range, 37–76 years). Eight patients underwent ^{18}F -FDG PET/CT scans before steroid treatment, and two of them underwent scans at the 6-months follow-up after initiation of steroid treatment. The remaining 13 patients

received steroid therapy, and seven of them underwent follow-up scans during the study period. Consequently, 21 patients had a total of 30 ^{18}F -FDG-PET/CT scans.

Imaging protocols

All patients were instructed to fast for ≥ 18 h before PET/CT, which resulted in a mean plasma glucose level of 107 mg/dl (range, 68–154 mg/dl) immediately before ^{18}F -FDG intravenous injection.

All ^{18}F -FDG PET/CT examinations were performed on a Discovery MI PET/CT (GE Healthcare, Milwaukee, WI). First, low-dose CT covering the entire heart was performed (slice thickness, 3.75 mm; pitch, 1.375 mm; 120 keV; auto mA [40–100 mA depending on patient body mass]; reconstructed matrix size, 512×512) with the transaxial and cranio-caudal field of view (FOV) of 70 cm and 20 cm that was used for attenuation correction of the PET images. Thereafter, ^{18}F -FDG ($227 \text{ MBq} \pm 28$ [range, 179–286 MBq]) was injected, and dynamic PET (single-bed) images covering the same cranio-caudal FOV as that of the above CT were acquired with the following PET frames. The acquisition began at the injection, with scan times of 10s/frame for the first 2 min, 3 min/frame for the next one frame, and 5 min/frame thereafter for a total of 60 min.

Generation of the Patlak Ki and SUV static images

To determine the ^{18}F -FDG kinetic parameters within the lesion, a linear approximation of the mathematical representation of the standard two-compartmental model with irreversible trapping was used according to Patlak analysis [12]. From $C_i(t_k)$, the ^{18}F -FDG activity concentration in the lesion ($\text{Bq mL}_{\text{tissue}}^{-1}$) at a given time t_k after injection, the analytical solution of the two-compartment model is given as:

$$C_i(t_k) = K_i \int_0^{t_k} C_p(t) dt + V_p C_p(t_k)$$

where $C_p(t_k)$ represents the ^{18}F -FDG activity concentration in blood plasma at time t_k ($\text{Bq mL}_{\text{blood}}^{-1}$) and V_p is the total blood distribution volume (i.e, the unmetabolized fraction of ^{18}F -FDG in blood and interstitial volume).

The compartmental transfer rates, k_1 (from blood to cell), k_2 (from cell to blood), and k_3 (from ^{18}F -FDG to ^{18}F -FDG-6-phosphate), were used to calculate K_i , the net influx rate, as follows:

$$K_i = (k_1 \times k_3) / (k_2 + k_3).$$

The transfer rate k_4 from ^{18}F -FDG-6-phosphate to ^{18}F -FDG is negligible because the Patlak analysis assumes unidirectional uptake of ^{18}F -FDG ($k_4=0$). The K_i unit is mL/g/min .

In this study, the non-invasive plasma arterial input function estimation technique using a Patlak graphical plot method was applied to calculate the K_i for generating the K_i images [12]. We characterized the input function by using blood time-activity curves derived from PET image. A region of interest was drawn in the ascending aorta to determine the arterial input function, and the Patlak analysis was performed over the period from 10 to 60 min after injection during a steady state. The data were reconstructed by using a matrix size of 128×128 with a Bayesian penalized likelihood (BPL) reconstruction algorithm [18] (with point spread function incorporated as a default setting (Q.Clear, GE Healthcare, Milwaukee, WI) with a beta value (penalization factor) of 700 and transaxial FOV of 50 cm as the K_i image.

The PET frames acquired 53–60 mins after ^{18}F -FDG injection were corrected for attenuation by using the CT data, and these attenuation corrected images were reconstructed by using a matrix size of 128×128 with BPL reconstruction algorithm with a beta value of 350 and transaxial FOV of 50 cm as the static SUV image (SUV image).

