

# Volume-based glucose metabolic analysis of FDG PET/CT: The optimum threshold and conditions to suppress physiological myocardial uptake

Osamu Manabe, MD, PhD,<sup>a</sup> Markus Kroenke, MD,<sup>a,b</sup> Tadao Aikawa, MD,<sup>c</sup> Atsuto Murayama, MSc,<sup>a</sup> Masanao Naya, MD, PhD,<sup>c</sup> Atsuro Masuda, MD, PhD,<sup>d</sup> Noriko Oyama-Manabe, MD, PhD,<sup>e</sup> Kenji Hirata, MD, PhD,<sup>a</sup> Shiro Watanabe, MD, PhD,<sup>a</sup> Tohru Shiga, MD, PhD,<sup>a</sup> Chietsugu Katoh, MD, PhD,<sup>f</sup> and Nagara Tamaki, MD, PhD<sup>a,g</sup>

<sup>a</sup> Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

<sup>b</sup> Department of Nuclear Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

<sup>c</sup> Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

<sup>d</sup> Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan

<sup>e</sup> Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Sapporo, Japan

<sup>f</sup> Faculty of Health Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan

<sup>g</sup> Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Received Jul 5, 2017; accepted Oct 24, 2017

doi:10.1007/s12350-017-1122-6

**Objective.** FDG PET/CT plays a significant role in the diagnosis of inflammatory heart diseases and cardiac tumors. We attempted to determine the optimal FDG uptake threshold for volume-based analyses and to evaluate the relationship between the myocardial physiological uptake volume in FDG PET and several clinical factors.

**Methods.** A total of 190 patients were retrospectively analyzed. The cardiac metabolic volume (CMV) was defined as a volume within the boundary determined by a threshold (SUVmean of blood pool  $\times$  1.5).

**Results.** The SUVmean of the blood pool measured in the descending aorta (DA) ( $r = 0.86$ , intraclass correlation coefficient [ICC] = 0.93,  $P < 0.0001$ ) and that in the left ventricle (LV) cavity ( $r = 0.87$ , ICC = 0.90,  $P < 0.0001$ ) showed high inter-operator reproducibility. However, the SUVmean in the LV cavity showed a significant correlation with the CMV ( $P = 0.0002$ ,  $r = 0.26$ ). The CMV in the patients who fasted  $< 18$  hours were significantly higher ( $49.7 \pm 73.2$  vs.  $18.0 \pm 53.8$  mL,  $P = 0.0013$ ) compared to the patients with  $> 18$ -hour fasting. The multivariate analysis demonstrated that only the fasting period  $> 18$  hours was independently associated with CMV = 0.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s12350-017-1122-6>) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

Osamu Manabe and Markus Kroenke contributed equally to this article.

Reprint requests: Osamu Manabe, MD, PhD, Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, N15 W7, Kita-Ku, Sapporo, 0608638 Hokkaido, Japan; [osamumanabe817@med.hokudai.ac.jp](mailto:osamumanabe817@med.hokudai.ac.jp)

1071-3581/\$34.00

Copyright © 2017 American Society of Nuclear Cardiology.

**Conclusion.** Our findings revealed that the DA is suitable to decide the threshold for the volume-based analysis. The fasting time was significantly associated with the cardiac FDG uptake. (J Nucl Cardiol 2019;26:909–18.)

**Key Words:** <sup>18</sup>F-Fluorodeoxyglucose • PET • physiological uptake • Metabolism: PET • fasting

#### Abbreviations

CMV	Cardiac metabolic volume
DA	Descending aorta
FDG	<sup>18</sup> F-fluorodeoxyglucose
LV	Left ventricle
MTV	Metabolic tumor volume
PET	Positron emission tomography
SUVmax	Maximum standardized uptake value
SUVmean	Mean standardized uptake value
TLG	Total lesion glycolysis
VOI	Volume-of-interest

---

**See related editorial, pp. 919–921**

---

## INTRODUCTION

<sup>18</sup>F-fluorodeoxyglucose (FDG) is widely used as a positron emission tomography (PET) tracer to assess malignant and inflammatory diseases.<sup>1</sup> The most frequently used index to assess the disease activity is the maximum standardized uptake value (SUVmax). Volume-based parameters such as metabolic tumor volume (MTV) or total lesion glycolysis (TLG) have been used mainly in oncological studies.<sup>2</sup> The MTV is defined as the hypermetabolic volume, mostly with a SUV greater than a predefined threshold. TLG is calculated by multiplying the mean standardized uptake value (SUV-mean) by the MTV.<sup>3</sup> As the TLG is either semi- or fully automatically calculated, higher reproducibility was shown compared to a visual assessment shown for cardiac sarcoidosis.<sup>4</sup> Volume-based analyses of the FDG uptake have recently been applied for cardiac sarcoidosis.<sup>5,6</sup> The cardiac metabolic volume (CMV) was defined as a volume within a given boundary determined using the FDG uptake threshold. The SUVmax reflects the maximal pixel value in the VOI, which is one of the most widely used parameters in clinical practice due to its ease of use. However, the SUVmax is not representative of the metabolism of the entire target lesion. The cardiac metabolic volume (CMV) is similar in concept to the MTV for assessing malignant tumors, which is measured by contouring margins defined by thresholds.<sup>5</sup> Compared to the SUVmax, the CMV has a theoretical advantage in terms of evaluating the total volume of metabolically active disease or the function of an organ. Several regions, such as left ventricle (LV) cavity,<sup>6,7</sup> the

blood pool in the aorta<sup>8</sup> and the liver<sup>1</sup> were each reported to provide a useful threshold to estimate the metabolic volume. The ideal threshold has not been fully established. The patient's fasting period and the cardiac physiological uptake might influence these values.<sup>9</sup>

Physiological FDG uptake is frequently observed in the myocardium, which degrades the diagnostic value for the assessment of active inflammatory lesions in the heart.<sup>1</sup> There have been few reports about volume-based analyses of physiological myocardial accumulation and its correlation with clinical status.<sup>1</sup> To achieve an accurate diagnosis and quantification of the uptake volume, the suppression of the physiological FDG accumulation in the myocardium is needed. Long patient-fasting periods such as > 12 and > 18 hours are reported to suppress the physiological FDG uptake.<sup>1,10</sup>

In the present study, our first goal was to identify the optimal threshold for use in the volume-based analysis of cardiac FDG PET. Our second goal was to evaluate the relationship between the myocardial uptake volume in FDG PET and several clinical factors. We also explored the conditions needed to effectively suppress the physiological myocardial uptake.

