Diagnosis and Detection of Myocardial Injury in Active Cardiac Sarcoidosis

– Significance of Myocardial Fatty Acid Metabolism and Myocardial Perfusion Mismatch –

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Background: Myocardial injury can be detected more sensitively using ^{123}I -radioiodinated 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) than thallium-201 (TL). The present study investigated whether ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) uptake as an index of active inflammation in patients with cardiac sarcoidosis (CS) is associated with BMIPP and TL findings, and whether dual single-photon emission computed tomography (SPECT) can facilitate diagnosis of CS.

Methods and Results: We retrospectively enrolled 52 consecutive patients with suspected CS who were assessed on FDG-PET/computed tomography (CT) and BMIPP/TL dual SPECT. The SPECT images were divided into 17 segments and then BMIPP and TL total defect scores (BMDS, TLDS) as well as mismatch scores (BMDS-TLDS: sumMS) were calculated. Maximum standardized uptake value (SUVmax) in the entire myocardium was obtained from FDG-PET/CT. SUVmax was much higher in patients with, than without CS ($P < 0.0001$). BMDS was higher and sumMS much higher in CS ($P < 0.05$ and $P < 0.0001$, respectively). The sensitivity and specificity of sumMS to detect CS were 74% and 80%, respectively. SUVmax was not associated with either BMDS or sumMS in the patients with CS. On multivariate analysis, the combination of sumMS and SUVmax had greater prognostic significance compared with each parameter on its own.

Conclusions: BMIPP and TL dual-tracer mismatch is a useful finding to diagnose CS, and adds greater diagnostic value to SUVmax on FDG-PET/CT. (*Circ J* 2015; **79**: 2669–2676)

Key Words: Cardiac sarcoidosis; Inflammation; Metabolic imaging; Myocardial perfusion; Positron emission tomography

Cardiac sarcoidosis (CS) is reportedly present in approximately 25% of patients with systemic sarcoidosis,¹ but CS is often difficult to diagnose because highly specific diagnostic tests of endomyocardial biopsy (EMB) for histological confirmation are unreliable and not sufficiently sensitive.² Therefore many patients with CS might present with asymptomatic myocardial injury followed by congestive heart failure, atrioventricular block (AVB) or ventricular arrhythmia that are not appropriately treated and thus lead to sudden cardiac death.³

Non-invasive cardiac imaging has recently been developed: cardiac magnetic resonance (CMR) and ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) were added to the Japanese Ministry of Health and Welfare (JMHW) modified diagnostic criteria for CS in 2006.⁴ With regard to FDG-PET, however, physiological myocardial FDG uptake was a critical drawback for the diagnosis of CS. A recent report suggested that long-term fasting or strict carbohydrate diet for >18h enabled visualization of active inflammation with sufficient inhibition of physiological uptake,⁵ which has contributed greatly to the diagnosis and detection of active inflammation in CS.^{6,7} This has considerably improved the ability to diagnose CS when EMB is negative in patients with suspected CS.

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In contrast, the assessment of myocardial injury and left ventricular (LV) function are clinically important for future risk management in CS patients. ^{123}I -radioiodinated 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) is a branched-chain fatty acid that was developed to evaluate fatty acid metabolism.⁸ This tracer is widely used in Japan to detect myocardial ischemia without stress tests in patients with unstable or vasospastic angina.⁹ This phenomenon is based more on severely damaged fatty acid metabolism as “ischemic memory” than upon perfusion injury caused by myocardial ischemia.^{10,11} The uptake of BMIPP was found to be more impaired than that of the myocardial perfusion tracer, thallium-201 (TL) in patients with CS,¹² but only a low number of patients were assessed in that study.

Many reports have also suggested that isolated CS can exist without extracardiac disease, based on the JMHW criteria 2006.^{13–17} These reports showed that many patients with isolated CS have been misdiagnosed for years because of negative EMB and lack of apparent extracardiac sarcoidosis.

