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REVIEW ARTICLE

Recent advances in cardiac positron emission tomography for quantitative perfusion analyses and molecular imaging

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Abstract
Positron emission tomography (PET) has been used to noninvasively evaluate myocardial perfusion and metabolism. For clinical assessments of myocardial perfusion, the quantitative capability of PET permits precise assessments of ischemia and microcirculatory dysfunction, playing an important role in patient management and outcome analyses. ^{18}F-fluorodeoxyglucose (FDG) PET has recently been used to identify active cardiovascular lesions such as cardiac sarcoidosis, endocarditis, and aortitis. This may hold promise for the early and accurate diagnosis of such fatal diseases, as well as for patient management. This review covers new and clinical roles of cardiac PET in treatment strategies and patient outcomes.

Keywords Cardiac PET · Myocardial blood flow · Active myocardial lesions · Quantitative analysis

Introduction

With the rapid development of imaging modalities, a variety of new applications for the noninvasive imaging of cardiac diseases have appeared [1, 2]. Positron emission tomography (PET) has long been used as a functional imaging modality that uses several PET tracers to target perfusion, metabolism, innervation, and inflammatory conditions [3–8]. More recently, this imaging technique has played important roles in many clinical conditions such as early clinical diagnosis, patient management, and monitoring treatment response [9]. Here we review the recent clinical applications of cardiac PET for cardiovascular diseases, with a focus on quantitative myocardial perfusion imaging and inflammatory imaging using PET.

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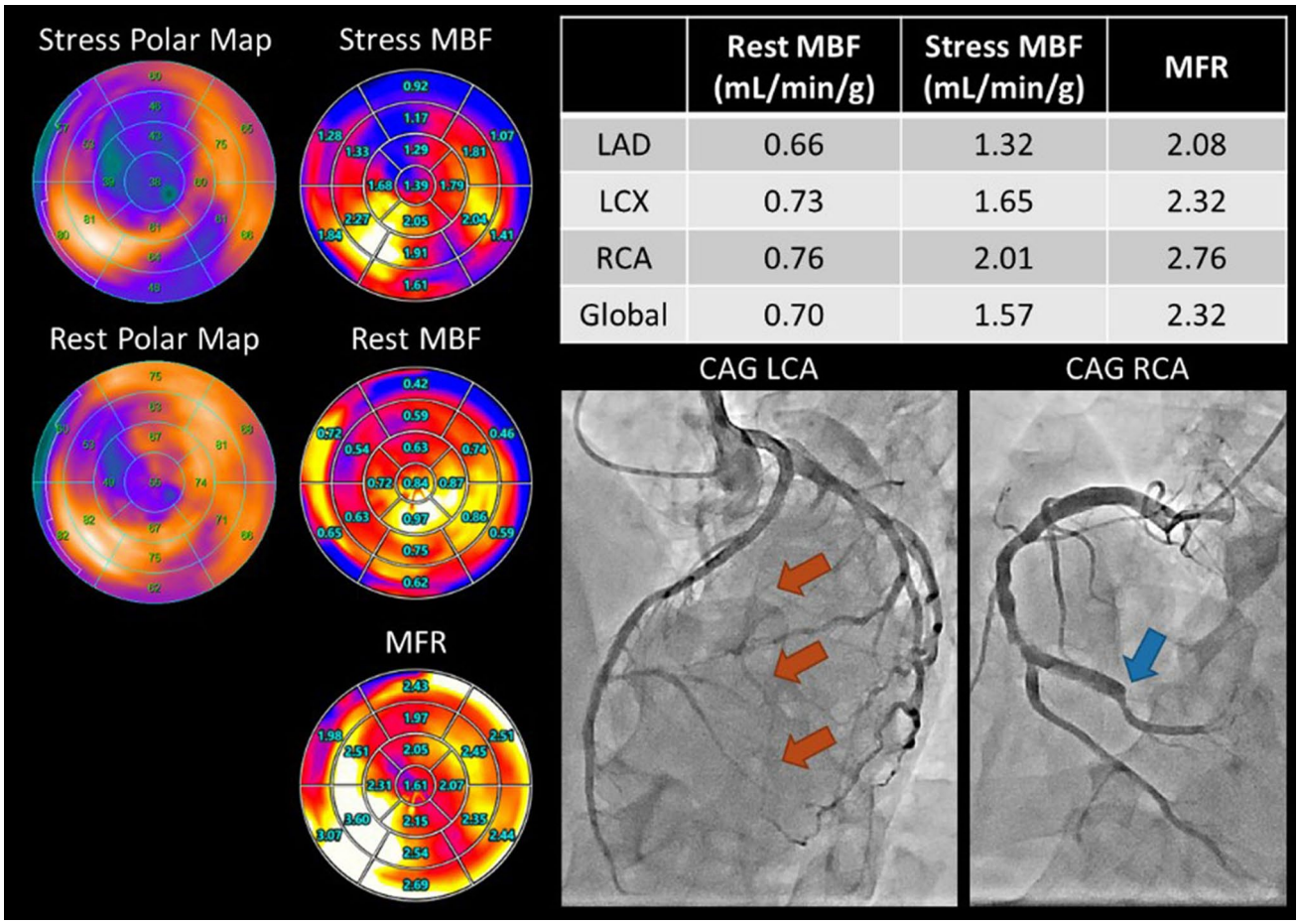
Advantages of PET perfusion assessments

