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Assessment of Myocardial Blood Flow and Cardiac FDG Uptake Using Positron Emission Tomography: The 17th Society Award of Japanese Society of Nuclear Cardiology

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Abstract

Cardiac positron emission tomography (PET) has evolved over the several decades since its introduction. In current clinical practice and research, cardiac PET imaging is accepted as a valuable noninvasive modality for assessing various cardiac diseases such as coronary artery disease (CAD), cardiac tumors, and inflammatory diseases including cardiac sarcoidosis (CS). PET enables the imaging and evaluation of the cardiovascular system by myocardial perfusion with ^{82}Rb, ^{13}N-NH_3 and ^{15}O-H_2O, and those of metabolism and inflammation using ^{18}F-fluorodeoxyglucose (^{18}F-FDG). PET has demonstrated superior diagnostic accuracy for the detection of CAD and also has well-established prognostic value. The combination of qualitative and absolute quantifications of myocardial blood flow enhances the diagnostic accuracy for multiple-vessel disease and provides incremental functional and prognostic information. In this review, we focus on the current and future roles of cardiac PET imaging, on the basis of our own experience.

Keywords: ^{18}F-fluorodeoxyglucose, Cardiac PET, Inflammation, Myocardial blood flow, Perfusion, Positron emission tomography

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Several positron emission tomography (PET) tracers are used for the evaluations of cardiac diseases. The most widely used tracers are ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and myocardial perfusion tracers such as ^{82}Rb, ^{13}N-NH_3, and ^{15}O-H_2O (1). ^{18}F-FDG PET is known to be a sensitive modality for detecting hibernating viable myocardium as well as for the noninvasive determination of the malignancy of cardiac tumors. In 2012, the Japanese Ministry of Health, Labour, and Welfare (JMHLW) expanded the health care coverage for cardiac ^{18}F-FDG PET to include the detection of inflammatory lesions of cardiac sarcoidosis (CS) and the coverage for ^{13}N-NH_3 PET to the assessment of ischemic heart disease. In this review, we summarize the roles of cardiac PET on the basis of our own experience for evaluating coronary artery disease and cardiac inflammatory diseases.

^{18}F-FDG PET

^{18}F-FDG PET is used in various ways, including the evaluation of the viability of myocardium, cardiac tumors, and lesions with active inflammation such as those observed in CS.

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Table 1 Japanese Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) 2015 criteria for cardiac sarcoidosis

1. Histological diagnosis group
   Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with a histological or clinical diagnosis of extracardiac sarcoidosis.
2. Clinical diagnosis group
   Cardiac sarcoidosis is confirmed when, although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid cell granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and the following conditions and the following diagnostic criteria are satisfied:
   (a) Two or more of the five major criteria are met
   OR
   (b) One of the five major criteria and two or more of the three minor criteria are met

Major criteria
1. Advanced atrioventricular block or sustained ventricular tachycardia
2. Basal thinning of the interventricular septum or morphological abnormality (aneurysm, wall thinning, or wall thickening)
3. Depressed ejection fraction (<50%) or regional wall motion abnormality
4. Abnormal uptake of 67Ga or 18F-fluorodeoxyglucose in the heart
5. Late gadolinium enhancement on cardiac magnetic resonance

Minor criteria
1. Abnormal electrocardiographic findings: ventricular arrhythmias (non-sustained ventricular tachycardia or multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q-waves
2. Perfusion defects on nuclear imaging
3. Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration of moderate grade

The myocardium can derive energy from a variety of sources including free fatty acids (FFAs), glucose, lactate, and ketone bodies (2). ^{18}F-FDG, an analog of glucose, is thus taken up in viable myocardial cells by the glucose transporter (GLUT).

Approaches to assess the viability of myocardium

In examinations of the viability of myocardium, the ^{18}F-FDG administration is performed after the subject has fasted for 6-12 hr and oral or intravenous glucose loading has been achieved. The ^{18}F-FDG uptake by viable myocardium is maximized under the glucose-loaded condition, which leads to high image quality due to the reduced regional variation in myocardial accumulation. A region of reduced myocardial perfusion but preserved ^{18}F-FDG uptake indicates viable myocardium, which has possibility for functional recovery after adequate revascularization (3).