## PATIENTS AND METHODS

### Patients

We retrospectively analyzed the cases of 237 consecutive patients who received FDG PET/CT scan in January and February 2013. Electronic medical records were reviewed for clinical laboratory, chest X-ray, and electrocardiography results. The fasting duration was obtained from the patient interview record before FDG injection. Patients who were < 20 years old, with a history of coronary artery disease or any other known heart disease such as myocarditis, valvular heart disease or cardiomyopathies, those with abnormal findings in electrocardiography (including bradycardia [ $< 50$  beats per min or bpm]), tachycardia ( $> 100$  bpm), atrioventricular block, left bundle branch block, atrial fibrillation, any ST change), abnormal findings in chest X-ray examinations (including cardiomegaly [chest-thoracic ratio  $> 50\%$ ] and pleural effusion) or with high blood glucose ( $> 150$  mg/dl) before the FDG administration were excluded from the study. Patients who had an intrathoracic tumor or metastatic lesion close to the

heart were excluded as well. This retrospective study was approved by the Institutional Review Board of Hokkaido University Hospital, with a waiver of the need for written informed consent.

### FDG PET/CT Imaging Acquisition

Patients are instructed not to consume any food other than plain water for  $\geq 6$  hours prior to the time of FDG injection. Patients scheduled to undergo an FDG PET/CT examination in the morning-to-early afternoon period are instructed to eat nothing after midnight. A special diet preparation such as a low-carbohydrate diet was not used for the patients' preparation in this study. PET data were acquired using a Biograph 64 TruePoint PET scanner with TrueV (Siemens Healthcare, Tokyo). First, 4.5 MBq/kg of FDG was intravenously administered under resting conditions. Next, 60 min after the administration of FDG, a static FDG scan was performed. The acquired datasets were corrected for attenuation by low-dose CT Images, and were reconstructed using a point spread function-based iterative algorithm (TrueX, Siemens) with two iterations per 21 subsets, a matrix size of  $168 \times 168$ , a voxel size of  $4.1 \times 4.1 \times 2.0$  mm, and a Gaussian filter at 4.0 mm full-width at half-maximum. The transaxial and axial field of views were 58.5 and 21.6 cm, respectively.

### Study Protocol and Image Analysis

**Threshold determination:** Two different operators (O.M. and A.Mu.) set a 1-cm-dia. spherical volume-of-interest (VOI) in the descending aorta (DA) and LV cavity to compare the inter-operator reproducibility in the first 30 consecutive patients (Figure 1A, B). We assessed the correlation between the fasting period and the SUVmean in the LV cavity, DA, and liver uptakes in all included patients. An automated method provided by Hirata et al. was used for objectively placing the liver VOI in FDG PET/CT (Figure 1C).<sup>11</sup> With this method, the SUVmean and its standard deviation (SD) inside the VOI were used to determine the threshold value as follows:  $\text{threshold} = \text{SUVmean} + 3 \times \text{SD}$ . Each dataset was analyzed independently by the two operators, who were blind to the results of the other observer. The physicians were blinded to the patients' clinical information to avoid possible bias.

The SUVmean values of the LV cavity, the DA, and the liver uptakes were compared between fasting periods, which were  $< 12$ , 12–18, and  $> 18$  hours, to assess the relationships between the fasting period and each FDG uptake threshold. To assess the relationships between the SUVmean of each region and the cardiac uptake, we divided the patients into two groups: the

patients with a  $\text{CMV} < 128.8$  and the patients with a  $\text{CMV} \geq 128.8$  (which is the mean value of the cardiac metabolic volume of the diffuse left ventricular uptake from the previous study using the same PET/CT settings).<sup>1</sup> We defined  $\text{CMV} = 0$  (ml) (CMV0) as complete suppression of physiological cardiac uptake.

### Correlation Between Cardiac Metabolism and Clinical Factors

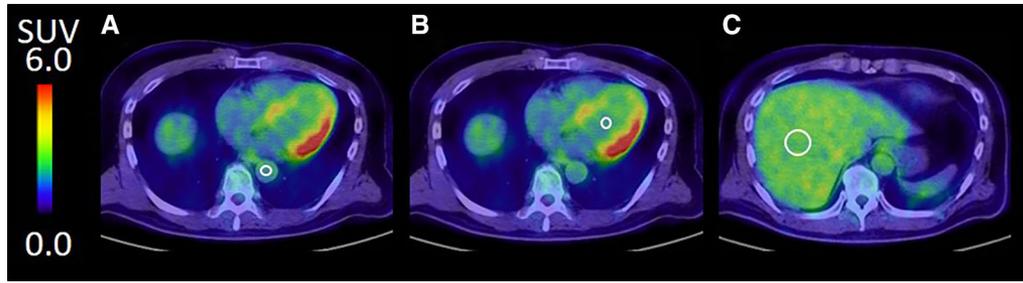
The glucose metabolism of the heart was estimated using the SUVmax and CMV. The SUVmax was measured in the axial images encompassing the whole myocardium. The CMV was defined as the volume within the boundary determined using the threshold defined as the  $\text{SUVmean}$  of the blood pool  $\times 1.5$ .<sup>12</sup> We examined the correlations between the SUVmax and CMV with clinical factors including age, gender, body mass index (BMI), fasting period (12 and 18 hours), fasting blood sugar (FBS), and hospitalization status (inpatient vs. outpatient).<sup>10,13–15</sup>

### Statistical Analyses

Data are expressed as the mean  $\pm$  SD. A  $P$  value of  $< 0.05$  was considered significant. Inter-operator repeatability was assessed using linear regression analyses, Bland-Altman plots and intraclass correlation coefficient (ICC). The Wilcoxon signed-rank test was used for intra-group comparisons. Fisher's exact test was used to compare discrete data. Since the myocardial uptake used to explore predictors of CMV0 could be a potential confounding factor in this study, we performed an additional multivariate logistic regression analysis using the forced inclusion model including age, gender, BMI, FBS, hospitalization status, and fasting period ( $< 12$ , 12–18, and  $> 18$  hours) based on clinical relevance.<sup>10,13,16</sup> Statistical calculations were carried out using SAS (JMP ver. 12, SAS, Cary, NC, USA).