Image analysis

Two nuclear medicine radiologists, who were aware of the study purpose but blinded to clinical information, interpreted the SUV and K_i images together to reach in a consensus. First, the radiologists visually scored the ^{18}F -FDG myocardial uptake by using a five-point scale for each SUV image as follows, 0, no visible uptake; 1, ^{18}F -FDG uptake lower than; 2, similar to; 3, somewhat higher than; and 4, noticeably higher than hepatic uptake [19]. To determine the disease activity of CS, scores of 0–1 and 2–4 were assigned as negative and positive, respectively. Thereafter, they visually assessed each K_i image as negative (myocardial visibility was lower than or similar to that of liver) or positive (myocardial visibility was higher than that of liver).

The following quantitative parameters were obtained in the interpreted positive (visible) myocardium; the maximum SUV (SUVmax), mean SUV (SUVmean), cardiac metabolic volume (CMV), and cardiac metabolic activity (CMA) for SUV images, and maximum and mean K_i values (K_i max and K_i mean) and K_i volume for K_i images. The third nuclear medicine radiologist set the volumes of interest (VOIs) separately for SUV images and K_i images. He placed the VOIs manually on a suitable reference fused axial image and then defined the cranio-caudal and mediolateral extent encompassing the entire positive myocardial lesion, excluding any avid extracardiac structures, to obtain SUVmax and K_i max. He next set a 40% threshold of SUVmax [20] or of K_i max to automatically delineate a VOI equal to or greater than the 40% threshold of SUVmax or K_i max to calculate the SUVmean, CMV, and CMA or K_i mean and K_i volume, respectively. The CMA was defined as the SUVmean $\times$ CMV. Workstations (Xeleris or Advantage Windows Workstation 4.5; GE Healthcare) calculated the SUVmax, SUVmean, CMV, CMA and the K_i max, K_i mean and K_i volumes automatically.

Ascertainment of SCEs

Echocardiography was performed within 1 month of the ^{18}F -FDG-PET/CT (mean $\pm$ SD, 6 days $\pm$ 8; range, -26 to +26 days), and the echocardiography report was used as the reference standard for cardiac function. Cardiac dysfunction was defined as a left ventricular ejection fraction (LVEF) $<50\%$ [21]. Patients were also assessed to determine if arrhythmic events, including sustained VT or AVB were presented within 1 month of the ^{18}F -FDG-PET/CT (mean $\pm$ SD, 8 days $\pm$ 8; range, -24 to +31 days). AVB was characterized as either second- or third-degree AVB or trifascicular block documented on 12-lead or Holter echocardiography [21, 22].

Statistical analysis

The incidence of each SCE was compared between the positive and negative images by using Fisher's exact test. Quantitative variables were compared between scans with and without SCEs by using the Mann–Whitney U test. The Spearman rank correlation was used to assess the relationship between two quantitative variables. Receiver operating characteristic (ROC) curve analysis was performed to examine the diagnostic performance of each parameter between the presence and absence of SCEs, and the Youden index was used to determine the best cutoff point for each parameter [23]. The statistical significance of differences between the areas under the ROC curves (AUCs) were analyzed by using the DeLong method [24]. The association between each parameter and presence of SCEs was analyzed by logistic regression analysis.

Data are presented as medians and interquartile ranges (IQRs). A value of $p < 0.05$ was considered to be indicative of statistical significance, and all P values were two-tailed. MedCalc Statistical Software (MedCalc Software Ltd, Acaciaaan 22, 8400 Ostend, Belgium) was used for the statistical analyses.

Results

SCEs at ^{18}F -FDG PET/CT scan

The median LVEF was 36.4% (IQR: 32.6–55.1%; range: 23.5–79.9%). Cardiac dysfunction and normal cardiac function were observed by obtaining 18 and 12 ^{18}F -FDG PET/CT scans, respectively. Of the 18 scans of patients with cardiac dysfunction, six and twelve were performed before treatment and under treatment, respectively. On the other hand, of the 12 scans of patients with normal cardiac function, two and 10 were performed before treatment and under treatment, respectively. Arrhythmic events were observed for 10 ^{18}F -FDG PET/CT scans, and seven and three scans were performed before treatment and under treatment, respectively. On the other hand, of 20 scans of patients without arrhythmic events, one and 19 were performed before treatment and under treatment, respectively.