Approaches to eliminate physiological myocardial ^{18}F-FDG uptake

In assessments of a cardiac tumor or inflammatory disease, the physiological ^{18}F-FDG uptake sometimes causes a false positive result or difficulties in the assessment (4). Several methods to reduce the physiological myocardial ^{18}F-FDG uptake have been proposed. A prolonged fasting time leads a metabolic shift of myocardium from glucose use to FFA use under the absence of dietary glucose supply and carbohydrate intake (2). A low-carbohydrate and high-fat food intake can induce a decrease of glucose production and glucose oxidation, whereas FFA is mobilized from adipose tissue and the increased FFA becomes an alternative fuel in the myocardium. The FFA level is thus an important factor inhibiting physiological ^{18}F-FDG uptake (2). Unfractionated heparin (UFH) rapidly increases the FFA level via an activation of the lipoprotein lipase (5). However, patients with and without physiological ^{18}F-FDG uptake could not be distinguished by their FFA levels after 15 min of UFH administration (2). A combination of methods such as prolonged fasting, take a low carbohydrate and or high-fat food and UFH administration might be required to suppress the physiological ^{18}F-FDG uptake, although this remains a matter of open question.

The degree of ^{18}F-FDG uptake in a tumor or inflammatory lesion is related to the cellular metabolic activity and the expression of GLUT. As do malignant tumor cells, active inflammatory cells such as macrophages, neutrophils, and lymphocytes demonstrate an increased expression of GLUT.

Assessment of cardiac tumor

Malignant cardiac tumors show a higher uptake of ^{18}F-FDG compared to benign cardiac tumors (6, 7) with some exceptions (8). The use of ^{18}F-FDG PET can thus contribute to the noninvasive preoperative determination of malignancy. Whole body ^{18}F-FDG PET/computed tomography (CT) also has the advantage of detecting metastases of malignant cardiac tumors or other sites in cases of malignant lymphoma (7).

Clinical role of ^{18}F-FDG PET in CS

Cardiac involvement is a critical prognostic factor in patients with systemic sarcoidosis. CS is an inflammatory myocardial process that includes non-caseating granulomas (9). The most commonly referenced clinical criteria for the diagnosis of CS were established by JMHLW, as revised by Japanese Society of Sarcoidosis and other Granulomatous Disorders (JSSOG) in 2015 (Table 1) (10, 11). An Expert

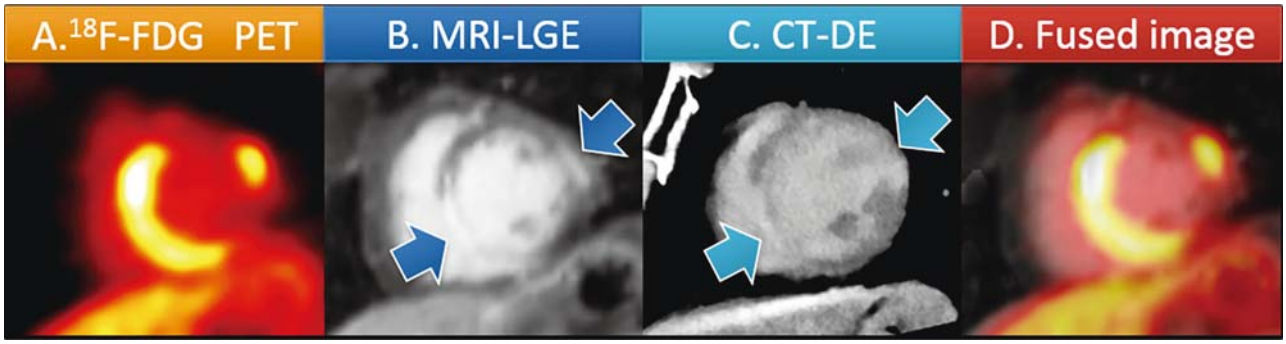

Fig. 1 Image comparison of cardiac sarcoidosis.
Short axis image of ^{18}F-FDG PET (**a**), late gadolinium-enhanced MRI (MRI-LGE) (**b**), delayed contrast-enhanced CT (CT-DE) (**c**), and fused image of ^{18}F-FDG PET and MRI-LGE (**d**) are displayed. Focal uptakes of ^{18}F-FDG are seen at the septal to inferior wall and anterolateral wall, which indicate the active inflammation due to the cardiac sarcoidosis. Hyper-enhancements are seen on the similar sites at MRI-LGE and CT-DE which could indicate scar tissues or granulomas (arrows).