## RESULTS

Of the 237 patients' cases, 47 were excluded because of the patient's age, abnormal findings in chest X-ray or electrocardiography, abnormal blood glucose levels or an intrathoracic tumor or metastatic lesion near the heart. Patients  $< 20$  years old ( $n = 1$ ) or with a history of heart disease ( $n = 12$ ), abnormal electrocardiography results ( $n = 20$ ), abnormal chest X-ray findings ( $n = 22$ ), or high blood glucose ( $n = 15$ ) before the FDG administration and those who had a tumor close to the heart ( $n = 3$ ) were excluded from the study. Some patients' above conditions overlapped, and thus of the 237 patients' cases, 47 were excluded.



**Figure 1.** Volume of interest (VOI) for the optimal threshold to assess volume-based analysis. The thresholds were obtained from descending aorta (A), left ventricle cavity (B), and liver (C) to estimate the cardiac metabolic volume.

**Table 1.** Characteristics of included patients

	Reproducibility (n = 30)	Total patients (n = 190)
Age (years)	62.0 ± 11.6	60.7 ± 13.9
Male	13 (43%)	101 (53%)
BMI (kg/m <sup>2</sup> )	22.5 ± 3.4	22.1 ± 3.6
FBS (mg/dl)	110.4 ± 17.0	108.8 ± 13.3
FDG dosage (MBq/kg)	4.1 ± 0.7	4.3 ± 1.0
SUVmax of myocardium	4.7 ± 4.1	5.6 ± 4.6

BMI, Body mass index; FBS, fasting blood sugar, FDG, <sup>18</sup>F-fluorodeoxyglucose; SUVmax, maximum of standardized uptake value

Therefore, a total of 190 patients (60.7 ± 13.9 years old, 101 males and 89 females) were included (Table 1). All patients suffered from a malignant disease or had been treated for a malignant disease. Thirty-five patients suffered from malignant lymphoma. The other malignant tumors were as follows (the primary focus of which was lung, 26; thyroid, 16; larynx, 13; pharynx, 8; colon, 8; bone, 8; uterine, 5; pancreas, 5; ovary, 5; bile duct, 5; liver, 4; ear canal, 4; brain, 4; parotid gland, 3; mediastinal, 3; gastric, 3; breast, 3; esophageal, 2; cervical, 2; and the other 10 [urinary, tongue, testicular, peritoneal, nose, eye, gonadal, gallbladder, duodenal, spinal cord]): 9 of malignant melanoma, 2 of Paget disease, 1 of gastrointestinal stromal tumor, and 6 of squamous cell carcinoma with unknown primary lesion. Seventeen patients had diabetes mellitus.

### Optimal Threshold for the Volume-Based Analysis

The SUVmean values of the blood pool measured in the DA ( $r = 0.86$ , ICC = 0.93,  $P < 0.0001$ ), in the LV cavity ( $r = 0.87$ , ICC = 0.90,  $P < 0.0001$ ), and in the liver ( $r = 1.00$ , ICC = 1.00,  $P < 0.0001$ ) showed high reproducibility (Figure 2).

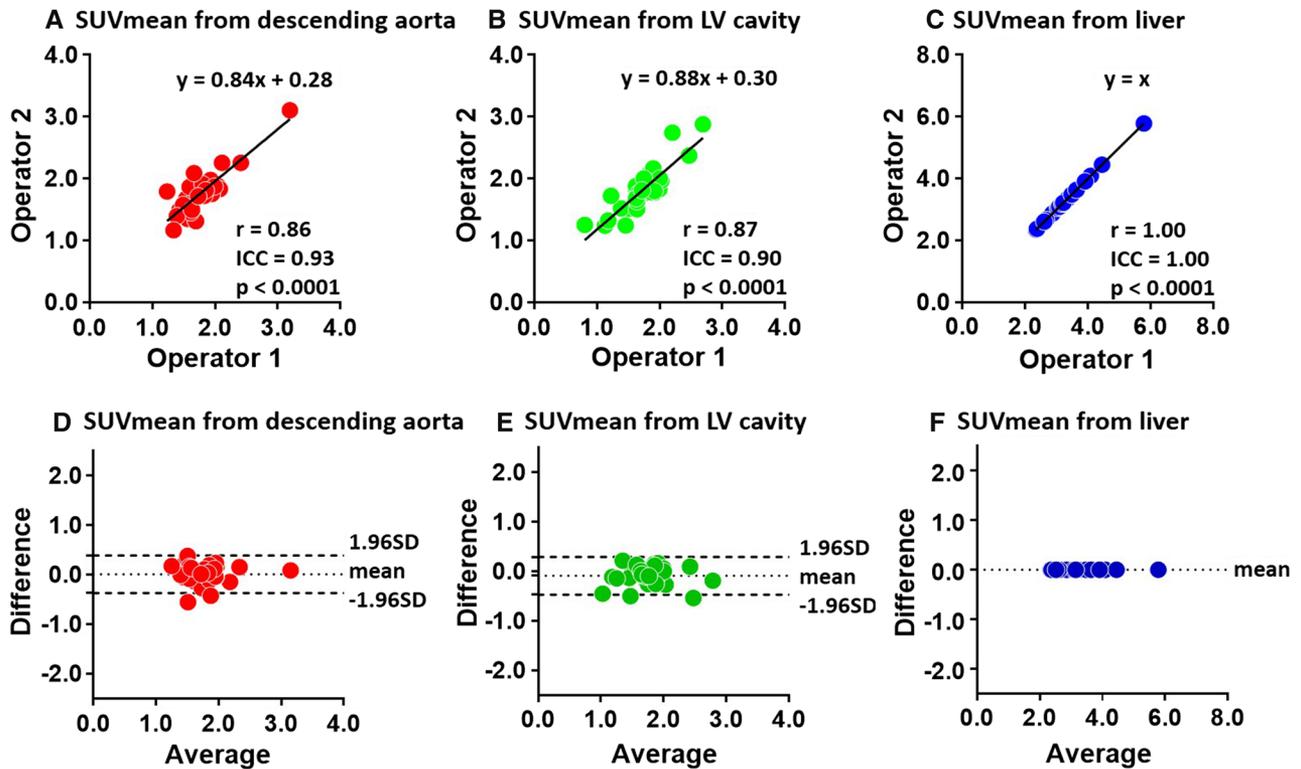
Regarding the SUVmean of the LV cavity, patients with a high CMV (i.e.,  $\geq 128.8$  ml) showed