The present study investigated whether dual tracer single-photon emission computed tomography (SPECT) is useful to diagnose CS and whether FDG uptake as a parameter of active inflammation is associated with myocardial injury detected on BMIPP and TL in patients with CS.

Methods

Study Patients

Among 109 consecutive patients with CS or suspected CS who were initially assessed on cardiac FDG-PET/CT between August 2012 and December 2014 at Tokyo Women's Medical University Hospital, those who met the following criteria were retrospectively enrolled in the present study. The inclusion criteria consisted of age ≥ 20 years and BMIPP/TL dual SPECT assessment within 3 months before or after FDG-PET/CT. The exclusion criteria consisted of known myocardial infarction, angina pectoris, already known hypertrophic cardiomyopathy (HCM), other known etiologies of cardiomyopathy and previous steroid treatment. The institutional review board approved the retrospective study design.

FDG-PET/CT

The patients were placed on strict carbohydrate restriction for 12 h followed by 12-h fast and then infused with 50 IU/kg heparin at 15 min before i.v. injection of FDG (3.7 MBq/kg). Whole body FDG-PET was acquired, starting 60 min later, with a 2-min emission per bed position in the craniocaudal direction from the skull base to the mid-thigh using a Biograph mCT64 PET/CT scanner (Siemens Medical Systems, Erlangen, Germany). Whole body CT was acquired with shallow breath under 120 kVp and 50 mAs for attenuation correction.

Subsequently, cardiac PET was obtained in a 2-bed position with a 10-min emission. Cardiac CT was acquired with respiratory gating or shallow-expiration breath-holding to prepare transmission maps for attenuation correction. Images were reconstructed using time-of-flight (TOF)-ordered subset expectation maximization (OSEM). CT and PET data were accurately coregistered using dedicated software (e-soft, Siemens) to generate fusion images.

BMIPP and TL Dual SPECT

Patients were simultaneously injected with TL (74 MBq) and BMIPP (111 MBq) while at rest and then BMIPP and TL dual SPECT images were acquired starting 20 min thereafter using an ECAM dual-headed gamma camera (Toshiba, Tokyo, Japan)

equipped with low-energy general-purpose collimators. Data were acquired over 180° in 32 steps of 50 s each in a 64×64 matrix with electrocardiographic gating of 8 frames per cardiac cycle. The TL and BMIPP data were obtained using symmetrical 72 ± 10 - and 159 ± 10 -keV windows, respectively, to separate the distribution of the isotopes.¹⁸

CMR

Patients without the relevant contraindication underwent CMR.

Cardiac MR images were acquired on either Intera Achieva 1.5T (Phillips) or Ingenia 3.0T (Phillips) with a cardiac-dedicated phased-array coil. Cine images were acquired in multiple short-axis, vertical long-axis and 4-chamber view for assessment of LV function. Ten minutes after the additional administration of 0.1 mmol/kg gadolinium-DTPA, short-axis and 4-chamber images were obtained with spin echo to assess for the presence of late gadolinium-enhancing (LGE) lesions.

Image Analysis

The maximum standardized uptake value (SUVmax) as FDG uptake in the entire myocardium was automatically measured using Syngo.via® (Siemens, Erlangen, Germany). The SPECT images were divided into 17 segments¹⁹ and BMIPP and TL defects were visually scored by 2 experienced nuclear medicine staff in each segment according to a 0–4 scale (0, normal; 4, absent). Total BMIPP and TL defect scores in the entire LV were calculated as BMDS and TLDS. Summed mismatch score (sumMS) was obtained as the sum of each mismatch score in the 17 segments as shown in our previous study.¹⁸ Cardiac function was assessed on quantitative gated TL-SPECT to generate LV ejection fraction (LVEF; %) and end-diastolic volume (EDV; ml). For CMR images, LGE pattern was classified as subepicardial, midwall, subendocardial and transmural types.²⁰

Diagnostic Criteria

CS was diagnosed based on the modified 2006 JMHW criteria.¹⁷ FDG-PET was also added to the diagnostic criteria. On visual assessment, CS was negative if myocardial FDG uptake was visually lower than blood pool uptake, or positive if cardiac FDG uptake was distributed in a “focal” or “focal and diffuse” pattern, based on the Japanese Society of Nuclear Cardiology Recommendations²¹ in patients who fulfilled the JMHW criteria.

