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REVIEW ARTICLE

Current Status and Future Direction of PET/MR in Cardiology

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Abstract

PET/MR is a hybrid imaging modality that enables simultaneous acquisition of PET and MR images, and fuses functional or metabolic information obtained using PET and superior soft tissue contrast acquired using MR. Although PET has mostly been used for oncologic indications, PET/MR has significant potential for evaluating cardiac diseases. ^{18}F-fluorodeoxyglucose PET/MR can evaluate not only inflammation and myocardial glucose metabolism, but also cardiac function, tissue edema, and myocardial fibrosis, simultaneously. Furthermore, using specific PET tracers, PET/MR enables the evaluation of various cardiac diseases. Although there are several technical issues that remain to be solved, PET/MR is a key modality for evaluating the pathophysiology of cardiac diseases.

Keywords: ^{18}F-fluorodeoxyglucose, ^{13}N-ammonia, Cardiac sarcoidosis, Coronary artery atherosclerosis, Myocardial viability, PET/MR

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SPECT and PET are widely used in clinical nuclear cardiology. Hybrid imaging modalities, including SPECT/CT and PET/CT, enable fused images to be obtained with precise alignment and orientation, and improve diagnostic accuracy for various diseases. Although the coexistence of PET and MR in the same machine had been thought to be difficult, a hybrid PET/MR machine was developed and made commercially available in 2012 (1). The hybrid PET/MR scanner combines the functional information obtained using PET with the excellent functional analysis and tissue characterization obtained using MR. The hybrid PET/MR is significantly useful for clinical indications, especially in oncology. Additionally, PET/MR has an important potential role in the detection of cardiac diseases.

In this review article, we report an early experience of cardiac PET/MR. First, we discuss the technical aspects of the PET/MR system, as well as several specific considerations for cardiac application. We then review the application of PET/MR to the evaluation of cardiac sarcoidosis, coronary artery atherosclerosis, and other inflammatory cardiac diseases, as well as myocardial viability and myocardial blood flow (MBF).

Technical aspects

PET/MR systems

Two different types of PET/MR systems are currently commercially available. The first is a separated PET and MR system, in which the PET and MR machines are positioned at either end of a single bed (Philips Ingenuity TF PET/MR) (2). The second system is a fully integrated PET/MR machine that allows simultaneous acquisition of PET and MR images (Siemens Biograph mMR, GE SIGNA PET/MR) (1, 3). The latter approach enables the simultaneous evaluation of the findings of both PET and MR. This has a fundamental benefit for the evaluation of diseases in which the patient's state rapidly changes, such as in the acute phase of inflammatory diseases.

Avalanche photodiodes (APDs) are used in the Biograph mMR instead of the conventional photomultiplier tubes. APDs are insensitive to strong magnetic fields, and allow the coexistence of PET and MR in the same machine (4). On the other hand, a photomultiplier made from silicon is used in the SIGNA PET/MR. This photomultiplier allows time-of-flight acquisition for PET/MR (3).

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Simultaneous acquisition

The fully integrated PET/MR system allows simultaneous acquisition of PET and MR images with no bed motion. Co-registration of the acquired images of PET/MR is considered to be more accurate than that of PET/CT images. However, there is a technical challenge for the simultaneous acquisition of PET and MR images (5). Cardiac PET is usually acquired during free breathing for several tens of minutes. On the other hand, cardiac MR images are acquired during an expiratory or inspiratory phase with breath holding. The difference of the breathing conditions may affect the image quality, especially in the PET images. Sometimes the PET images are blurred by repeated breath holding. To solve this problem, two methods have been considered: free-breathing acquisition of MR images, and a "double-trigger" acquisition (6). Free-breathing MR acquisition is technically possible, but can result in the removal of several key images, including T1 mapping, T2-weighted images, and tagged cine images due to reduced image quality. The "double-trigger" method acquires images with both electrocardiography gating and respiratory gating. This method of acquisition may be the only one that retains the quality of both PET and MR images.

The other PET/MR system, which has separated PET and MR scanners, acquires images sequentially. This separated PET/MR system can avoid the aforementioned problems; however, more time is needed to acquire both PET and MR images.