significantly higher values compared to the patients with a low CMV ( $< 128.8$  ml) ( $1.88 \pm 0.48$  vs.  $1.59 \pm 0.30$ ,  $P = 0.0025$ ), whereas the SUVmean of the DA ( $1.77 \pm 0.29$  vs.  $1.69 \pm 0.25$ ,  $P = 0.23$ ) and that of the liver did not show a significant difference between the high- and low-CMV groups ( $2.78 \pm 0.30$  vs.  $2.92 \pm 0.49$ , respectively;  $P = 0.13$ ) (Figure 3).

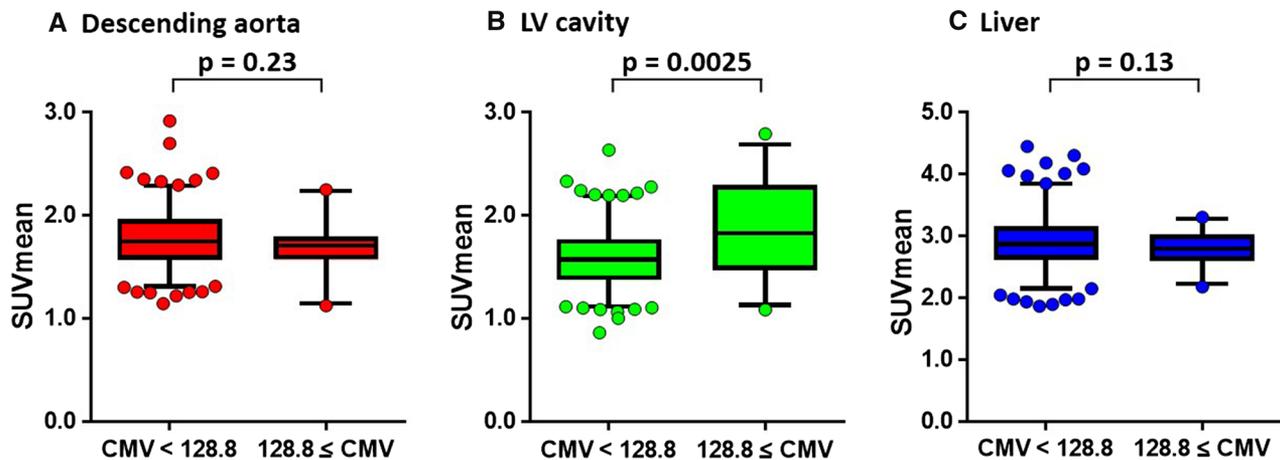
The SUVmean of the liver was significantly associated with the fasting period; that is, the longer the fasting period, the higher the SUVmean of the liver was ( $P = 0.0094$ ). The SUVmean values from the DA and the LV cavity were not associated with the fasting period ( $P = 0.079$  and  $0.74$ , respectively) (Table 2). The SUVmean from the DA was more suitable for the threshold due to the high inter-operator reproducibility and without associated to the fasting period. We adopted the SUVmean of the DA  $\times 1.5$  as the delineation threshold from the previous reports.<sup>6,12</sup>

### Relationship Between the Cardiac FDG Uptake and Clinical Factors

The SUVmax and CMV in the patients who heard  $< 18$  hours were significantly higher (SUVmax:  $5.9 \pm 4.7$  vs.  $4.1 \pm 4.0$ ,  $P = 0.0074$ , CMV:  $49.7 \pm 73.2$  vs.  $18.0 \pm 53.8$  mL,  $P = 0.0013$ ), and the frequency of CMV = 0 mL (CMV0) was significantly



**Figure 2.** Inter-observer reproducibility of the thresholds. The inter-observer reproducibility of the SUVmean from the descending aorta (A, D), left ventricle cavity (B, E), and liver (C, F) was assessed using a linear regression analysis and Bland-Altman plot. The SUVmean of the blood pool measured in the descending aorta ( $r = 0.86$ ,  $ICC = 0.93$ ), left ventricle cavity ( $r = 0.87$ ,  $ICC = 0.90$ ), and liver ( $r = 1.00$ ,  $ICC = 1.00$ ) showed high reproducibility.