Consensus Statement regarding the diagnosis and management of CS was published by the international Heart Rhythm Society (HRS) (12). In that statement, the criteria for cardiac involvement are based on one or more of the following findings: (a) Steroid- and/or immunosuppressive-responsive cardiomyopathy or heart block, (b) Unexplained reduced left ventricular ejection fraction <40%, (c) Unexplained sustained (spontaneous or induced) ventricular tachycardia, (d) Mobitz type II second- or third-degree heart block, (e) Patchy uptake at dedicated cardiac ^{18}F-FDG PET (in a pattern consistent with CS), (f) Late gadolinium enhancement (LGE) at cardiac magnetic resonance (MR) imaging (in a pattern consistent with CS), and (g) Positive ^{67}Ga scintigraphy uptake (in a pattern consistent with CS) in patients with a histologic diagnosis of extra-cardiac sarcoidosis. In addition, other causes of cardiac manifestations have been reasonably excluded.

In both the JSSOG criteria and the HRS's consensus statement, ^{18}F-FDG PET/CT and the LGE of cardiac magnetic resonance (CMR) imaging are important noninvasive assessments of CS. Our group demonstrated that delayed contrast-enhanced CT also showed high sensitivity for detecting CS compared to CMR (Fig. 1) (11).

^{18}F-FDG PET is a useful tool for the detection of active CS lesions as well as for the monitoring of the treatment response and for early recurrence, because the ^{18}F-FDG uptake reflects active inflammation (13). A patient's ^{18}F-FDG uptake value and the extent of LGE sometimes show a discrepancy because ^{18}F-FDG uptake may not be seen in a chronic but inactive lesion (14).

^{18}F-FDG uptake patterns are conventionally divided into four groups: (i) without myocardial ^{18}F-FDG uptake, (ii) definite diffuse uptake in the entire left ventricular (LV) wall, (iii) focal ^{18}F-FDG uptake, and (iv) focal on diffuse ^{18}F-FDG uptake in the LV wall. Group (i) is considered to be a negative uptake pattern; in group (ii) the ^{18}F-FDG uptake is generally physiological and does not indicate an abnormality, and groups (iii) and (iv) are considered to be positive for CS (4).

The determination of the location of ^{18}F-FDG uptake is important for the diagnosis of CS, and focal ^{18}F-FDG uptake in the interventricular septum in particular is associated with atrioventricular block (5). ^{18}F-FDG uptake in the right ventricle (RV) due to CS is less frequent but more specific in the diagnosis of CS, because physiological uptake in the RV is less common and less intense compared to that in the LV (15).

Quantitative analysis of ^{18}F-FDG uptake

The maximum standardized uptake value (SUVmax) has been used for semi-quantitative measurements to assess the intensity of ^{18}F-FDG uptake. However, the SUVmax reflects only the value of a single voxel and thus does not account for the entire metabolic condition of the focus of disease. A volume-based analysis using ^{18}F-FDG PET has emerged as another approach to assess the extent and activity of ^{18}F-FDG uptake (2, 10). Ahmadian et al. applied a volume-based analysis to CS and reported that the metabolic activity estimated by ^{18}F-FDG PET was a reliable independent predictor of cardiac events in CS patients (16).

Perfusion PET

Myocardial perfusion imaging (MPI) using ^{82}Rb or ^{82}N-NH_3 PET allows both qualitative and quantitative measurements. Establishing the reproducibility of MBF measurements is important for serial PET measurements of flow changes after various therapeutic interventions. Our study using ^{82}Rb PET demonstrated that rest and hyperemic MBF measurements and CFR had good repeatability (17). A qualitative assessment of PET MPI provides high diagnostic accuracy for the detection of obstructive CAD due to its high spatial resolution and reproducibility (17, 18). The quantification of myocardial