Relationship between visual findings of SUV or Ki images and SCEs (Table 1)

The SUV and Ki images were both rated as positive in 19 scans and negative in 11 scans, respectively, and for both the median LVEF was significantly lower in the positive images than in the negative images (positive vs. negative: 32.9% vs. 56.3%, $p = 0.001$). The rate of cardiac dysfunction was significantly higher in the positive images than in the negative images (positive vs. negative: 78.9% [15/19] vs. 27.2% [3/11], $p = 0.009$). The arrhythmic events were only observed in the positive images, and the rate of arrhythmic events was significantly higher in the positive images than in the negative images (positive vs. negative: 65.5% [10/19] vs. 0% [0/11], $p = 0.004$).

Correlations between quantitative parameters

Quantitative analyses were performed in each positive SUV or Ki image ($n = 19$). Significant positive correlations were observed between SUVmax and Ki max ($\rho = 0.90$, $p < 0.001$), between SUVmean and Ki mean ($\rho = 0.88$, $p < 0.001$) and between CMV and Ki volume ($\rho = 0.66$, $p = 0.002$), respectively.

Relationship between SUV or Ki parameters and SCEs (Table 2)

No significant differences between the scans of patients with cardiac dysfunction ($n = 15$) and normal cardiac function ($n = 4$) in the SUVmax, SUVmean, and CMV were found ($p > 0.05$, each). The median CMA was higher in cardiac dysfunction than in normal cardiac function, but this difference was not significant ($p = 0.057$). No significant correlations were observed between any of the SUV parameters and LVEF (SUVmax, $\rho = 0.018$, $p = 0.94$; SUVmean, $\rho = 0.037$, $p = 0.88$; CMV, $\rho = -0.13$, $p = 0.60$; CMA, $\rho = -0.16$, $p = 0.52$, respectively).

The median SUVmean was significantly higher in the presence of arrhythmic events ($n = 10$) than in the absence of arrhythmic events ($n = 9$) ($p = 0.041$). The median SUVmax, CMA and CMV were higher in the presence of arrhythmic events than in the absence of arrhythmic events, but these differences were not significant ($p = 0.060$, 0.066, 0.060, respectively).

No significant differences in the Ki max, Ki mean and Ki volume between cardiac dysfunction and normal cardiac function were found ($p > 0.05$, each). No significant correlations were observed between each Ki parameter and LVEF (Ki max, $\rho = 0.21$, $p = 0.39$; Ki mean, $\rho = 0.24$, $p = 0.32$; Ki volume, $\rho = -0.16$, $p = 0.52$).

All three Ki parameters were significantly higher in the presence of arrhythmic events than in the absence of arrhythmic events (Ki max, 222.0×10^{-3} ml/g/min vs. 106.2×10^{-3} ml/g/min, $p = 0.041$; Ki mean, 146.4×10^{-3} ml/g/min vs. 55.2×10^{-3} ml/g/min, $p = 0.038$; Ki volume, 79.5 cm^3 vs. 14.6 cm^3 , $p = 0.003$, respectively).

Parameters for assessing the risk of SCEs (Tables 3 and 4)

The AUCs for the ability to assess the risk of the cardiac dysfunction were 0.80 for CMV ($p = 0.031$) and 0.82 for CMA ($p = 0.020$) (Table 3). The logistic analysis revealed that no parameters were significantly associated with cardiac dysfunction ($p > 0.05$, each) (Table 4).