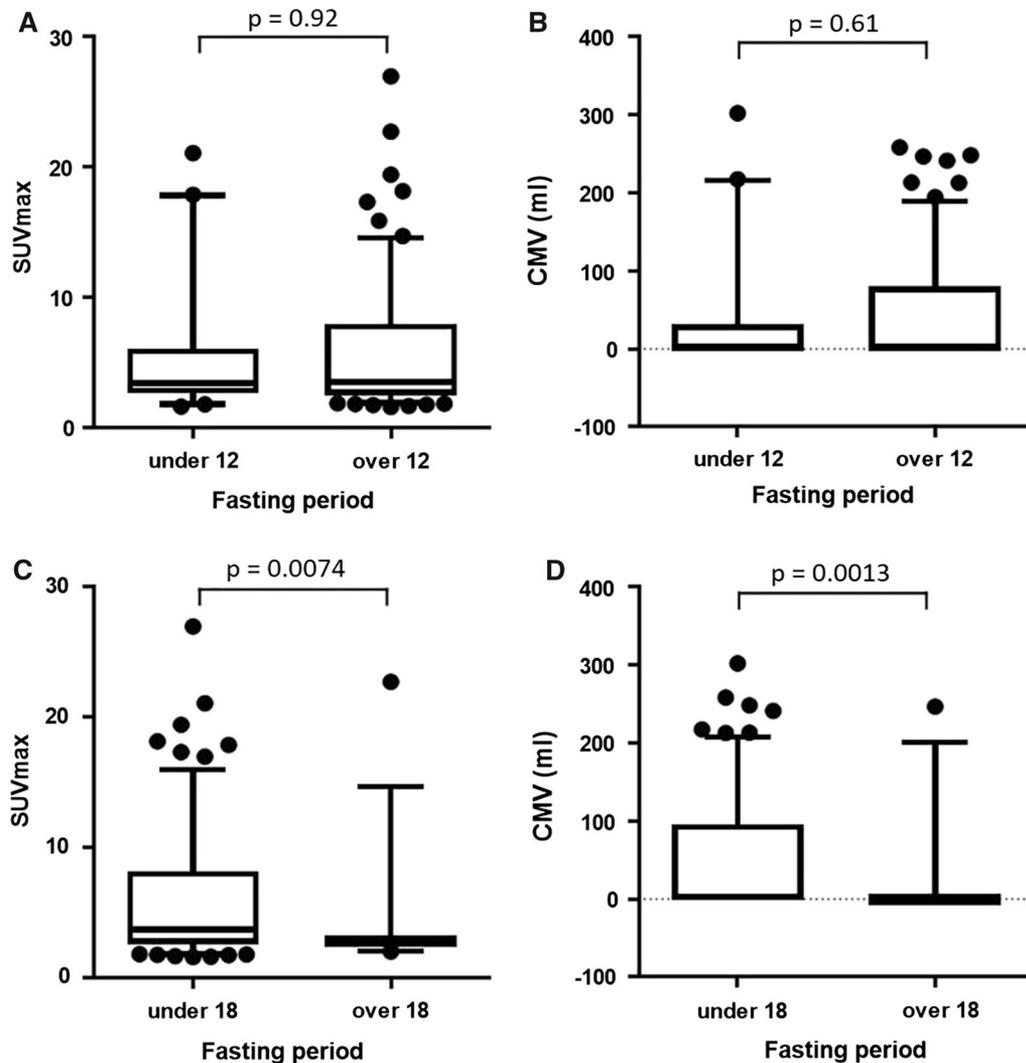


**Figure 3.** Relationship between cardiac metabolic volume (CMV) and each threshold. The correlation between the CMV obtained using the threshold from the SUVmean of the descending aorta  $\times 1.5$  and the thresholds from the descending aorta (A), LV cavity (B), and liver (C) are displayed. The SUVmean of the LV cavity showed a significant correlation with CMV ( $P = 0.0025$ ), whereas the SUVmeans from the descending aorta ( $P = 0.23$ ) and liver do not ( $P = 0.13$ ).

**Table 2.** The relationships between fasting period and the SUVmean from each region

Fasting period	< 12 hours	12-18 hours	> 18 hours	P value
n	41	116	33	-
Descending aorta	1.71 ± 0.29	1.75 ± 0.27	1.85 ± 0.32	0.079
LV cavity	1.61 ± 0.33	1.63 ± 0.38	1.67 ± 0.27	0.74
Liver	2.78 ± 0.49	2.89 ± 0.45	3.11 ± 0.47*†	0.0094

\*P < 0.0078 vs. fasting period < 12 hours  
†P < 0.039 vs. fasting period between 12 and 18 hours



**Figure 4.** Relationship between the fasting period and cardiac uptake. The CMV and SUVmax showed no significant difference between the patients who fasted <12 hr and those who fasted >12 hr (A, B). However, the CMV and SUVmax of the patients who fasted <18 hr were higher than those who fasted >18 hr (C, D).

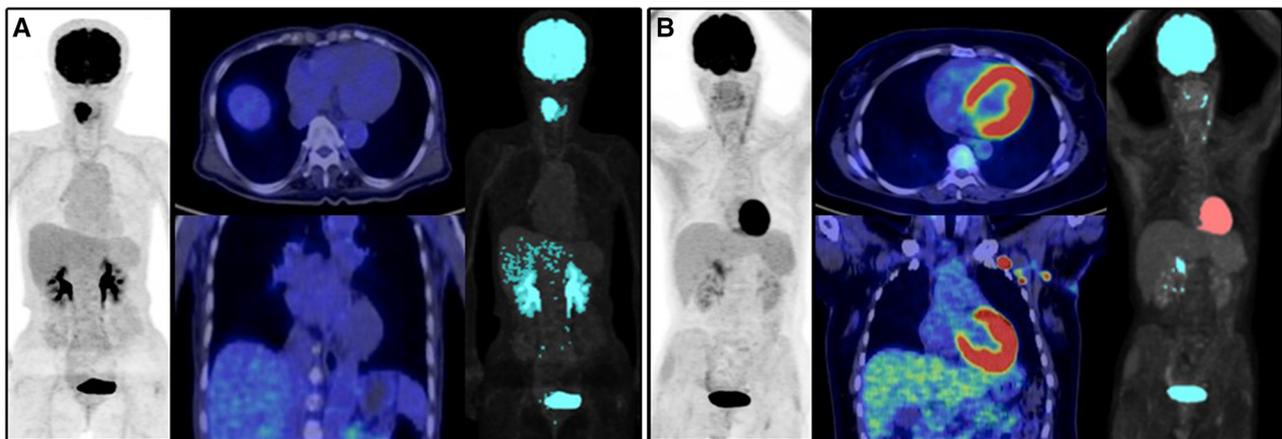
lower (36.3% vs. 63.6%,  $P < 0.01$ ) compared to the patients who fasted > 18 hours. Both the SUVmax ( $5.9 \pm 4.7$  vs.  $4.4 \pm 4.2$ ,  $P = 0.046$ ) and the CMV

( $49.8 \pm 74.0$  mL vs.  $21.9 \pm 53.2$  mL,  $P = 0.036$ ) of the outpatients were significantly higher than those of the inpatients.

