FOCUS ISSUE ON CARDIAC SARCOIDOSIS

Focus Issue on Cardiac Sarcoidosis from International Congress of Nuclear Cardiology and Cardiac CT (ICNC 12) Symposium: Improving the Detectability of Cardiac Sarcoidosis—Practical Aspects of ^{18}F-fluorodeoxyglucose Positron Emission Tomography Imaging for Diagnosis of Cardiac Sarcoidosis—

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Abstract

Cardiac sarcoidosis (CS) increases the risk of cardiovascular event such as conduction abnormalities, ventricular arrhythmia and heart failure in patients with sarcoidosis. Recently the Heart Rhythm Society (HRS) issued a consensus on the detection of CS. In this report, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is employed in the diagnosis of CS. In 2012, the Japanese Ministry of Health, Labor, and Welfare (JMHLW) approved cardiac ^{18}F-FDG PET for the detection of inflammatory lesions in CS. The clinical use of ^{18}F-FDG PET has significantly increased worldwide. However, a study protocol and diagnostic criteria still need to be established.

Keywords: Cardiac involvement, ^{18}F-fluorodeoxyglucose, Positron emission tomography, Sarcoidosis

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Sarcoidosis is a systemic autoimmune disease characterized by granulomatous formations in various organs including skin, eye, lung, liver, spleen, central nervous system and heart (1,2). The cause of sarcoidosis is still unknown. Genetic susceptibility and environmental exposure are now considered to be possible risk factors for sarcoidosis (3). In fact, several fire fighters and others who responded following the attacks on the World Trade Center in the United States are now sarcoidosis patients (4). Exposure to various substances may have triggered sarcoidosis in this circumstance.

The epidemiology of sarcoidosis is 4.7 to 64 per 10 million in the general population. Scandinavia has the highest incidence rate at 50 to 60 per 10 million population. In contrast, Japan has a lower rate of occurrence at 1 to 2 patients per 10 million population (2). In general, sarcoidosis has a good outcome and the mortality rate is less than 5% (5). In contrast, cardiac sarcoidosis (CS) is less frequent but is a major cause of mortality. Though the Japanese population has a relatively lower disease rate, the incidence of CS is higher in Japan (6). Japanese research groups are therefore heavily focused on detection of and treatments for CS (7).

A recent study by Kandlin et al. reported a significant

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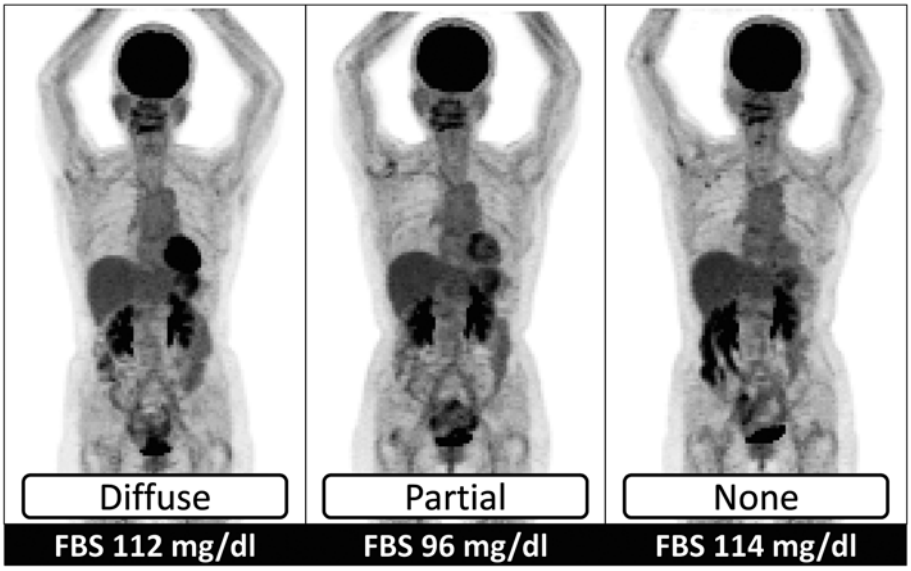