The AUCs for the ability to assess the risk of arrhythmic events were 0.76 for SUVmax ($p = 0.034$), 0.78 for SUVmean ($p = 0.018$), 0.75 for CMV ($p = 0.031$), 0.76 for CMA ($p = 0.034$), 0.78 for Ki max ($p = 0.014$), 0.79 for Ki mean ($p = 0.009$) and 0.90 for Ki volume ($p < 0.001$) (Table 3). The specificity was 100% for all parameters. The sensitivity ranged from 50.0% (SUVmax, CMV, CMA) to 90.0% (Ki volume), and the accuracy ranged from 73.7% (SUVmax, CMV, CMA) to 94.7% (Ki volume) (Table 3). No significant differences in AUC were found among any of the parameters ($p > 0.05$, each). The logistic analysis revealed that Ki volume was the only parameter significantly associated with arrhythmic events (Odds ratio: 1.11, 95% confidence interval: 1.01–1.23, $p = 0.047$) (Table 4).

The SUV and Ki images of the representative positive and negative scans of CS were shown in Figs. 1–3.

Discussion

SUV images for evaluating the risk of SCEs

Previous studies have reported that ^{18}F -FDG SUV images have been important in the assessment of CS [10, 11]. A recent meta-analysis reported a sensitivity of 89% and specificity of 78% for detection of CS on ^{18}F -FDG SUV images [25]. The relationships between ^{67}Ga scintigraphy or ^{18}F -FDG SUV images and clinical events in CS patients have been reported previously [26–28]. Banba et al. [26] performed ^{67}Ga scintigraphy in 15 CS patients, and gallium uptake has been documented in 80% of AVB patients. McArdle et al. [27] examined the degree of ^{18}F -FDG myocardial uptake assessed by SUV parameters, and higher SUVmax and SUVmean were observed in CS patients with VT than in those with AVB or who were clinically silent. Ahmadian et al. [28] reported that CMA calculated by the SUV threshold using the 1.5 LV blood pool SUVmax was significantly higher in CS patients with an EF < 50% than in those with an EF > 50%, but SUVmax was not significantly different between them when only ^{18}F -FDG positive cases were analyzed.

In our study, the rate of cardiac dysfunction or arrhythmic events was significantly higher in the visually analyzed positive SUV images than in the negative images, suggesting that visual assessment of SUV images might be useful for evaluating the risk of SCEs. On the other hand, in quantitative analyses of the SUV positive scans, although each parameter was higher in the presence of cardiac dysfunction than in its absence and higher in the presence of arrhythmic events than in their absence, the difference was only significant for the SUVmean for arrhythmic events ($p = 0.041$). The discrepancy among the study results of SUV parameters for evaluating the clinical events may be because of the differences in the analysis methods. We performed the quantitative analyses only for visual ^{18}F -FDG positive scans and chose an SUVmax threshold of 40% for CMV delineation, as was performed in a previous report [20].

Ki images for evaluating the risk of SCEs

Dynamic PET imaging has been used in oncology for characterizing the kinetic FDG model [29, 30]. Wang et al. [29] reported a significant difference in both the SUVmax and Ki between benign and malignant pulmonary lesions with a high significant correlation between SUVmax and Ki and stated that parametric Ki images were useful for distinguishing malignant lesions from normal tissue.

We found only one study that used dynamic ^{18}F -FDG-PET/CT images to diagnose CS [16], and the researchers reported that heterogeneous myocardial glucose metabolism assessed by using a normalized coefficient of variation of the Ki could be useful for diagnosis of CS. However, no study has examined the relationship between Ki images and clinical events in CS patients.

In our study, on visual analyses of Ki images, the rate of cardiac dysfunction or arrhythmic events was significantly higher in the positive Ki scans than in the negative Ki scans, suggesting that the visual assessment of Ki images might be useful for evaluating the risk of SCEs.

On quantitative analyses of Ki positive scans, although none of the Ki parameter were significantly different between cardiac dysfunction and normal cardiac function, they were significantly higher with the arrhythmic events than without them. Moreover, Ki volume alone was significantly associated with arrhythmic events, suggesting that Ki volume might be the most useful parameter for evaluating the risk of arrhythmic events. Despite the significant correlations between SUV and Ki parameters, there were discrepancies in the results of these parameters concerning the association with clinical events in CS. Thus, Ki images may have the potential to provide additional value to the SUV images for evaluation of the clinical events in CS patients.