PET has a number of advantages. It provides higher quality myocardial perfusion images than conventional single-photon emission computed tomography (SPECT) imaging. PET myocardial perfusion imaging (MPI) thus provides more accurate diagnostic values and a higher incremental prognostic value than SPECT–MPI in patients with coronary artery disease (CAD) [10–13]. Another major advantage of PET over SPECT is the ability to quantify tracer concentrations. PET, therefore, permits the quantitative analysis of myocardial blood flow (MBF; in mL per g per min) and the myocardial flow reserve (MFR: as the ratio of the MBF at peak hyperemia to the MBF at rest), using a suitable radiotracer kinetic model. Along with perfusion imaging and coronary angiography, quantitative MBF and MFR values provide cardiologists with unique insights into diagnostic and prognostic values (Fig. 1). In fact, there has been growing evidence of the usefulness of the MBF and MFR in assessments of CAD patients [14–17].

Since MBF and MFR analyses play important roles in determining the severity of CAD, a quantitative analysis similar to that used for the MBF has been reported in the uses of dynamic acquisition with cardiac computed



	Rest MBF (mL/min/g)	Stress MBF (mL/min/g)	MFR
LAD	0.66	1.32	2.08
LCX	0.73	1.65	2.32
RCA	0.76	2.01	2.76
Global	0.70	1.57	2.32

Fig. 1 This patient had a history of myocardial infarction in the left anterior descending (LAD) artery. In the chronic phase, ^{13}N-ammonia PET/CT revealed severe myocardial perfusion defects in the broad anterior and inferior walls during stress, which are partially reversible at rest (left figure). Quantitative myocardial blood flow at rest and stress were estimated (right upper figure). Invasive coronary angiography showed that the main LAD was patent, but the diagonal branch was jeopardized by the stent of the LAD and the obstructive posterolateral branch of the right coronary artery (bottom right)

tomography (CT), magnetic resonance imaging (MRI), and SPECT with a kinetic model analysis similar to that used with PET [18–22]. Most of the quantitative parameters have been validated by a comparison with cardiac PET. Such quantitative analyses may add important value to CAD assessments in addition to the coronary structure and myocardial functional analyses afforded by CT and MRI. On the other hand, CT and MRI contrast agents, as well as SPECT perfusion tracers, may not be suitable for the quantitative assessments of the MBF since the extraction fractions of contrast agents are not very high in the high-flow range compared to commonly used PET tracers such as O-15 water and N-13 ammonia [10, 18, 19, 23]. Doppler echocardiography can be used to estimate the coronary flow (velocity) reserve based on the vasodilator capacity, defined as the ratio of the maximal hyperemic coronary blood flow to the resting flow [24, 25].

PET applications for risk analyses and interventional therapy

The MFR estimated by PET has emerged as a powerful marker of the risk for adverse cardiovascular outcomes including cardiac death [14, 15, 26, 27]. The MFR is an integrated measure of the entire coronary vasculature, reflecting epicardial coronary anatomy and microvascular dysfunction [28]. Using the fractional flow reserve (FFR) is another approach to evaluations of the functional consequences of coronary stenosis; a determination of the FFR measures the pressure differences across a coronary artery stenosis during maximum hyperemia [29]. Since coronary angiography is often insufficient in guiding a percutaneous coronary intervention (PCI) procedure, the FFR has gained wide acceptance for estimating whether a coronary lesion may cause myocardial ischemia requiring coronary revascularization.