Isolated CS was diagnosed as follows: (1) presence of cardiac symptoms such as heart failure, ventricular tachycardia or ≥ 2 nd degree AVB that developed at < 60 years of age;³ and (2) positive cardiac FDG uptake distributed in a focal or focal and diffuse pattern and partly overlapping the region of LGE on CMR if available, or partly overlapping the region of a perfusion defect on TL SPECT regardless of extra-cardiac lesions.^{7,22} Subepicardial or transmural LGE pattern is reported to be a characteristic finding of CS,²⁰ and this was considered as a helpful finding for diagnosis of isolated CS. Cardiologists in the study group and the nuclear cardiology staff discussed the final diagnosis of isolated CS.

Statistical Analysis

Data are expressed as average $\pm$ SD of continuous variables. Group differences between all CS, non-CS, JMHW CS and isolated CS patients for SUVmax, BMDS, TLDS and sumMS were analyzed using unpaired Student t-test or Mann-Whitney U-test as appropriate. Categorical data including clinical characteristics and LGE pattern were analyzed using the Chi-squared test to compare between the non-CS and 2 CS groups.

Table 1. Imaging and Clinical Findings of Isolated CS Not Proved on EMB

Patient ID no.	Age (years)	FDG-PET positive	FDG on TL defect	FDG on LGE	LGE pattern	Clinical characteristics		
						cAVB	VT	EF<50%
1	65	+	+	ND	ND	+	+	+
2	20	+	–	+	Epi+MW	+	–	–
3	55	+	+	+	MW	–	+	–
4	50	+	+	+	Epi+TM	–	–	+
5	62	+	+	+	Epi	–	+	+
6	62	+	+	ND	ND	+	–	–
7	62	+	–	+	Epi+TM	–	+	+
8	68	+	+	+	Epi+TM	–	–	+
9	70	+	+	+	Epi+TM	–	+	+
10	58	+	+	+	Epi	–	–	+
11	71	+	+	+	Epi	–	–	+

cAVB, complete atrioventricular block; CS, cardiac sarcoidosis; EF, ejection fraction; EMB, endomyocardial biopsy; Epi, subepicardial; FDG, ^{18}F -fluorodeoxyglucose; FDG-PET, FDG-positron emission tomography; LGE, late gadolinium enhancement; MW, midwall; ND, cardiac magnetic resonance not done; TL, thallium-201; TM, transmural; VT, ventricular tachycardia.

Table 2. Clinical Patient Characteristics vs. Presence of CS

	Total	Non-CS	CS			P-value (non-CS vs. CS) [†]
			All	JMHW CS	Isolated CS	
n	52	25	27	15	12	
Age (years)	56±13	55±14	57±13	56±12	58±14	0.64
Male	30 (58)	16 (64)	14 (52)	6 (40)	8 (67)	0.38
Extracardiac sarcoidosis	17 (33)	3 (12)	14 (52)	15 (100)	0 (0)	NE
Histologically proven CS	5 (9.6)	0 (0)	5 (19)	4 (27)	1 (8.3)	NE
cAVB	23 (44)	11 (44)	12 (44)	8 (53)	4 (33)	0.97
VT	29 (56)	15 (60)	14 (52)	8 (53)	6 (50)	0.55
ICD or CRTD	14 (27)	8 (32)	6 (22)	3 (20)	3 (25)	0.48
Lysozyme (μg/ml)	5.4±2.8	4.4±2.3	6.2±2.9* [†]	6.6±3.4	5.7±2.2	0.026
ACE (U/L)	11.3±6.6	9.9±5.8	12.4±7.0	15.2±7.3* [‡]	8.5±4.4	0.20
BNP (pg/ml)	131±199	105±126	151±243	158±255	144±242	0.44
EDV (ml)	105±41	112±45	99±37	91±42	108±30	0.26
ESV (ml)	65±38	70±43	60±33	69±9.3	63±8.4	0.36
EF (%)	43±14	43±15	44±14	46±16	40±11	0.73