There were some study limitations that should be considered when interpreting our results. First, this was a retrospective study with a small sample. Therefore, a prospective study with a large sample is needed to confirm the validity of the present findings. Second, the different treatment statuses at the time of the dynamic ^{18}F -FDG-PET/CT scans could have affected the positivity of the SUV and Ki images, which may have led to biased quantitative analysis. Third, we did not compare other useful imaging techniques, such as cardiac magnetic resonance imaging (MRI) or myocardial perfusion imaging with SUV or Ki images because only a minority of patients underwent cardiac MRI ($n = 6$) or myocardial perfusion imaging ($n = 2$). Finally, in the absence of guidelines on optimal reconstruction parameters for Ki images, we used different beta values of 350 and 700 for reconstruction of the SUV and Ki images, respectively. Further investigations of optimal reconstruction protocols for Ki imaging are warranted.

Conclusion

Patlak Ki images may add value to SUV images for evaluating the risk of SCEs in CS patients.

Abbreviations

AUC: Areas under the ROC curve; AVB: Atrioventricular block; BPL: Bayesian penalized likelihood; CMA: Cardiac metabolic activity; CMV: Cardiac metabolic volume; CS: Cardiac sarcoidosis; CT: Computed tomography; ^{18}F -FDG: ^{18}F -fluorodeoxyglucose; FOV: Field of view; IQR: Interquartile ranges; LVEF: Left

ventricular ejection fraction; PET: Positron emission tomography; ROC: Receiver operating characteristic; SCE: Severe clinical event; SD: Standard deviation; SUV: Standardized uptake value; VOI: Volume of interest; VT: Ventricular tachycardia

Declarations

Acknowledgements

Not applicable.

Authors' contribution

MN and AT contributed to the conception and design of the study. MN, SO, AT, MJ, TK and MO contributed to acquiring and interpreting data. HK and AH contributed to the technical support for generating the Patlak Ki image. MN and TY contributed to drafting of the manuscript together. All authors have read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethical approval

All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest except employment by GE Healthcare Japan (Hirofumi Kawakami and Akira Hirayama).

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Tables

Table 1 Relationship between visual SUV or Ki myocardial findings and clinical events in 30 ¹⁸F-FDG PET/CT scans of 21 patients with cardiac sarcoidosis

Visual SUV and Ki image findings				
LVEF	Positive	Negative	<i>p</i> value	
Median	32.9%	56.3%	0.001	
IQR	30.38-43.75%	40.05-70.95%		
Range	23.5-58.8%	35.0-56.3%		
Cardiac function	Positive	Negative	Total	<i>p</i> value
Dysfunction (LVEF <50%)	15	3	18	0.009
Normal (LVEF >50%)	4	9	12	
Total	19	11	30	
Arrhythmic events	Positive	Negative	Total	<i>p</i> value
Presence	10	0	10	0.004
Absence	9	11	20	
Total	19	11	30	
<i>LVEF</i> left ventricular ejection fraction, <i>LV</i> left ventricular, <i>IQR</i> interquartile range				

Table 2 Relationships between quantitative SUV or Ki parameters and clinical events in 19 ¹⁸F-FDG positive myocardia patients