The DEFER study, which included subjects with stable chest pain, showed that a prognostic factor of CAD was the ability to induce myocardial ischemia as reflected by an FFR < 0.75, whereas a prognosis of FFR ≥ 0.75 was excellent and the risk of cardiac death or myocardial infarction related to the stenosis was < 1% per year and was not decreased by stenting [30]. The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study involving 1005 patients with multivessel CAD demonstrated that functional consequences of coronary stenoses revealed by the FFR were associated with significantly lower morbidity and mortality than a PCI guided only by anatomical coronary stenosis [31, 32]. Both the DEFER and FAME studies re-emphasized the importance of assessing the physiologic stenosis of the coronary artery.

A number of studies show a correlation between the MFR and FFR for estimating the functional significance of coronary stenosis. An initial comparison study revealed a close correlation between the MFR and FFR in patients with mostly single-vessel stenosis [33]. A quantitative estimation of the severity of stenosis by MFR does not depend on an intervessel comparison even for multivessel disease. However, several studies of patients with multivessel disease showed modest (not high) agreement between their MFR and FFR values [34].

Discordance between the MFR and FFR is explained in part by the fact that the FFR is a specific index of the epicardial artery, whereas the MFR is influenced not only by epicardial stenosis but also by microvascular disease [35]. In that study, the relative expansion of focal and diffuse disease reflected the linearity of the relationship between the MFR and FFR. Lesions with both an FFR ≥ 0.8 and an MFR ≥ 2.0 were concordant for the normal coronary artery, and lesions with both an FFR < 0.75 and an MFR < 2.0 were concordant for CAD with focal stenosis and microvascular disorder. Lesions with discordant MFR and FFR values (i.e., FFR < 0.75 and MFR ≥ 2.0, FFR ≥ 0.8 and MFR < 2.0) may reflect the degree and extent of focal and diffuse disease [36].

It is quite important to determine whether the MFR can be used to select appropriate CAD patients for optimal medical therapy (OMT), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Since the MFR is an integrated measure of the entire coronary vasculature, reflecting the epicardial coronary anatomy and microvascular dysfunction, both coronary revascularization and medical therapy may increase the MFR. Importantly, several studies have demonstrated that coronary revascularization for CAD is associated with early post-procedural improvements in the regional MFR [37–40]. Conversely, in a single-center retrospective study, a prognostic difference between CABG and PCI was seen only among patients with very low MFRs [15]. That study observed good outcomes for the patients with a preserved MFR by OMT, PCI, or CABG but significantly different outcomes for those with a reduced MFR, indicating microvascular dysfunction. The study's authors suggested that CABG may be a suitable treatment for these patients, with better outcomes than PCI or OMT [15]. The study assessed a total of 329 consecutive patients including patients with diabetes mellitus (40.1%), hypertension (88.2%), and dyslipidemia (73.3%), which indicates that much of the patients had an increased risk of microvascular dysfunction. For patients with microvascular dysfunction and CAD comorbid conditions, complete revascularization with CABG might be a more effective approach for global cardiovascular risk reduction. Although it was a single-center observational study, its results offer important insights into how to manage CAD patients, particularly those with microvascular dysfunction. In addition, a quantitative MFR analysis by PET should play an important role in appropriately managing many CAD patients [41].

We have analyzed global and regional MFR values before and 6 months after coronary revascularization using O-15 water PET in patients with obstructive CAD [17, 42] (Fig. 2). We observed a significant increase in the MFR only in the patients undergoing CABG (not OMT or PCI) in general. Among the patients with a reduced MFR (< 2.0), both PCI and CABG significantly improved the MFR [17]. The increases in global and regional MFR values were correlated with the degree of angiographic improvement after coronary revascularization. Such improvement was not related to the presence of subendocardial infarction assessed by MRI [42]. Given the fact that the effects of coronary revascularization depended on both the angiographic CAD burden before revascularization and the degree of angiographic improvement after revascularization, complete revascularization has great potential to improve the MFR in patients with high-risk CAD.