**Table 3.** The relationships between each fasting period and clinical factors

Fasting period	12 hours			18 hours		
	Under	Over	<i>P</i> value	Under	Over	<i>P</i> value
n	41	149	-	157	33	-
Age (years)	58.3 ± 16.0	61.4 ± 13.3	0.21	60.6 ± 14.0	61.1 ± 13.5	0.85
Male	21 (51%)	80 (54%)	0.78	81 (52%)	20 (61%)	0.34
FBS (mg/dl)	109.3 ± 12.5	108.6 ± 13.6	0.78	109.8 ± 13.3	103.9 ± 12.4	0.02
FDG dosage (MBq/kg)	4.3 ± 1.1	4.3 ± 0.9	0.75	4.3 ± 1.0	4.2 ± 0.7	0.43
SUVmax	5.5 ± 74.9	5.6 ± 4.6	0.92	5.9 ± 4.7	4.1 ± 4.0	0.04
CMV (mL)	41.5 ± 79.8	45.0 ± 68.8	0.78	49.7 ± 73.2	18.0 ± 53.8	0.02
Frequency of CMV0 (%)	41.5	40.9	0.95	36.3	63.6	< 0.01

FBS, Fasting blood sugar; SUV, standardized uptake value; LV, left ventricle, CMV, cardiac metabolic volume; CMV0, cardiac metabolic volume = 0 (mL)



**Figure 5.** Representative cases. FDG PET/CT images of patients with a 18.5-hour fasting period (A) and a 7-hour fasting period (B). The measured CMV and SUVmax were 0.0 ml and 1.31 for the former, and 206.4 mL and 14.9 for the latter, respectively.

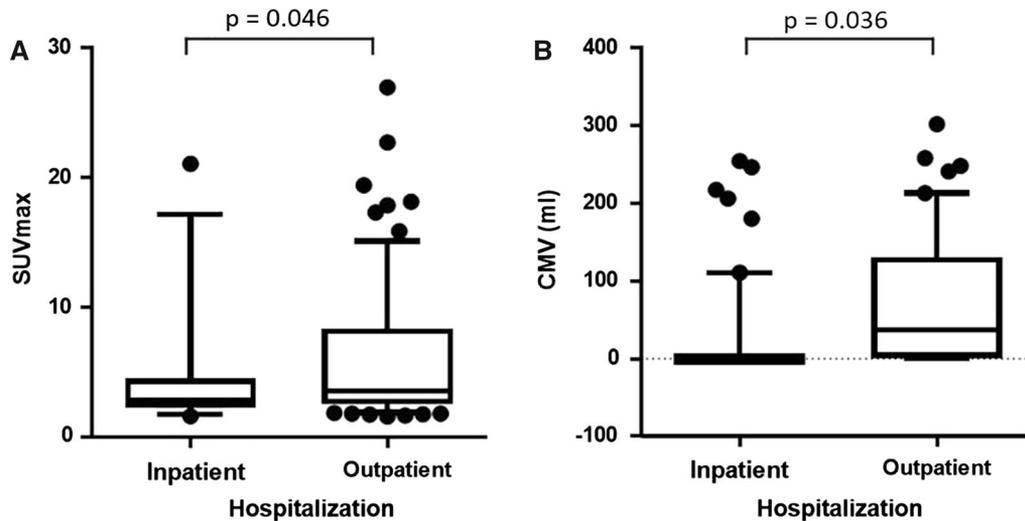
The SUVmax and CMV were significantly higher in the patients who fasted < 18 hours (SUVmax: 5.9 ± 4.7 vs. 4.1 ± 4.0, *P* = 0.0074, CMV: 49.7 ± 73.2 mL vs. 18.0 ± 53.8 mL, *P* = 0.0013) compared to the patients who fasted > 18 hours (Figure 4A, B). The frequency of CMV0 was significantly lower in the shorter-fasting group than in the longer-fasting group (36.3% vs. 63.6%, *P* < 0.01). However, there were no significant differences in the SUVmax and CMV between < 12 and > 12 hours of fasting (SUVmax: 5.5 ± 4.9 vs. 5.6 ± 4.6, *P* = 0.92, CMV: 41.5 ± 79.8 mL vs. 45.0 ± 68.8 mL, *P* = 0.61) (Figure 4C, D), and the frequency of CMV0 showed no significant difference (Table 3). Representative cases are shown in Figure 5.

The outpatients showed significantly higher SUVmax (5.9 ± 4.7 vs. 4.4 ± 4.2, *P* = 0.046) and CMV

(49.8 ± 74.0 vs. 21.9 ± 53.2 mL, *P* = 0.036) compared to the inpatients (Figure 6). The frequency of CMV0 showed no significant difference between the inpatients and outpatients (52.6% vs. 38.2%, *P* = 0.14). Neither BMI nor FBS showed a relationship with the CMV (*P* = 0.12 and 0.21, respectively). The multivariate analysis demonstrated that only the fasting period > 18 hours was independently associated with CMV0 (Table 4).

## DISCUSSION

We conducted a quantitative analysis of the physiological FDG uptake in the heart. Our findings revealed that the DA is suitable to determine the threshold for the volume-based analysis of the cardiac FDG PET, and that



**Figure 6.** Correlation between hospitalized status and cardiac uptake. Both the SUVmax and CMV of the outpatients were significantly higher than those of the inpatients.