Data given as average±SD or n (%). *P<0.05. [†]CS(–) vs. CS(+) all; [‡]JMHW vs. isolated CS. ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; CRTD, cardiac resynchronization therapy defibrillator; EDV, end-diastolic volume; ESV, end-systolic volume; ICD, implantable cardioverter defibrillator; JMHW CS, CS fulfilling the Japanese Ministry of Health and Welfare criteria; NE, not evaluated. Other abbreviations as in Table 1.

P<0.05 was considered statistically significant. Sensitivity and specificity for a diagnosis for CS were analyzed using receiver operating characteristic curves (ROC). Pairwise analysis was used for comparison of the ROC curves. All data were analyzed using MedCalc® (MedCalc Software, Ostend, Belgium).

Results

Of the 109 registered patients, 52 met the inclusion criteria and were enrolled in the study. CS was finally diagnosed in 27 patients (52%), among whom 15 met the JMHW criteria. Isolated CS was diagnosed in the remaining 12 patients. Twenty-six of 27 patients with CS underwent coronary angiography (CAG) and showed no significant stenosis, but one did not undergo CAG because of young age (20 years old). Nineteen of 25 patients without CS (non-CS) underwent CAG, and also showed no significant coronary stenosis. The other 6 patients with non-CS who did not have CAG were less likely to have

ischemic heart disease considering their low clinical coronary risk factors or previously performed stress perfusion imaging results. Among 5 patients (19%) with CS confirmed on EMB, one had isolated CS. The other 11 patients with isolated CS were diagnosed based on imaging and clinical findings as listed in Table 1. There were 3 patients (patients 1, 2, 6) with complete AVB that developed at the age of 58, 20, and 57 years, respectively. The patients who were not diagnosed with CS (n=25) were diagnosed with dilated cardiomyopathy (n=13), complete AVB alone (n=4), non-cardiac pulmonary sarcoidosis (n=2), dilated HCM (DHCM; n=2), apical hypertrophy (n=1), myotonic dystrophy-induced cardiomyopathy (n=1) and cardiomyopathy of unknown etiology (n=2).

Table 2 lists the clinical characteristics of the enrolled patients. The frequency of complete AVB, ventricular tachycardia, and of implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRTD) implantation did not differ significantly between patients with and

Figure 1. Comparison of indicators in hearts of patients with and without cardiac sarcoidosis (CS). (A) Maximum standardized uptake value (SUVmax) was significantly higher in whole hearts of patients with, than without, CS. (B) ^{123}I -radioiodinated 15-(*p*-iodophenyl)-3(*R,S*)-methylpentadecanoic acid (BMIPP) and thallium-201 (TL) defect scores (BMDS and TLDS, respectively) of patients with and without CS. (C) BMDS and summed mismatch scores (sumMS) were significantly higher in patients with CS.

without CS. Lysozymes were significantly higher in patients with, than without CS ($P<0.05$). Neither angiotensin-converting enzyme (ACE), brain natriuretic peptide, nor end-systolic volume (ESV) or EF differed significantly. Among the CS patients, ACE was higher ($P=0.012$) in JMHWS than in isolated CS. LV functional parameters including EDV, ESV and EF were all similar between the 2 groups.