Attenuation correction

PET/MR generates attenuation maps by methods different from the one used by CT. A two-point Dixon MR sequence is one such method, and uses water- and fat-weighted images to generate an attenuation map consisting of four segments: air, lung, fat, and soft tissue (7). In this method, a μ-map is generated by these four segments with fixed attenuation values. Non-attenuation corrected PET images are then corrected according to the attenuation values. Metal implants cause artifact in this method; they reduce T1 values and appear as signal voids (8). A contrast agent may also cause this artifact. Another approach, one that uses dedicated T1-weighted MR images, can be used to generate an attenuation map (9).

Clinical application of PET/MR

Patient preparation for FDG PET acquisition

Patient preparation for PET image acquisition is important for evaluating various myocardial pathologies, and diet modification is always needed for FDG PET preparation.

Several methods to suppress the physiological FDG uptake in the heart have been investigated. A low-carbohydrate, high-fat diet was reported to be effective (10, 11), as was extended fasting of 18 hours or more (12). Moreover, carbohydrate restriction or the combination of carbohydrate restriction and extended fasting is thought to be effective (13-15). Kobayashi et al. reported that carbohydrate restriction (<10 g of carbohydrate) for 24 hours or more with a low-carbohydrate, high-fat diet more effectively suppressed physiological FDG uptake compared with a fasting only protocol (15). Intravenous injection of unfractionated heparin combined with extended fasting is also reported to be effective in suppressing physiological FDG uptake (16, 17). Unfractionated heparin increases serum free fatty acid, which suppresses myocardial glucose metabolism (18). However, several reports suggested that the injection of unfractionated heparin has more limited effects to suppress physiological FDG uptake compared with the diet modification (19, 20). In addition, unfractionated heparin may cause hemorrhagic complications and heparin-induced thrombocytopenia. Currently, diet modification including carbohydrate restriction, extended fasting of 18 hours or more, or a combination of these methods is a simple way to suppress physiological FDG uptake. The optimal duration of diet modification prior to FDG injection has yet to be investigated, and further study is required to clarify this issue.

^{18}F-fluorodeoxyglucose (FDG)

1. Cardiac sarcoidosis

Sarcoidosis is a systemic disease that forms non-caseating granulomas on various organs, including the myocardium. Cardiac involvement causes fatal arrhythmias and heart failure, and is associated with a poor prognosis. Therefore, early diagnosis of cardiac involvement is important for sarcoidosis patients.

^{18}F-FDG PET has a high sensitivity for the diagnosis of cardiac sarcoidosis, and FDG uptake is useful for evaluating the effects of oral steroid therapy (21, 22). Cardiac MR imaging has also been used for the diagnosis and evaluation of cardiac sarcoidosis (23). Both FDG uptake in the myocardium and T2-weighted MR images indicate an active inflammatory process. FDG uptake signifies infiltration of inflammatory cells (24), and T2 elongation indicates tissue edema caused by active inflammation. In addition, late gadolinium enhancement (LGE) of MR images indicates an expansion of extracellular space due to myocardial fibrosis, as well as active inflammation (25). Both PET and MR images are key image modalities for diagnosing cardiac sarcoidosis.

In preparation for PET image acquisition, suppression of physiological FDG uptake is necessary. A low-carbohydrate diet (<5 g of carbohydrate) followed by an extended fasting of 12 hours or more is recommended for FDG PET preparation by the Japanese Society of Nuclear Cardiology (26).