Fig. 1 Physiological myocardial ^{18}F-FDG uptake in patients with malignant lymphoma without heart disease. This patient underwent two fasting ^{18}F-FDG PET/CT studies. The myocardial ^{18}F-FDG uptake showed various patterns and was not associated with fasting blood sugar level.
FBS = fasting blood sugar

incidence of CS in patients with idiopathic advanced atrioventricular（AV）block in the young to middle-aged population（8）. Many cardiologists have therefore recognized the importance of a CS diagnosis. Based on this premise, the Heart and Rhythm Society（HRS）issued a consensus report on detecting CS that mentioned the role of ^{18}F-fluorodeoxyglucose（^{18}F-FDG）positron emission tomography（PET）in detecting cardiac lesions（9）. However, the preparation for and interpretation of ^{18}F-FDG PET/computed tomography（CT）for detecting CS have not been established. In 2014 the Japanese Society of Nuclear Cardiology（JSNC）issued guidelines for the diagnosis of CS using ^{18}F-FDG PET and is still working on standardization（10）. In this review, we will address recent developments in study preparation for and image interpretation of ^{18}F-FDG PET/CT imaging to detect CS.

Patient preparation

Myocardial metabolism

In a fasting state, myocardial metabolism consists of fatty acid metabolism and glucose metabolism. Fatty acid metabolism is the main source of myocardial energy, providing more than 90% of it（11,12）. The remaining 10% of energy comes from metabolism of glucose and other substances. Theoretically, glucose metabolism is very limited under fasting conditions. However, myocardial glucose metabolism varies among individuals. In some cases, for those with more than minimal glucose metabolism under fasting conditions, there can be physiological myocardial ^{18}F-FDG uptake during a PET study（Fig. 1）. In fact, Inglese et al. observed that myocardial ^{18}F-FDG uptake in 3 consecutive PET studies in the same patients was heterogeneous（13）. Yousef et al. reported that ^{18}F-FDG PET had high sensitivity in detecting CS and also had a significant inconsistency index for specificity（14）. The heterogeneity of specificity may be associated with physiological ^{18}F-FDG uptake. Therefore, some groups have come up with methods to suppress myocardial physiological glucose use（^{18}F-FDG uptake）. The following three preparation approaches have been applied to reduce physiological myocardial ^{18}F-FDG uptake（7,10）.

^{18}F-FDG preparation protocol

Fasting period

In light of the fact that physiological myocardial ^{18}F-FDG uptake occurs in the presence of glucose, a ^{18}F-FDG PET/CT protocol for detecting CS involves fasting conditions（7,10,15）. For oncology studies, guidelines of the Society of Nuclear Medicine and Molecular Imaging（SNMMI）in the United States recommend at least 4 to 6 h of fasting prior to ^{18}F-FDG PET/CT（16）. In accordance with the guidelines for oncology studies, earlier cardiac ^{18}F-FDG PET studies for the assessment of CS were performed after 5-12 h of fasting preparation（Table 1）（17-19）. As Yousef et al. noted, these studies showed heterogeneous specificity（14）. Physiological myocardial ^{18}F-FDG uptake has been considered to play

Table 1 Fasting time for FDG PET/CT

Author	Year	Patients (n)	Fasting time (h)	Sensitivity (%)	Specificity (%)
Yamagishi et al.（19）	2003	17	>5h	82	N/A
Okumura et al.（18）	2004	22	>12h	100	91
Ishimaru et al.（31）	2005	32	>12h	100	82
Ohira et al.（17）	2008	21	>12h	88	39
Langah et al.（20）	2009	76	>18h	85	90
Manabe et al.（32）	2013	67	>6h	96	62
Blankstein et al.（38）	2014	118	>3h	71	45