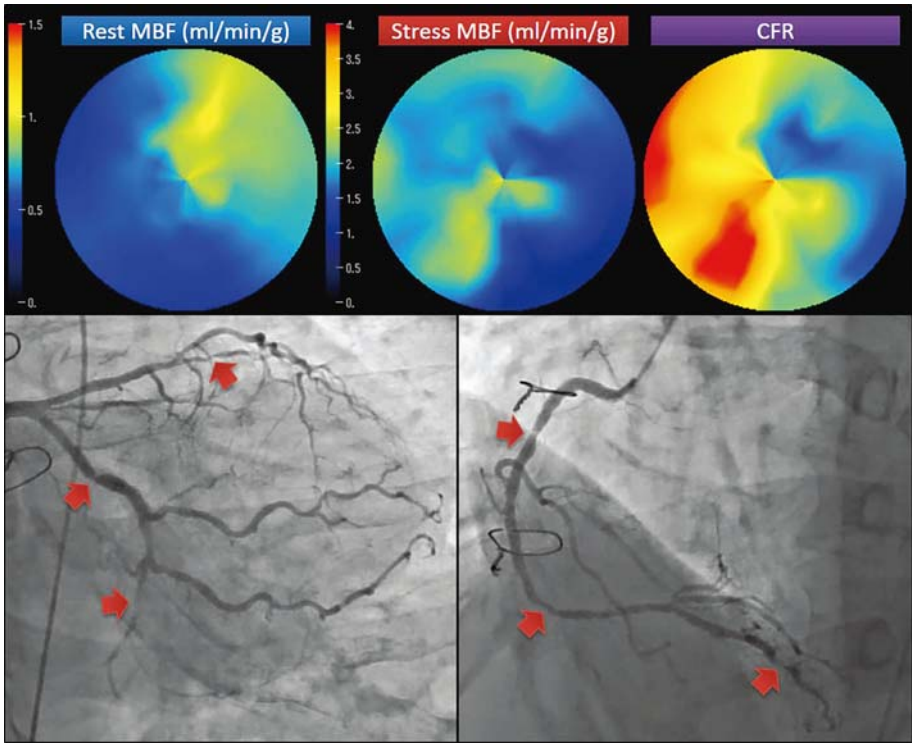

Fig. 2 Assessment of coronary artery disease using PET.
Abnormal wall motion was pointed out by echocardiography in a patient who had received the mitral valve replacement due to infective endocarditis. ^{15}O-H_2O PET and coronary angiography were undergone for scrutiny of coronary artery disease. Polar maps of rest myocardial blood flow (MBF), stress MBF and coronary flow reserve (CFR) estimated by ^{15}O-H_2O PET and coronary angiography (CAG) of the left coronary artery and right coronary artery are displayed. Multiple-vessel disease with several narrowing lesions are found in the CAG (red arrows). The estimated MBF at rest, MBF at stress and CFR were 0.71 ml/min/g, 1.84 ml/min/g and 2.57, respectively. ^{15}O-H_2O PET show a large area of CFR decrease involving the anterolateral, lateral and inferior wall.

blood flow (MBF) and coronary flow reserve (CFR) with a dynamic imaging analysis demonstrated additional values beyond those provided by a visual assessment for the evaluation of the functional severity of CAD (19). ^{15}O-water is the ideal tracer to estimate MBF values due to the linear relationship it provides between first-pass extraction and perfusion; however, it is difficult to assess ^{15}O-water visually due to its low signal-to-noise ratio (20). Quantitative measurement has advantages for detection of multi-vessel disease and the risk stratification (Fig. 2). CFR can give the combined information of epicardial stenosis and abnormality in microvascular function which is an early manifestation of coronary atherosclerosis.

New MBF quantification approaches

Our group recently reported the capability of both dynamic multidetector computed tomography (MDCT) (21) and dynamic perfusion MRI (22) to quantify the MBF and CFR in comparisons with ^{15}O-water PET results.

In a unique way, PET is used to assess vascular endothelial dysfunction, which is the earliest abnormality in the development of coronary atherosclerosis and which is affected by several coronary risk factors (23-25). PET scanning with a cold pressor test demonstrated that cigarette smoking impaired coronary endothelial function. Our group revealed that coronary endothelial dysfunction due to cigarette smoking was reversible by short-term smoking cessation in young smokers, but not in middle-aged smokers (23). Long-term smoking exposure could lead to more advanced coronary endothelial dysfunction and atherosclerosis.

Conclusions

PET is a powerful functional imaging tool for the evaluation of cardiac disease. ^{18}F-FDG PET is useful for various purposes including evaluations of the viability of myocardium, cardiac tumors, and lesions with active inflammation such as those observed in CS. Myocardial perfusion tracers allow both qualitative and quantitative assessments of CAD. Quantitative measurements provide the advantage of detecting multivessel disease and contributing to risk stratification.

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Conflicts of interest

All authors declare that they have no conflict of interest to report.

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