Index	Cardiac function							Arrhythmic events						
	Normal (n=4)			Dysfunction (n=15)			<i>p</i> value	Absence (n=9)			Presence (n=10)			<i>p</i> value
	Median	IQR	Range	Median	IQR	Range		Median	IQR	Range	Median	IQR	Range	
SUVmax	3.91	2.68-6.03	2.47-7.12	3.99	3.08-7.52	2.91-11.69	0.37	3.15	2.97-4.23	2.89-5.82	6.18	3.54-8.51	2.47-11.69	0.060
SUVmean	2.71	2.46-3.70	2.29-4.60	3.08	2.68-4.12	2.58-6.84	0.32	2.69	2.61-3.06	2.58-3.37	3.87	2.73-4.65	2.29-6.84	0.041
CMV	8.15	3.50-33.15	2.4-54.6	41.8	11.15-132.8	5.6-233.0	0.072	14.0	7.63-29.3	4.6-82.7	101.3	11.7-161.0	2.4-233.0	0.066
CMA	19.4	11.5-89.6	11.0-152.3	114.1	29.7-655.4	15.1-1169.7	0.057	37.2	19.8-92.9	12.1-2678.8	330.5	27.2-930.2	11.0-1169.7	0.060
Ki max (x10 ⁻³)*	139.8	96.0-206.7	82.2-243.6	111.0	90.3-302.1	79.2-549.6	0.92	106.2	82.2-125.7	79.2-170.4	222.0	99.0-382.8	88.2-549.6	0.041
Ki mean (x10 ⁻³)*	73.5	54.0-135.3	47.4-184.2	63.6	52.4-177.0	42.0-333.0	1.00	55.2	45.5-69.3	42.0-87.0	146.4	54.0-227.4	47.4-333.0	0.038
Ki volume [†]	15.1	8.45-44.3	2.3-73.3	41.6	15.03-90.08	5.7-108.0	0.23	14.6	11.4-19.2	5.7-25.9	79.5	41.7-105.0	2.3-108.0	0.003
<i>IQR</i> interquartile range, <i>CMV</i> (cm3) cardiac metabolic volume, <i>CMA</i> cardiac metabolic activity														
* The unit of Ki max and Ki mean are ml/g/min.														
† The unit of Ki volume was cm ³ .														

Table 3 Ability of SUV and Ki parameters to discriminate between the presence and absence of severe clinical events

Index	Cardiac dysfunction					Arrhythmic events						
	Cutoff value	Sensitivity	Specificity	Accuracy	AUC	p value	Cutoff value	Sensitivity	Specificity	Accuracy	AUC	p value
SUVmax	>2.89	80.0 (12/15) 51.9-95.7*	50.0 (2/4) 6.8-93.2*	73.7 (14/19) 48.8-90.9*	0.67 0.42-0.86*	0.41	>5.82	50 (5/10) 18.7-81.3*	100 (9/9) 66.4-100*	73.7 (14/19) 48.8-90.9*	0.76 0.51-0.92*	0.034
SUVmean	>2.62	86.7 (13/15) 59.5-98.3*	50.0 (2/4) 6.8-93.2*	78.9 (15/19) 54.4-93.9*	0.67 0.42-0.86*	0.37	>3.37	60 (6/10) 26.2-87.8*	100 (9/9) 66.4-100*	78.9 (15/19) 54.4-93.9*	0.78 0.53-0.93*	0.018
CMV	>4.6	100 (15/15) 78.2-100*	50.0 (2/4) 6.8-93.2*	89.5 (17/19) 66.9-98.7*	0.80 0.56-0.95*	0.031	>82.7	50 (5/10) 18.7-81.3*	100 (9/9) 66.4-100*	73.7 (14/19) 48.8-90.9*	0.75 0.50-0.92*	0.031
CMA	>26.8	80.0 (12/15) 51.9-95.7*	75.0 (3/4) 19.4-99.4*	78.9 (15/19) 54.4-93.9*	0.82 0.58-0.95*	0.020	>268.8	50 (5/10) 18.7-81.3*	100 (9/9) 66.4-100*	73.7 (14/19) 48.8-90.9*	0.76 0.51-0.92*	0.034
Ki max [†]	>243.6 x10 ⁻³	26.7 (4/15) 7.8-55.1*	100 (4/4) 39.8-100*	42.1 (8/19) 20.2-66.5*	0.52 0.28-0.75*	0.92	>170.4 x10 ⁻³	60 (6/10) 26.2-87.8*	100 (9/9) 66.4-100*	78.9 (15/19) 54.4-93.9*	0.78 0.53-0.93*	0.014
Ki mean [†]	>184.2 x10 ⁻³	26.7 (4/15) 7.8-55.1*	100 (4/4) 39.8-100*	42.1 (8/19) 20.2-66.5*	0.50 0.27-0.73*	1.00	>87.0 x10 ⁻³	60 (6/10) 26.2-87.8*	100 (9/9) 66.4-100*	78.9 (15/19) 54.4-93.9*	0.79 0.54-0.94*	0.009
Ki volume [‡]	>15.6	73.3 (11/15) 44.9-92.2*	75.0 (3/4) 19.4-99.4*	73.7 (14/19) 48.8-90.9*	0.70 0.45-0.89*	0.21	>25.9	90 (9/10) 55.5-99.7*	100 (9/9) 66.4-100*	94.7 (18/19) 74.0-99.9*	0.90 0.68-0.99*	<0.001
<p>CMV (cm3) cardiac metabolic volume, CMA cardiac metabolic activity, AUC areas under the receiver operating characteristic curve</p> <p>* 95% confidence interval</p> <p>† The unit of Ki max and Ki mean are ml/g/min.</p> <p>‡ The unit of Ki volume was cm³.</p>												