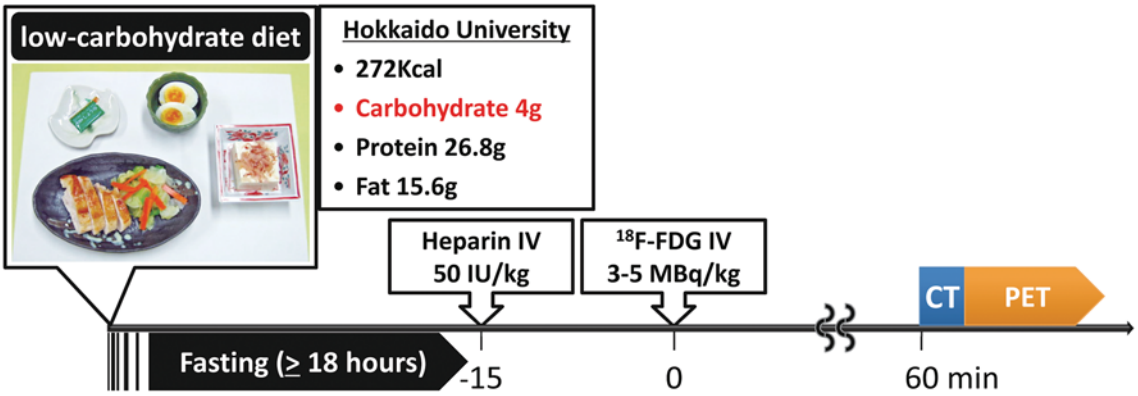

Fig. 2 Proposed ^{18}F-FDG PET/CT imaging protocol and sample low-carbohydrate diet menu（from Reference 7 with the permission of the authors and the publisher, Springer）.

an important role in reducing specificity, and some groups have therefore employed prolonged fasting in preparation for ^{18}F-FDG studies.

Langah et al. applied an 18-hour fast and reported high sensitivity in the diagnosis of cardiac sarcoidosis using ^{18}F-FDG PET（20）. This study also reported that the myocardial-to-blood pool ratio of ^{18}F-FDG decreased more significantly under the 18-h fasting condition than under a shorter fasting condition. In healthy individuals who followed a 24 h fast, there was a significant reduction in myocardial ^{18}F-FDG uptake（21）. When the JSNC committee issued guidelines for the diagnosis of CS using ^{18}F-FDG PET, it specified a minimum of 12 hours' fasting in preparation. At that time, there was insufficient evidence to support >18 hours fasting（10）. However, it now appears that many institutions are using 18 hours' fasting in preparation for ^{18}F-FDG PET（Fig. 2）（22,23）. While 18 hours' fasting may sound too long, in our institution, hospitalized patients have dinner at 6 P.M., then skip breakfast and come to the nuclear imaging laboratory at noon. The time from their last meal until they visit the nuclear medicine laboratory is approximately 18 hours. By the time patients complete some questionnaires and other preparations, more than 18 hours will have elapsed from the beginning of fasting until ^{18}F-FDG administration, so an 18-hour fast in preparation for PET is practicable.

Diet modification

Another approach that will reduce physiological myocardial ^{18}F-FDG uptake is diet modification. Dietary modification aims to make fatty acid metabolism exceed glucose metabolism and to suppress glucose metabolism in myocardium. A low-carbohydrate diet alone or a low-carbohydrate diet with an addition of a high-fat diet before ^{18}F-FDG PET/CT has been used along with fasting for ^{18}F-FDG PET（7,15,23）（Table 2）.

Lum et al. recommended carbohydrate withdrawal the night before ^{18}F-FDG PET/CT. They showed significantly suppressed physiological ^{18}F-FDG uptake in the entire myocardium（24）. In a randomized study of cancer patients, it was reported that the ingestion of a low-carbohydrate diet resulted in significantly reduced ^{18}F-FDG uptake in the entire myocardium, following a quantitative approach using maximum standardized uptake value（SUVmax）（20）. There has been no report on whether following a low-carbohydrate diet contributes to an improvement in diagnostic accuracy for cardiac sarcoidosis. However, a low-carbohydrate diet is a simple and clinically applicable approach（Fig. 3）（10）. Other cardiac ^{18}F-FDG PET studies to detect inflammatory lesions have also applied carbohydrate

Table 2 Diet modifications for FDG PET/CT

Author	Year	Patients (n)	Patients	Fasting time	Meal preparation
Lum et al.（24）	2002	69	Chest malignant tumor	Overnight fast	Low carbohydrate
Cheng et al.（28）	2010	63	Malignant tumor	15h	Low carbohydrate
Williams et al.（39）	2008	161	Malignant lymphoma	3-6h	Low carbohydrate and high fat
Wykrzykowska et al.（27）	2009	32	Suspected coronary artery disease		
Harisankar et al.（40）	2011	110	Malignant tumor	12h fasting 4h prior to high fat diet	Low carbohydrate and high fat（20.8g）