**Table 4.** Multivariate analysis

Factor	OR (95% CI)	P value
Age	0.58 (0.13-2.58)	0.47
Male	0.67 (0.36-1.25)	0.20
BMI	0.19 (0.03-1.06)	0.06
FBS	1.45 (0.26-8.06)	0.67
Hospitalization (inpatient)	1.69 (0.78-3.66)	0.19
12-18 hours fasting	0.98 (0.46-2.18)	1.00
> 18 hours fasting	3.90 (1.70-9.40)	0.0092

BMI, Body mass index; FBS, fasting blood sugar; OR, odds ratio

the fasting time and hospitalization status were significantly associated with the CMV and SUVmax.

Visual assessment is prone to low inter-observer correlation, as was recently shown in the assessment of cardiac sarcoidosis.<sup>4</sup> The basis of a reasonable (semi-) automatic volume-based assessment is a well-defined, individual threshold. Different thresholds based on the uptake in the LV cavity,<sup>17</sup> the liver<sup>11</sup> and the blood pool in the aorta<sup>12</sup> have been reported. The liver uptake showed excellent inter-operator correlation (as it was obtained semi-automatically), but it was correlated with the fasting period and dietary conditions are known to have a significant effect on hepatic FDG uptake.<sup>9</sup> In addition, hepatic diseases and resection of the liver can alter the uptake.<sup>18</sup> In cases of sarcoidosis, the liver might be involved and therefore the uptake might be overestimated.<sup>1</sup>

Using the threshold from the DA, the SUVmean of the LV cavity was significantly higher in our patients with a higher SUVmax and CMV. A possible reason for this result might be that the VOI used to obtain the threshold overlapped with the myocardium. The SUVmean obtained from the DA showed better inter-operator correlation than that obtained from the LV cavity, it was independent from the CMV, and there was no significant correlation with the fasting period. We therefore used the SUVmean of a VOI in the DA to compute the threshold of the CMV.

The benefit of a metabolic volume assessment in FDG PET/CT was reported not only in the field of malignant tumors but also in cardiac diseases. Osborn et al. reported that a reduction of the CMV from pre- to post-therapy of cardiac sarcoidosis patients was associated with improvement in the ejection fraction (EF), which suggested that serial PET scanning might help guide the titration of immunosuppressive therapy to improve or prevent heart failure.<sup>19</sup> Ahmadian et al. advocated the use of cardiac metabolic activity (CMA), which is calculated as  $CMV \times SUV_{mean}$ , similarly to the use of TLG in oncologic PET imaging. They also reported that an increased CMA is associated with lower left ventricular ejection fraction (LVEF) and a lower incidence of adverse clinical events.<sup>6</sup> The volume-based assessment was a more precise predictor of cardiac events compared to the SUVmax for cardiac sarcoidosis patients. An appropriate SUV threshold is important for the identification of the precise CMV, and our present findings confirmed that the SUVmean of a VOI in the DA is suitable with high inter-operator reproducibility and is not associated with the fasting period.

The myocardium can derive energy from FFA, glucose, lactate, and ketone bodies. FDG is an analog of glucose, and thus a physiological FDG uptake in the myocardium is often observed. In the clinical setting, a non-specific physiological FDG uptake in the myocardium is often seen, and its uptake patterns can be diffuse.<sup>20</sup> FDG PET for the evaluation of a cardiac inflammatory lesion or cardiac tumor is sometimes limited by this physiological uptake. Previous findings suggested that the degree of myocardial uptake was related to free fatty acids (FFA), FBS levels, and the fasting condition.<sup>13,21</sup> The expression of insulin-sensitive glucose transporter (GLUT)-4 was increased in the myocardium by feeding, which leads to an increase in myocardial FDG uptake. On the other hand, long fasting, low-carbohydrate food and high-fat food could shift the substrate use from glucose to FFA, and thus, these three conditions have been recommended as an approach to reduce myocardial FDG uptake.<sup>22,23</sup> In the absence of dietary glucose intake due to prolonged fasting, the myocardium makes a metabolic shift from the use of glucose to fatty acids. In our previous study, patients with higher plasma FFA levels showed significantly reduced physiological myocardial FDG uptake even when their fasting blood glucose levels were not significantly lower.<sup>1</sup> The fasting blood glucose level might influence the physiological myocardial FDG uptake, but it has less impact compared to FFA levels.

Long fasting periods such as > 12 and > 18 hours are reported to suppress the physiological FDG uptake.<sup>1,10</sup> Our present study's results demonstrated that the SUVmax of the myocardium and the CMV were significantly correlated with the patients' fasting period and hospitalization status. The frequency of CMV0 of physiological cardiac FDG uptake was more frequently seen in the patients who fasted longer (i.e., > 18 hours). Therefore, fasting > 18 hours, not > 12 hours, could reduce and often suppress the physiological cardiac FDG uptake measured by CMV. We also suspect that the difference between outpatients and inpatients might be related to different diets and different medical conditions.

### LIMITATIONS

This study has some methodological limitations. It was a retrospective study from a single center. Information about the patients' fasting times was based on self-reporting. At our institution, patients are instructed not to consume any food other than plain water for  $\geq 6$  hours prior to the injection of FDG. A nurse or doctor checks each patient's fasting duration before the FDG injection. We thus believe that the information given by the patients is reliable. Information about the

patients' diets and FFA levels before the scan was lacking; it is possible that dietary factors and the FFA level could affect the cardiac FDG uptake. In this study, unfractionated heparin (UFH) was not injected prior to the FDG injection. Therefore, the effect of UFH on the blood pool or liver uptake cannot be discussed. We also did not determine the clinical importance of volume-based analyses. Further clinical investigations into this issue are warranted.

### NEW KNOWLEDGE GAINED

Rather than the left ventricle cavity and liver, the descending aorta is suitable to determine the threshold for the volume-based analysis of cardiac FDG PET. The fasting time and hospitalization status were significantly associated with the cardiac metabolic volume and SUVmax.