Visually positive myocardial FDG uptake was observed in 27 patients (100%) with CS, and in 7 patients without CS (28%). SUVmax in the entire myocardium was much higher in patients with than without CS (7.09 ± 4.48 vs. 2.51 ± 1.64 , $P<0.0001$). TLDS did not significantly differ between patients with and without CS (10.0 ± 9.8 vs. 7.52 ± 7.33), but BMDS and summed mismatch score (sumMS) were significantly higher in patients with CS (BMDS: 14.9 ± 11.2 vs. 8.84 ± 7.81 , $P=0.029$; sumMS: 4.93 ± 3.20 vs. 1.32 ± 1.65 in, $P<0.0001$; **Figure 1**). On ROC analysis, SUVmax >2.4 had a sensitivity of 100% and specificity of 72% for the diagnosis of CS (area under the curve [AUC], 0.92), while sumMS ≥ 3 had a sensitivity of 74% and specificity of 80% (AUC, 0.84; **Figure 2**). Seven patients with SUVmax >2.4 were not diagnosed with CS because not only did they not meet the JMHWS criteria, but myocardial injury assessed on TL SPECT or LGE on CMR also did not correspond to regions of FDG uptake. The distribution of FDG uptake among these 7 patients appeared very similar to that of TL uptake.

In contrast, BMDS and TLDS each had lower diagnostic ability compared with sumMS (AUC 0.68 for BMDS; 0.55 for TLDS). There was a significant difference in ROC

curves between BMDS and sumMS ($P=0.015$); TLDS and sumMS ($P=0.0006$); and between BMDS and TLDS ($P=0.0006$; **Figure 2**).

Among the CS patients, there was no significant difference in BMDS, TLDS or sumMS between JMHWS and isolated CS. SUVmax was significantly higher in JMHWS than in isolated CS (9.25 ± 4.83 vs. 4.39 ± 1.86 , $P=0.0030$).

CMR was carried out in 27 patients (52%), of whom 16 had CS (JMHWS, $n=6$; isolated CS, $n=10$), and 11 had non-CS. All of the patients had positive LGE. LGE pattern on CMR had a low incidence of midwall pattern (30%) but a high incidence of subepicardial pattern in the CS group (90%) compared with the non-CS group (27%), and there was no significant difference in proportions of LGE patterns between the CS groups (**Table 3**).

The correlations between LVEF and BMDS and between LVEF and TLDS were both inverse (BMDS: $y=-0.498x+36.7$, $R^2=0.402$, $P<0.001$; TLDS: $y=-0.413x+28.0$, $R^2=0.363$, $P<0.001$), whereas there were no significant correlations between SUVmax, BMDS or TLDS and sumMS in patients with CS (**Figure 3**).

We determined the diagnostic value of CS from clinical and imaging parameters. On univariate analysis, only lysozyme was associated with diagnosis of CS (**Table 2**). On multivariate analysis, the combination of both imaging parameters SUVmax and sumMS had slightly improved diagnostic significance compared with either imaging parameter on its own (**Table 4**).

Figure 4 shows typical patients with and without CS.

Figure 2. Receiver operating characteristic analysis of maximum standardized uptake value (SUVmax) for (A) ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) and (B) ^{123}I -radioiodinated 15-(*p*-iodophenyl)-3(*R,S*)-methylpentadecanoic acid-thallium-201 (BMIPP-TL) dual single-photon emission computed tomography (SPECT) data for diagnosis of cardiac sarcoidosis. (A) Area under the curve (AUC) was 0.92 for SUVmax for FDG-PET. (B) In contrast, AUC was 0.84 for summed mismatch score (sumMS), 0.68 for BMIPP defect score (BMDS) and 0.55 for TL defect score (TLDS) for dual SPECT. There was a significant difference in ROC curves between BMDS and sumMS ($P=0.015$); TLDS and sumMS ($P=0.0006$); and BMDS and TLDS ($P=0.0006$).

Table 3. LGE Pattern vs. Presence and Type of CS

LGE pattern n (%)	Non-CS (n=11)	JMHW CS (n=6)	Isolated CS (n=10)	P-value for 3 groups	P-value (JMHW CS vs. isolated CS)
Subepicardial	3 (27)	6 (100)	9 (90)	0.0014	0.42
Midwall	8 (73)	2 (33)	3 (30)	0.105	0.89
Endocardial	0	0	0	—	—
Transmural	2 (18)	4 (67)	3 (30)	0.13	0.30

Abbreviations as in Tables 1,2.