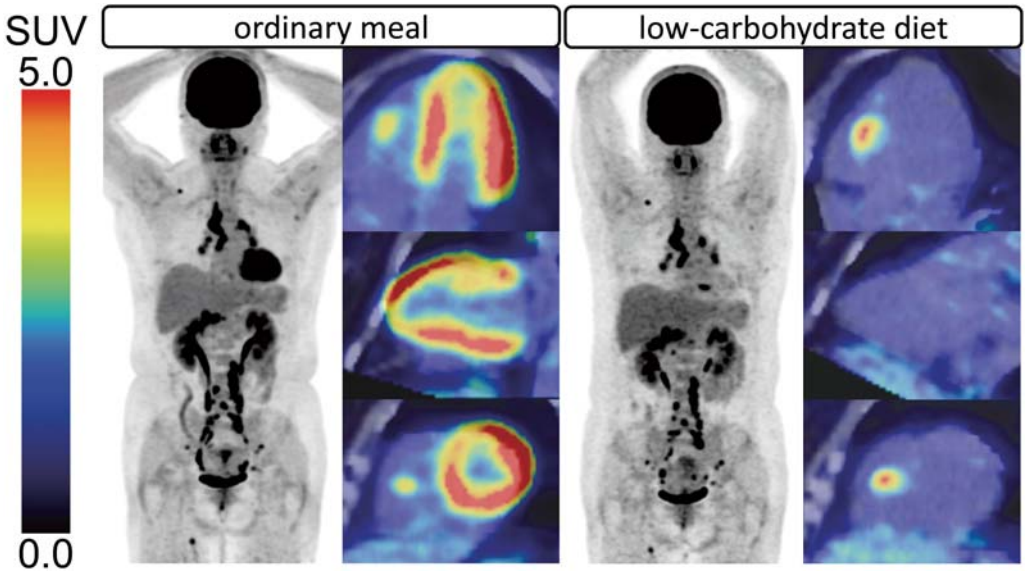

Fig. 3 Effects of low-carbohydrate diet
Physiological myocardial ^{18}F-FDG uptake was not found when the patient followed low-carbohydrate diet.
SUV＝standardized uptake value

restriction over 24 hours（25）.

In practice, the low-carbohydrate diet contains less than 5g of carbohydrate per meal. Ohira et al. developed a sample menu（Fig. 2）（7）. The starter is a boiled egg. The second appetizer is tofu with bonnet flakes and soy sauce. The main dish is grilled chicken breast with stir-fried vegetables. This menu does not include bread or rice. This meal includes a total of 272 kcal, including 4 g of carbohydrates, 26.8 g of protein, and 15.6 g of fat. The idea behind our menu is for patients to feel they have a full stomach without eating bread or rice. One piece of tofu may be able to make patients feel full. One boiled egg may also enhance the feeling of fullness. These are key aspects of our menu. Other facilities use low-carbohydrate bread developed for diabetes patients and that could be part of an alternative menu.

Another dietary modification is to eat a high-fat meal before ^{18}F-FDG injection. Williams et al. at Beth Israel Deaconess Medical Center specified a low-carbohydrate diet the night before and a high-fat diet 3 to 6 h before patients underwent ^{18}F-FDG -PET/CT. This method produced a significant reduction in ^{18}F-FDG uptake in the entire myocardium（SUVmax）（26,27）. However, another group reported no significant decrease in myocardial ^{18}F-FDG uptake in the group in which a high-fat diet was followed, as compared with results for the group following a 12-hour fast alone. Currently there is no established view on the advantage of a high-fat diet（28）. This approach may be useful but its usefulness has yet to be established and will be the subject of future investigation.

Heparin use

Long fasting and diet modification aim to gradually suppress myocardial glucose metabolism. In contrast, heparin administration is a different concept which aims to rapidly increase plasma free fatty acids（FFAs）（29）. Doing so may induce the reduction of myocardial glucose metabolism（30）. On the basis of these findings, Ishimaru et al. developed a heparin administration