Molecular imaging using PET

PET has a great advantage over any other noninvasive imaging for performing various types of molecular imaging. ^{18}F-fluorodeoxyglucose (FDG)-PET has long been used for cardiovascular diseases. One of the classical applications of PET is for myocardial viability assessments. FDG-PET assesses glucose metabolism in the heart and thus the myocardial viability [43–46]. A region with preserved FDG uptake indicates the presence of viable myocardium. For this purpose, glucose administration with oral loading or an insulin–glucose clamp is applied to increase the FDG uptake in both the normal and ischemic but viable myocardium, whereas it does not induce FDG uptake in infarcted tissue.

FDG-PET has also been used to identify active inflammatory lesions, because glucose is also consumed in the inflammatory process [47, 48]. Depending on the

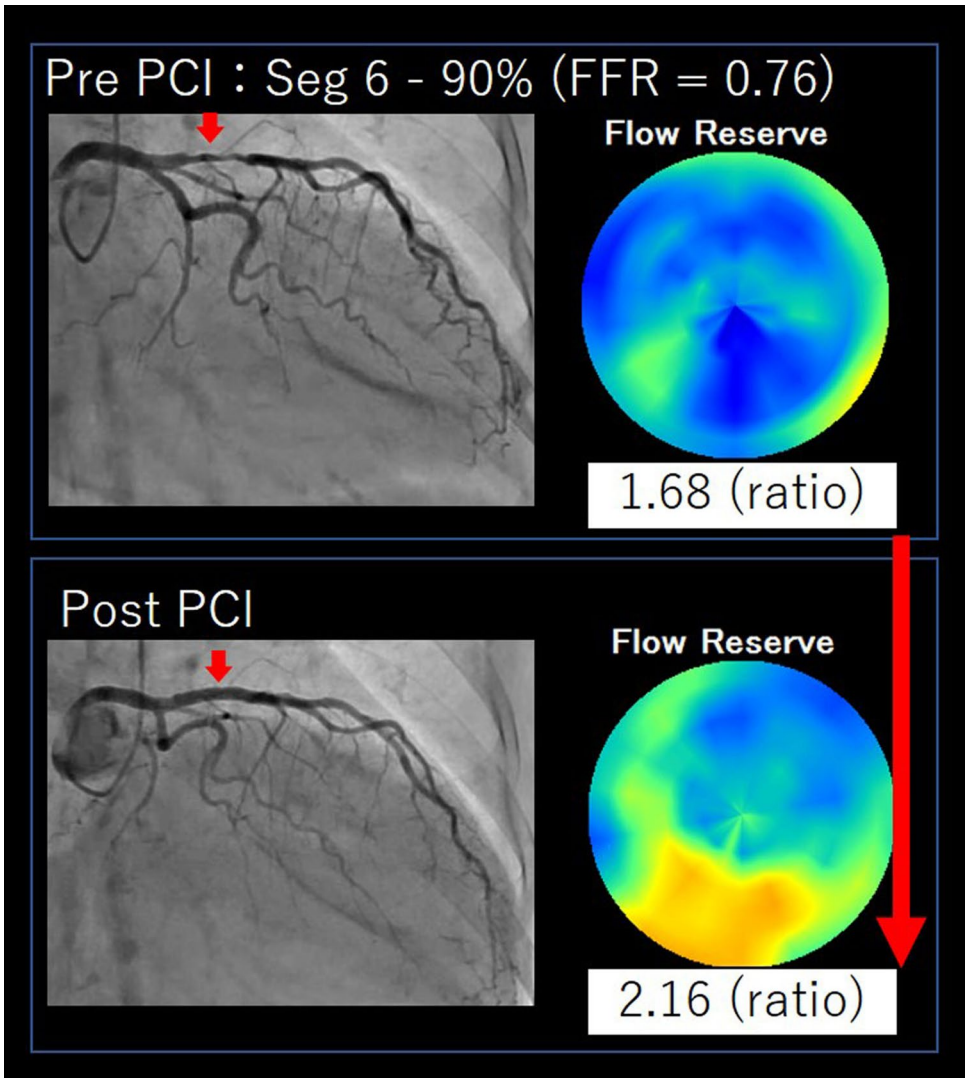


Fig. 2 The left figure shows a patient with obstructive disease in the left anterior descending artery. Six months after a percutaneous coronary intervention (PCI) with optical medical therapy, the global MFR increased

purposes of in vivo functional imaging, patients should be prepared carefully before the administration of FDG [49, 50]. Postprandial condition, glucose loading, or an insulin clamp is applied for a myocardial viability assessment in which FDG accumulates in both normal and ischemic but viable myocardium. A long fasting period with or without the administration of heparin is required to identify active inflammatory lesions with suppressed physiological myocardial FDG uptake. Patient preparation before the FDG administration is quite important since the FDG uptake in the myocardium is dependent on either the physiological uptake or an abnormal active uptake depending on the patient's condition. The activation of granulocytes and macrophages during inflammation enhances the uptake of FDG. Thus, FDG-PET is useful for detecting active cardiovascular inflammation [47, 51].