Table 4. Logistic analysis for association between each parameter and presence of severe clinical events

Index	Cardiac dysfunction				Arrhythmic events			
	χ^2	Odds ratio	95% CI	<i>p</i> value	χ^2	Odds ratio	95% CI	<i>p</i> value
SUVmax	0.48	1.20	0.72-1.98	0.49	3.31	1.81	0.95-3.44	0.069
SUVmean	0.47	1.59	0.42-6.06	0.50	3.13	5.26	0.84-33.13	0.077
CMV	1.30	1.03	0.98-1.07	0.25	3.44	1.02	0.99-1.05	0.064
CMA	0.91	1.01	0.99-1.02	0.34	2.34	1.01	0.99-1.01	0.13
Ki max	0.40	1.00	0.99-1.01	0.53	2.84	1.02	0.99-1.04	0.092
Ki mean	0.21	1.00	0.99-1.02	0.65	2.35	1.03	0.99-1.08	0.13
Ki volume	1.09	1.02	0.98-1.06	0.30	3.95	1.11	1.01-1.23	0.047
<i>CMV</i> cardiac metabolic volume, <i>CMA</i> cardiac metabolic activity, <i>CI</i> confidence interval								

Figures

Figure 1

A 70-year-old female patient with CS who showed VT and cardiac dysfunction (EF: 40.0 %) before treatment. The SUV images [maximum intensity projection (MIP) (a), transaxial (b), coronal (c), and sagittal (d)] and Ki images [MIP (e), transaxial (f), coronal (g), and sagittal (h)] both show the positive myocardium for which the VOIs were automatically determined. The SUV (SUVmax:8.51 g/ml, SUVmean:4.36 g/ml, CMV:229.0 cm³, CMA:998.4 g) and Ki parameters (Ki max:382.8 x 10⁻³ ml/g/min, Ki mean:227.4 x 10⁻³ ml/g/min, Ki volume:108.0 cm³) were all positive for the risk of arrhythmic events according to each threshold criterion.

Figure 2

A 68-year-old male patient with CS who showed VT and cardiac dysfunction (EF: 25.3 %) under steroid treatment (prednisolone, 10 mg daily). The SUV images [MIP (a), transaxial (b), coronal (c), and sagittal (d)] and Ki images [MIP (e), transaxial (f), coronal (g), and sagittal (h)] both show the positive myocardium for which the VOIs were automatically determined. The Ki volume (34.7 cm³) was the only parameter positive for the risk of arrhythmic events according to each threshold criterion.

Figure 3

A 69-year-old female patient with CS who showed no arrhythmic events with normal cardiac function (EF: 70%) under steroid treatment (prednisolone, 10mg daily). The SUV images [MIP (a), transaxial (b), coronal (c), and sagittal (d)] and Ki images [MIP (e), transaxial (f), coronal (g), and sagittal (h)] both show the negative myocardium.