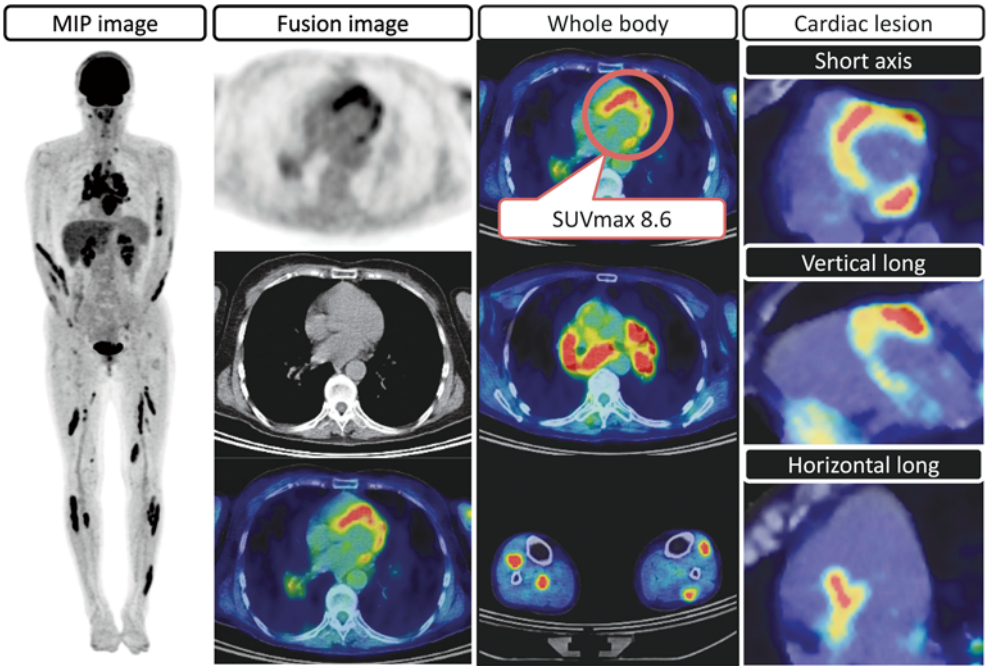

Fig. 4 Standard approach to interpretation of fasting ^{18}F-FDG PET/CT images

Table 3 Practical protocols and image interpretations for FDG PET/CT

	Protocol
Preparation	
Fasting time	Greater than 18 hours
Diet modification	Low carbohydrate diet（carbohydrate less than 5g）
Heparin administration	15 minutes prior to ^{18}F-FDG administration 50 IU/kg
Image interpretation	
Intensity of FDG uptake	Uptake or counts greater than liver uptake
Positive pattern	Focal and focal on diffuse Patchy

protocol for ^{18}F-FDG PET in the diagnosis of CS（31）. They administered heparin at a dose of 50 IU/kg. Blood FFA levels increase rapidly following heparin administration, so heparin is administered intravenously 15 min before ^{18}F-FDG administration（Fig. 2）（31，32）. Issues to be considered with heparin use include effectiveness and dose. There has been no report examining the relationship between the dose of heparin and the suppression of myocardial ^{18}F-FDG uptake. With regard to the effect of heparin use on myocardial ^{18}F-FDG uptake, Ishimaru et al. conducted a study of 30 healthy subjects and found that myocardial ^{18}F-FDG uptake was not fully suppressed（14 cases, 47%）, and that it was diffuse（31）. Heparin preadministration was considered to produce the suppression effect in only some patients. Heparin preadministration is considered to be effective in theory. Some reports even suggest the usefulness of heparin preadministration in the diagnosis of cardiac sarcoidosis. However, it is not an established method according to JSNC recommendations at this time（10）. Therefore, future studies and the development of an appropriate protocol are required.

Practical issues related to ^{18}F-FDG PET imaging for diagnosis of CS are addressed in Table 3.

Image interpretation

Although we are focusing on the detection of cardiac involvement, sarcoidosis is generally a multi-organ disease. Therefore, the initial approach to looking at ^{18}F-FDG PET/CT images is to examine a whole-body image of maximum intensity projection（MIP）to see which organs are most affected（Fig. 4）. The next step is to look at coronal PET/CT fusion images. The PET and CT fusion images are particularly useful to distinguish between lung, lymph node, and cardiac involvement. In the case of positive myocardial uptake, heart signal counts should be compared to physiological liver activity using either SUVmax or visual assessment（33）. If the heart signal counts are greater than those of the liver according to either SUVmax or visual assessment,