PET applications for assessing active cardiovascular lesions

Sarcoidosis is a noncaseating granulomatous disease with multi-organ involvement and generally a good prognosis. However, cardiac involvement in sarcoidosis is often associated with morbidity and death, mainly as a result of left ventricular dysfunction and arrhythmia such as ventricular tachyarrhythmia and conduction disturbance [52, 53]. Because of the lower sensitivity of histopathology-based diagnoses, imaging tools are important for the evaluation of cardiac sarcoidosis. In Japan, guidelines for the diagnosis of cardiac sarcoidosis were first published in 1992, and even in the 2006 revision of the guidelines, FDG-PET was not included in the diagnostic criteria. With the technological progress and the establishment of its usefulness for cardiac

sarcoidosis, FDG-PET was approved in 2012 by the Japanese Ministry of Health, Labour and Welfare and covered by insurance as an assessment tool for inflammatory cardiac sites. The guidelines for the diagnosis and treatment of cardiac sarcoidosis published in 2019 by the Japanese Society of Nuclear Cardiology included FDG-PET findings for one of the major criteria [54].

FDG-PET has been considered a useful tool for identifying cardiac and other organ involvement. The accumulation of FDG is associated with an active inflammatory process, thus allowing for the activity of the inflammatory disease to be evaluated [55–58] (Fig. 3). The Heart Rhythm Society (HRS) and the Japanese Society of Nuclear Cardiology (JSNC) recommend using FDG-PET and cardiovascular magnetic resonance (CMR) for the diagnosis of cardiac sarcoidosis [59, 60]. The late gadolinium enhancement (LGE) technique using CMR relies on the delivery of a chelated gadolinium contrast agent to the myocardium. This agent is biologically inert and distributes freely in the extracellular space. Therefore, a relative accumulation of the agent is seen in areas with increased extracellular volume such as fibrotic scars and sites of the formation of a non-caseating epithelioid cell granuloma in the delayed images [61]. Since the accumulation mechanisms of FDG and MRI contrast media are different, the information obtained does not necessarily correspond [62, 63].

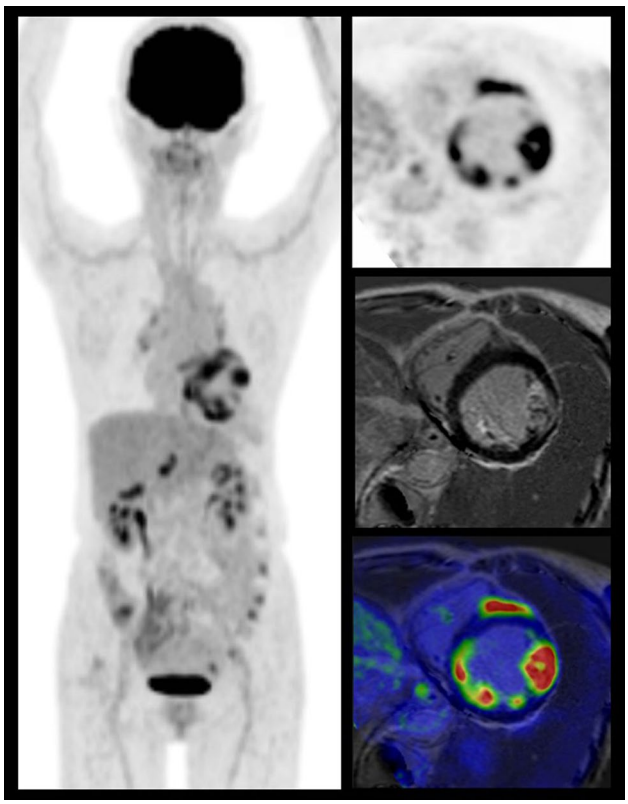


Fig. 3 A case of cardiac sarcoidosis scanned by a digital PET/CT scanner. Significant FDG uptake concordant with late gadolinium enhancement was observed by MRI. Digital PET improves the spatial resolution and might be useful to detect small inflammatory sarcoidosis lesions