### CONCLUSIONS

We conducted a quantitative and highly reliable analysis of the cardiac FDG uptake in patients without heart disease. The individual FDG uptake threshold should be determined from the descending aorta rather than from the LV cavity and the liver, since the descending aorta showed high inter-operator reliability and independence from dietary relations. The fasting time and hospitalization status were significantly associated with the cardiac metabolic volume. A fasting period of more than 18 hr was suitable to evaluate inflammatory or malignant diseases of the heart without physiological myocardial uptake.

### Acknowledgements

*We thank Shigeo Oomagari, MSc, Yuki Tomiyama, PhD, and Eriko Suzuki for their support of this study.*

### Disclosure

*All authors have no conflicts of interest to disclose.*

### References

1. Manabe O, Yoshinaga K, Ohira H, et al. The effects of 18-h fasting with low-carbohydrate diet preparation on suppressed physiological myocardial (18)F-fluorodeoxyglucose (FDG) uptake and possible minimal effects of unfractionated heparin use in patients with suspected cardiac involvement sarcoidosis. *J Nucl Cardiol.* 2016;23:244–52.
2. Hyun SH, Choi JY, Shim YM, et al. Prognostic value of metabolic tumor volume measured by <sup>18</sup>F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. *Ann Surg Oncol.* 2010;17:115–22.

- Burger IA, Casanova R, Steiger S, et al.  $^{18}\text{F}$ -FDG PET/CT of non-small cell lung carcinoma under neoadjuvant chemotherapy: background-based adaptive-volume metrics outperform TLG and MTV in predicting histopathologic response. *J Nucl Med.* 2016;57:849–54.
- Ohira H, Mc Ardle B, de Kemp RA, et al. Inter- and intra-observer agreement of FDG-PET/CT image interpretation in patients referred for assessment of Cardiac Sarcoidosis. *J Nucl Med.* 2017;58:1324–9.
- Manabe O, Ohira H, Yoshinaga K, Naya M, Oyama-Manabe N, Tamaki N. Qualitative and quantitative assessments of cardiac sarcoidosis using  $^{18}\text{F}$ -FDG PET. *Ann Nucl Cardiol.* 2017;3:125–30.
- Ahmadian A, Brogan A, Berman J, et al. Quantitative interpretation of FDG PET/CT with myocardial perfusion imaging increases diagnostic information in the evaluation of cardiac sarcoidosis. *J Nucl Cardiol.* 2014;21:925–39.
- Masuda A, Naya M, Manabe O, et al. Administration of unfractionated heparin with prolonged fasting could reduce physiological  $^{18}\text{F}$ -fluorodeoxyglucose uptake in the heart. *Acta Radiol.* 2016;57:661–8.
- Blomberg BA, Bashyam A, Ramachandran A, et al. Quantifying [(1)(8)F]fluorodeoxyglucose uptake in the arterial wall: the effects of dual time-point imaging and partial volume effect correction. *Eur J Nucl Med Mol Imaging.* 2015;42:1414–22.
- Choi Y, Hawkins RA, Huang SC, et al. Evaluation of the effect of glucose ingestion and kinetic model configurations of FDG in the normal liver. *J Nucl Med.* 1994;35:818–23.
- Ishida Y, Yoshinaga K, Miyagawa M, et al. Recommendations for (18)F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. *Ann Nucl Med.* 2014;28:393–403.
- Hirata K, Kobayashi K, Wong KP, et al. A semi-automated technique determining the liver standardized uptake value reference for tumor delineation in FDG PET-CT. *PLoS ONE.* 2014;9:e105682.
- Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50:122S–50S.
- Kaneta T, Hakamatsuka T, Takanami K, et al. Evaluation of the relationship between physiological FDG uptake in the heart and age, blood glucose level, fasting period, and hospitalization. *Ann Nucl Med.* 2006;20:203–8.
- Morooka M, Moroi M, Uno K, et al. Long fasting is effective in inhibiting physiological myocardial  $^{18}\text{F}$ -FDG uptake and for evaluating active lesions of cardiac sarcoidosis. *EJNMMI Res.* 2014;4:1.
- Youssef G, Leung E, Mylonas I, et al. The use of  $^{18}\text{F}$ -FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med.* 2012;53:241–8.
- Israel O, Weiler-Sagie M, Rispler S, et al. PET/CT quantitation of the effect of patient-related factors on cardiac  $^{18}\text{F}$ -FDG uptake. *J Nucl Med.* 2007;48:234–9.
- Manabe O, Yoshinaga K, Ohira H, et al. The effects of 18-h fasting with low-carbohydrate diet preparation on suppressed physiological myocardial F-fluorodeoxyglucose (FDG) uptake and possible minimal effects of unfractionated heparin use in patients with suspected cardiac involvement sarcoidosis. *J Nucl Cardiol.* 2015;23:244–52.
- Keramida G, Potts J, Bush J, Dizdarevic S, Peters AM. Hepatic steatosis is associated with increased hepatic FDG uptake. *Eur J Radiol.* 2014;83:751–5.
- Osborne MT, Hulten EA, Singh A, et al. Reduction in (1)(8)F-fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. *J Nucl Cardiol.* 2014;21:166–74.
- Ito K, Okazaki O, Morooka M, Kubota K, Minamimoto R, Hiroe M. Visual findings of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with cardiac sarcoidosis. *Intern Med.* 2014;53:2041–9.
- de Groot M, Meeuwis AP, Kok PJ, Corstens FH, Oyen WJ. Influence of blood glucose level, age and fasting period on non-pathological FDG uptake in heart and gut. *Eur J Nucl Med Mol Imaging.* 2005;32:98–101.
- Miyagawa M, Tashiro R, Watanabe E, et al. Optimal patient preparation for detection and assessment of cardiac sarcoidosis by FDG-PET. *Ann Nucl Cardiol.* 2017;3:113–6.
- Ohira H, Tsujino I, Yoshinaga K. (1)(8)F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. *Eur J Nucl Med Mol Imaging.* 2011;38:1773–83.