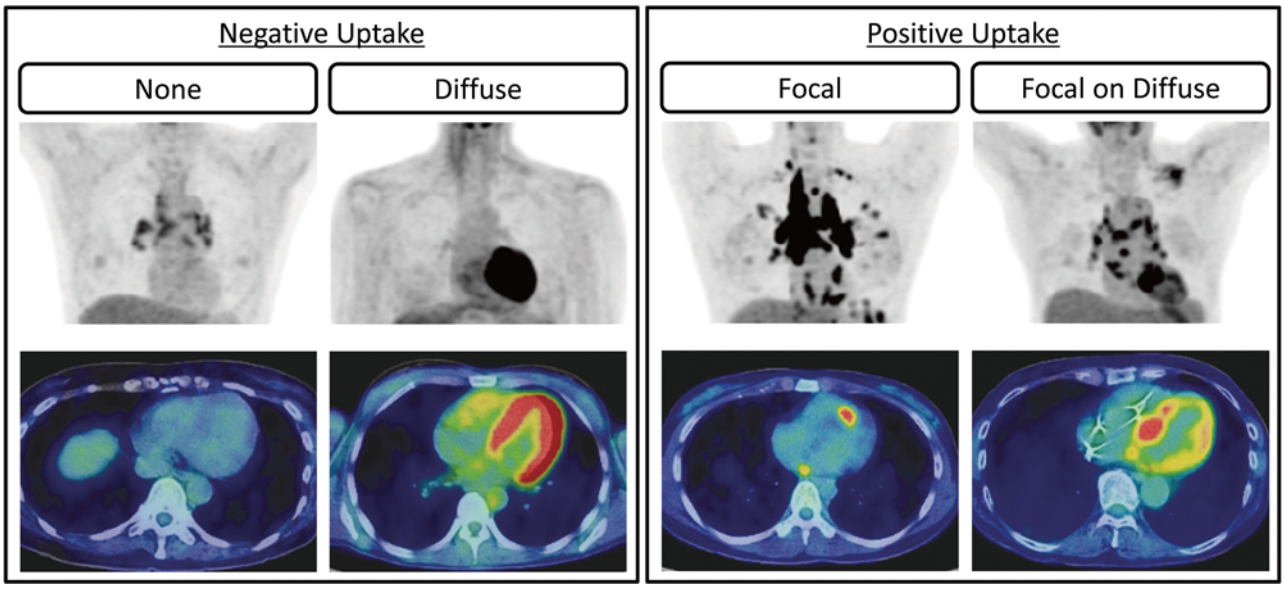

Fig. 5 Definition of positive ^{18}F-FDG uptake in diagnosis of cardiac sarcoidosis

uptake should be considered pathologically positive. When there is cardiac uptake and sufficient signal counts, cardiac-specific slices similar to those for cardiac perfusion imaging can be reconstructed. These detailed slices may help identify involved lesions. The Japanese Ministry of Health, Labor, and Welfare（JMHLW）has approved the use of ^{18}F-FDG PET to find the location of cardiac involvement in patients with CS（34），and therefore cardiac-specific slices are important.

The ^{18}F-FDG positive pattern was defined according to JSNC recommendations. Based on JSNC recommendations, focal uptake and focal on diffuse uptake are categorized as positive（Fig. 5）. The HRS statement referred to a patchy pattern as positive（9）. A patchy pattern may be similar to a focal pattern. Sarcoidosis is a granulomatous disease. Considering granuloma formations, focal patterns on ^{18}F-FDG PET should be appropriate. There have been intense discussions on whether a focal on diffuse pattern reflects CS or physiological myocardial ^{18}F-FDG uptake. In a heart-failure model, animal studies have suggested a switch to a more fetal form of energy metabolism in the heart, with increased glycolysis and suppression of FFA metabolism（35）. In the experimental model, the shift to glucose metabolism was associated with upregulating of GLUT4 in failing heart（36）. If this theory is applied to myocardial metabolism in the failing heart, a focal on diffuse pattern in CS with heart failure can be positive. On the other hand, Wallhause and Stone et al. reported that myocardial metabolic efficiency was reduced. The substrate use was changed as a result of inappropriate, catecholamine-induced, enhanced FFA use secondary to elevated levels of serum FFAs acting as a metabolic substrate for the myocardium by wasteful cycling of FFAs through intramyocardial lipolysis and suppression of glucose metabolism（37）. The focal on diffuse pattern definitely requires further investigation.

Conclusions and future directions

Diagnosing CS remains a challenge and is receiving increased attention in clinical cardiac practice. ^{18}F-FDG PET/CT has been recognized as an important diagnostic modality for detecting CS. In order to increase the accuracy of ^{18}F-FDG PET, preparation protocols and diagnostic criteria are very important. Efforts to standardize protocols and diagnostic criteria are ongoing.

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Conflicts of interest

None

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