Discussion

The present study found that patients with CS had more cardiac FDG uptake and a larger BMIPP-TL mismatch. Patients with CS were already reported to have BMIPP-TL mismatch in a previous study,¹² but there was no image comparison of SPECT and PET between CS and other cardiomyopathy. This is the first study to suggest the diagnostic potential of BMIPP-TL mismatch for CS as diagnosed on FDG-PET as well as JMHW.

Active inflammatory processes cause myocardial injury so gradually that metabolic disorders are more likely to occur before perfusion defects. In other words, mismatched segments might partly reflect ongoing cell damage by active inflammation as determined on FDG-PET. In contrast, patients without CS had large BMIPP defects but lower mismatch score. Thirteen patients had been diagnosed with dilated cardiomyopathy of unknown etiology but this might have included myocarditis-induced cardiomyopathy, in which regional myocardial injury was located as assessed on CMR.²³ These patients without active inflammation might not have had an ongoing

invasive focus inside or surrounding the injured scar tissue.

Isolated CS has not been listed as a disease category in the worldwide standard for diagnostic criteria, JMHW, but Chang et al described 5 patients with histologically proven isolated CS among 411 patients who received heart transplants between 2003 and 2011.¹⁴ Image-guided EMB has increased the success rates for histologically proven, isolated CS,¹⁶ and their data suggested that 33 (60%) of 52 patients with histologically proven CS had isolated CS.

Cardiac MR and FDG-PET/CT can detect isolated cardiac lesions more easily now than before.²² The present study also found isolated CS in 12 (44%) of 27 patients with CS. Despite the retrospective design, the prevalence of isolated CS in the present patients is similar to that in a previous study.¹⁶

We did not find a significant correlation between SUVmax and BMDS or sumMS in the present patients with CS. SUVmax is an index of inflammatory activity in patients with CS and such activity might vary during the process or according to the stage of the disease. Two patients with new-onset systemic sarcoidosis had high FDG uptake (SUVmax, 22.5 and 8.0) that was widely distributed in the LV, but no BMIPP

Figure 3. Correlations between (A) left ventricular ejection fraction (LVEF) and ¹²³I-radioiodinated 15-(*p*-iodophenyl)-3(*R,S*)-methylpentadecanoic acid (BMIPP) defect score (BMDS), and between (B) LVEF and thallium-201 (TL) defect score (TLDS) were both inverse (BMDS: $R^2=0.402$, $P<0.001$; TLDS: $R^2=0.363$, $P<0.001$). Relationship between (C) BMDS and maximum standardized uptake value (SUVmax) and between (D) summed mismatch scores (sumMS) and SUVmax in patients with CS ($n=27$): no correlation was seen.

Table 4. Diagnostic Accuracy for CS			
	SUVmax	sumMS	SUVmax+sumMS
F-value	23.1	25.5	28.7
R-value	0.562	0.581	0.735
P-value	<0.0001	<0.0001	<0.0001

sumMS, summed mismatch score; SUVmax, maximum standardized uptake value. Other abbreviations as in Table 1.

defects. Active inflammation during the very early phase of CS might not induce visible myocardial injury, which might become detectable only years later as chronic granulomatous inflammation on SPECT. In contrast, 2 patients had a relatively lower SUVmax (<5.0), but larger BMIPP defects (BMDS >15). Dilated cardiomyopathy had been diagnosed in both patients many years previously, but they were finally diagnosed with isolated CS due to its characteristic findings on CMR and FDG-PET/CT. In the present study, isolated CS had lower plasma ACE concentration and SUVmax on FDG-PET,

which indicated lower inflammation activity as compared with JMW CS. Matsui et al classified the pathology of CS on microscopy in 42 autopsies as exudative, granulomatous, combined and fibrotic.²⁴ The present 2 patients with high SUVmax in the early phase might be classified as having the exudative or granuloma type, whereas the latter 2 patients with isolated CS might be classified as having the combined granulomatous and fibrotic type, which proceeds to the end-stage of CS. In this stage, fibrotic change is predominant, and inflammation activity may be diminished.