The assessment of LGE is also valuable in the prognosis of cardiac sarcoidosis [64]. The combination of FDG and perfusion evaluation is useful not only for improving the accuracy of diagnoses but also for the predicting the outcomes of cardiac sarcoidosis [65]. A digital PET/CT scanner with high spatial resolution can improve the detection of patchy sarcoidosis lesions in the heart. In this case, digital PET clearly delineates epicardial and endocardial lesions at the left ventricle as well as patchy lesions at the right ventricular free wall in accord with the magnitude of severity, similar to the case with MRI (Fig. 3). Right ventricular FDG uptake may be more specific in the diagnosis of cardiac sarcoidosis [66], suggesting that digital PET/CT has the potential to improve the diagnosis of cardiac sarcoidosis (Fig. 3).

It is important to have patients fast for a long period to minimize the physiological FDG uptake in the myocardium for the assessment of cardiac sarcoidosis [50]. The long fasting and dietary modification prior to FDG-PET are important to suppress the physiological myocardial uptake, which provides major potential for a false-positive diagnosis of cardiac sarcoidosis. The JSNC states that the preparation of the patient for an FDG-PET examination should include a low-carbohydrate diet (< 5 g of carbohydrates) and prolonged fasting (a minimum of 12 h but up to 18 h if possible). A high-fat diet 3–6 h before the administration of FDG remains to be established, but there might be another approach to suppress the physiological myocardial uptake [54].

There have been a number of attempts to evaluate active cardiac sarcoidosis with no physiological myocardial uptake with the use of other PET tracers, including ^{18}F-fluorothymidine (FLT) and ^{18}F-fluoromisonidazole (FMISO) [67–70]. Although their uptake in active myocardial lesions is lower with these new techniques compared to the use of FDG, these other tracers have the potential to diagnose specific active sarcoidosis. In addition, these techniques may hold promise for identifying other active myocardial lesions — such as myocarditis — similar to FDG-PET.

Infective endocarditis can cause another type of severe cardiac inflammation, in which the diagnosis and management by FDG-PET plays important roles. Echocardiography, the mainstay for the diagnosis of infective endocarditis, can detect only structural damage in the heart. In addition to local damage in the myocardium, a metastatic infection, embolic phenomenon, or immune-mediated damage may result in considerable morbidity and mortality. In many cases, endocarditis can often be associated with a prosthetic valve. Cardiac CT and MRI thus have an inherent limitation for accurate image analyses. FDG-PET, in contrast, is a powerful tool not only for identifying active myocardial

lesions but also for detecting metastatic and embolic lesions throughout the body based on a whole-body PET survey [71–76]. In a meta-analysis of 13 studies involving 537 patients, PET/CT showed moderate sensitivity and specificity for the diagnosis of infective endocarditis [76]. However, the sensitivity improved when patients with suspected prosthetic-valve endocarditis were evaluated. These findings suggest that PET/CT has the potential to serve as an adjunctive diagnostic modality in challenging cases of possible infective endocarditis.

Aortitis is a generic term; it is defined as an inflammatory condition of infectious or noninfectious origin involving the aortic wall, such as Takayasu's arteritis, giant cell arteritis, and IgG4 autoimmune arteritis. This inflammatory process may deteriorate the aortic wall, resulting in potentially life-threatening vascular complications. It is, therefore, important to establish a diagnosis as early as possible. FDG-PET imaging has been used to accurately detect vascular inflammation in the aortic wall (Fig. 4), [77–83], and FDG-PET is considered a valuable tool for monitoring treatment effects in this disease.

FDG-PET/CT is widely used for the diagnosis, staging, and treatment response assessment for a wide range of hematologic and solid cancers (Figs. 5, 6). FDG-PET can be used for the noninvasive differentiation of benign and malignant cardiac tumors because most types of malignant tumors show increased glucose metabolism [84, 85]. Since CT and MRI also play important roles for this purpose, a combined analysis of anatomical/functional and molecular imaging should be applied to obtain an accurate diagnosis, to identify the tumor's location, for treatment planning, and for the treatment monitoring of cardiac tumors using integrated PET/CT and/or PET/MRI imaging [86, 87].

FDG-PET is commonly performed about 1 h after the administration of FDG in general clinical practice, mainly in oncological areas. However, an FDG-PET examination for cardiovascular imaging, PET imaging is preferably performed 90–120 min after the FDG administration. Residual blood pool activity remains with a slow blood pool clearance of FDG after a long fasting period. Better lesion contrast may thus be obtained slightly later than the conventional time after FDG administration [88].

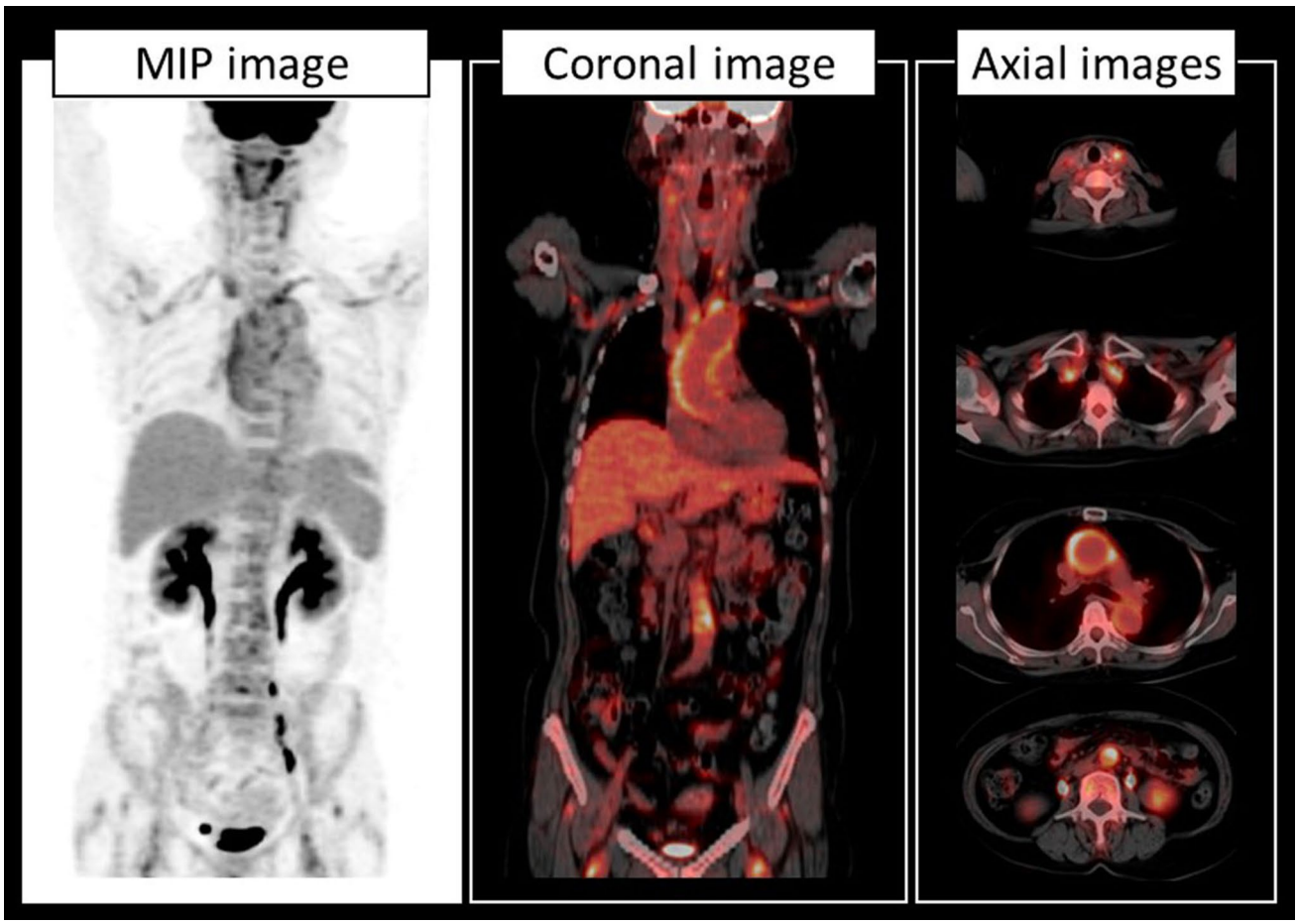


Fig. 4 A female in her 60 s presented with a 1-month history of unknown fever. The FDG PET/CT images showed intense uptake in the wall of the aorta, bilateral subclavian arteries, and common carotid artery compatible with a diagnosis of giant cell arteritis