FDG-PET was highly sensitive (100%) but relatively less specific (72%) for CS. Seven patients with SUVmax >2.4 were not diagnosed with CS because the distribution of FDG uptake appeared not on the injured myocardium but on the normal perfused region. The mechanism of the increased FDG uptake by the visually uninjured myocardium is unclear. Physiological myocardial FDG uptake is one cause, although the recent implementation of strict 24-h carbohydrate restriction suppresses physiological glucose metabolism, and is very reliable.^{25,26} Therefore the 7 patients probably did not have normal physiological FDG uptake but rather, they had abnormal metabolic uptake. SUVmax for 2 of them was >5.0. One had

dilated cardiomyopathy with New York Heart Association class III and repeated decompensated heart failure, thus glucose hyper-metabolism in the viable myocardium might have arisen due to a hemodynamically unstable state. The other was finally diagnosed with DHCM, which was determined clinically based on echocardiography, CMR and clinical history, but it was difficult to confirm the diagnosis. This patient had an exceptionally high SUVmax of 8.9. The FDG-PET findings of this disease on strict 24-h carbohydrate restriction diet preparation have not yet been reported. Further investigation to prove FDG uptake in HCM or DHCM is needed to differentiate inflammation from myocardial metabolic abnormalities.

A recent study by Yokoyama et al suggested that a threshold value of SUVmax to diagnose CS was >4.0 ,²⁷ which is higher than that in the present study (>2.4). The main reason for the different SUVmax threshold is the different definition of CS used in the present study. In the Yokoyama et al study, CS was diagnosed based only on JMW criteria, and no isolated CS was identified. If we also use the same definition for the diagnosis of CS, sensitivity and specificity were 100% and 79%, respectively (AUC, 0.94), for SUVmax >3.81 , which is similar to that in the Yokoyama et al study. Some isolated CS patients had low SUVmax, therefore the threshold value was

lower in the present study.

Mismatch between BMIPP and TL dual SPECT improved the diagnostic value of FDG-PET findings for the diagnosis of CS. This will contribute to the diagnostic stratification of non-ischemic cardiomyopathy. A BMIPP defect is closely associated with LVEF, and thus dual SPECT is especially useful to differentiate CS from other types of cardiomyopathy in patients with low LVEF. CMR is also useful to diagnose CS, particularly given that the subepicardial LGE pattern had a higher sensitivity (100%) for diagnosing CS in the present study (Table 3). In addition, FDG accumulation on LGE has diagnostic value for CS.¹⁷ Many patients with suspected CS, however, have received a pacemaker, ICD or CRTD, which are contraindicated for CMR, except for the recently introduced MR-conditional pacemaker.²⁸ Twenty-five patients (48%) could not undergo CMR for the diagnosis of CS, and 34 patients (65%) required cardiac-assist devices. SPECT is an essential tool to assess myocardial injury for such patients.

This study has some limitations. First, EMB from only a few patients were positive, therefore a diagnosis of isolated CS mainly depends on increased cardiac FDG uptake and perfusion or CMR. The effects of anti-inflammatory therapy might help to confirm the diagnosis, and thus further follow

up is needed. Second, the present study cohort was small. Nonetheless, a preliminary comparison of the sensitivity of BMIPP with FDG-PET to detect active inflammation was worthwhile.

Conclusions

BMIPP and TL dual-tracer mismatch is a useful finding to diagnose CS. The dual-tracer mismatch also improves the diagnostic value of SUVmax determined from FDG-PET/CT, in particular among patients with failing heart. The combination of both imaging modalities might help to elucidate the pathological processes of CS.

Conflicts of Interest

None.

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