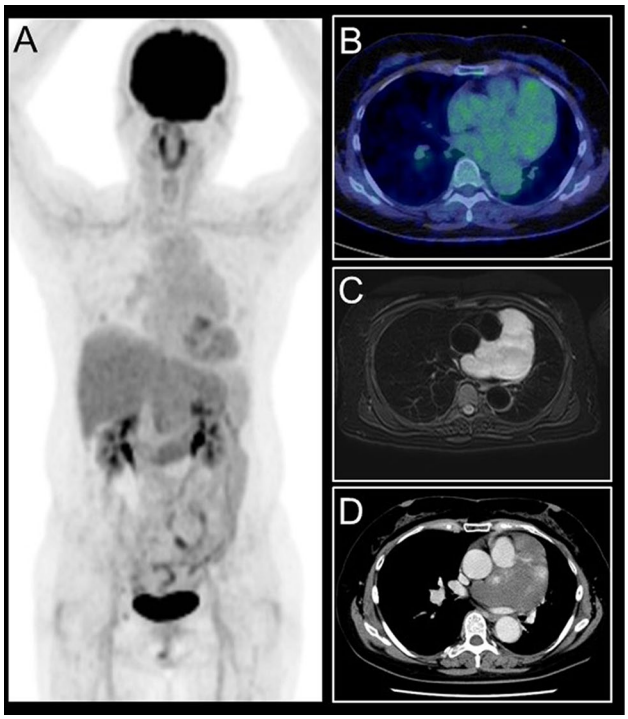


Fig. 5 A case of pericardial capillary haemangioma. The bulky mass attached to the anterior wall of the left ventricle showed low FDG uptake similar to a blood pool (**a**, **b**), a homogeneous hyperintense signal in T2-weighted image (**c**), and nodular enhancement on contrast-enhanced CT (**d**)

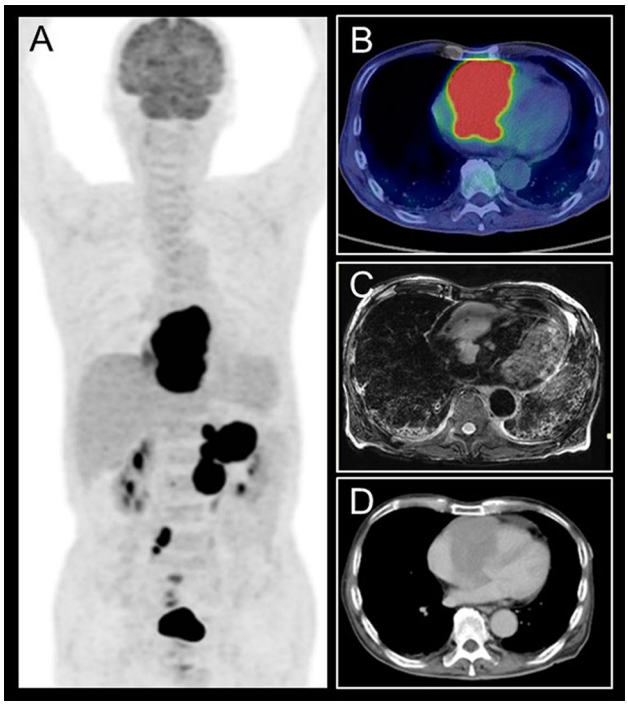


Fig. 6 A cardiac diffuse large B-cell lymphoma. Abnormal FDG uptakes are seen in the cardiac and abdominal lesions (**a**). The cardiac lesion demonstrated very high FDG uptake (**b**; SUVmax 29.0), a relatively high intense signal in a T2-weighted image (**c**), and homogeneous enhancement on contrast-enhanced CT (**d**)

Summary

Cardiac PET is a powerful noninvasive imaging technique that is increasingly used across clinical settings. For the clinical assessment of myocardial perfusion, the quantitative capability of PET permits the precise assessment of ischemia and microcirculatory dysfunction, which indicates an important role for PET in patient management and outcome analyses. In addition, PET holds promise for identifying active cardiovascular lesions. Technical advances in the development of PET instruments and radiopharmaceuticals will further enhance wide applications of cardiac PET in various clinical settings.

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