The simultaneous acquisition of PET and MR improves the

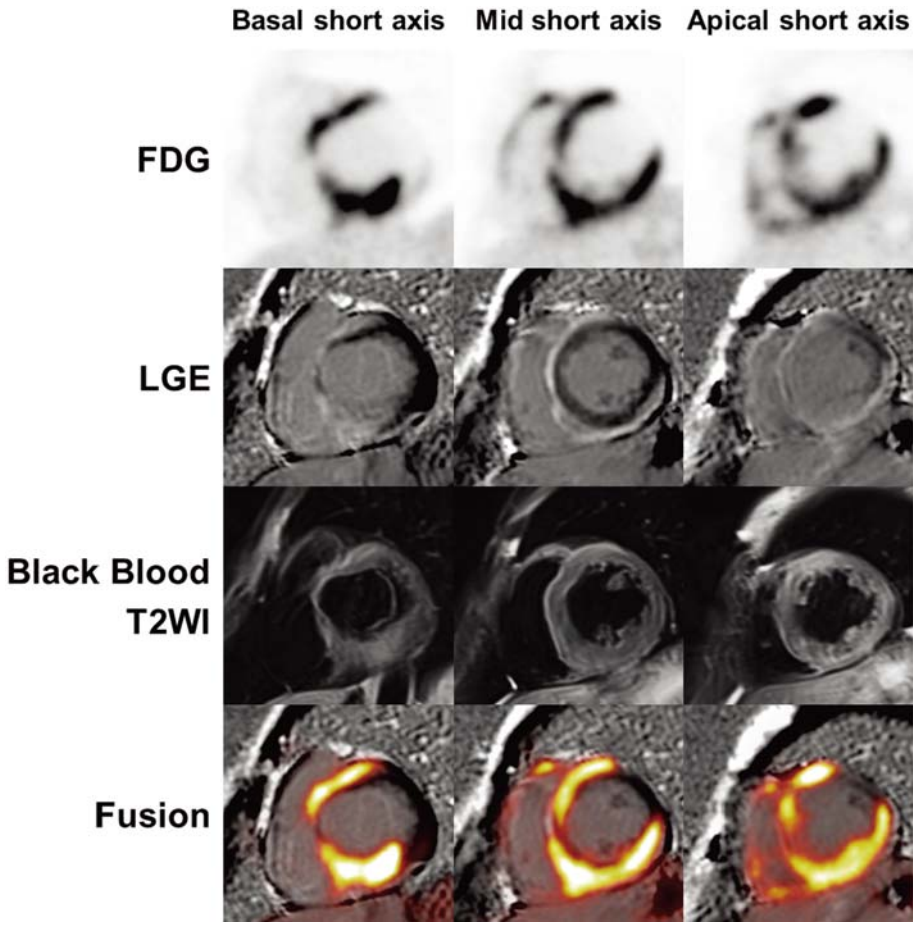

Fig. 1 ^{18}F-fluorodeoxyglucose PET/MR images of cardiac sarcoidosis.
FDG uptake was observed on the anterior, septal, inferior, and lateral walls in the left and right ventricles. Late gadolinium enhancement (LGE) was also detected on the anterior, septal, inferior, and lateral walls in both ventricles. Black blood T2-weighted images (T2WI) showed high intensity signals in accordance with the FDG uptake and LGE regions. Fused images clearly show the overlap of FDG uptake, LGE, and high intensity regions on the T2WI in most myocardial regions; however, it should be noted that there was a subtle discrepancy among those three images.
FDG: ^{18}F-fluorodeoxyglucose, LGE: late gadolinium enhancement, T2WI: T2-weighted image

evaluation of the pathology of cardiac sarcoidosis. Although FDG uptake and MRI findings were positive in a similar area, several different findings were also indicated as we previously reported (27). In that study, a subtle discrepancy was shown among FDG uptake, LGE, and black blood T2-weighted images in a patient with acute-phase cardiac sarcoidosis (Fig. 1). Further study is needed to clarify the difference of these findings, as well as the clinical importance. Evaluating both PET and MR images taken simultaneously may result in further pathological findings.

2. Myocardial viability

Myocardial viability evaluated by FDG PET is considered to be the gold standard. Myocardial metabolism is maintained mainly by fatty acids and glucose, and the metabolic shift from the former to the latter occurs during specific conditions, including after a meal, myocardial ischemia, or some other pathologic conditions. Myocardium exposed to repetitive hypoperfusion results in a hibernating myocardium, in which glucose metabolism is maintained in spite of reduced blood flow and wall motion (28). FDG PET can detect the hibernating myocardium noninvasively, and has been used in the clinical setting for a long time. FDG PET offers a high sensitivity (92%) and a moderate specificity (63%) for the diagnosis of myocardial viability. In particular, FDG PET has a negative predictive value of 87%, which is the highest among imaging modalities (29).

In preparation for PET image acquisition, glucose loading is necessary for evaluating myocardial viability. Oral intake of 25 to 100 g of glucose is a simple way to achieve maximizing physiological glucose metabolism; however, intravenous loading of glucose and insulin might be preferred for patients with diabetes mellitus (30).

Recently, late gadolinium enhancement (LGE) MR images have also been used for viability evaluation. LGE indicates the increase of the intercellular matrix. Therefore, LGE is indicative of myocardial scarring, and myocardial viability is

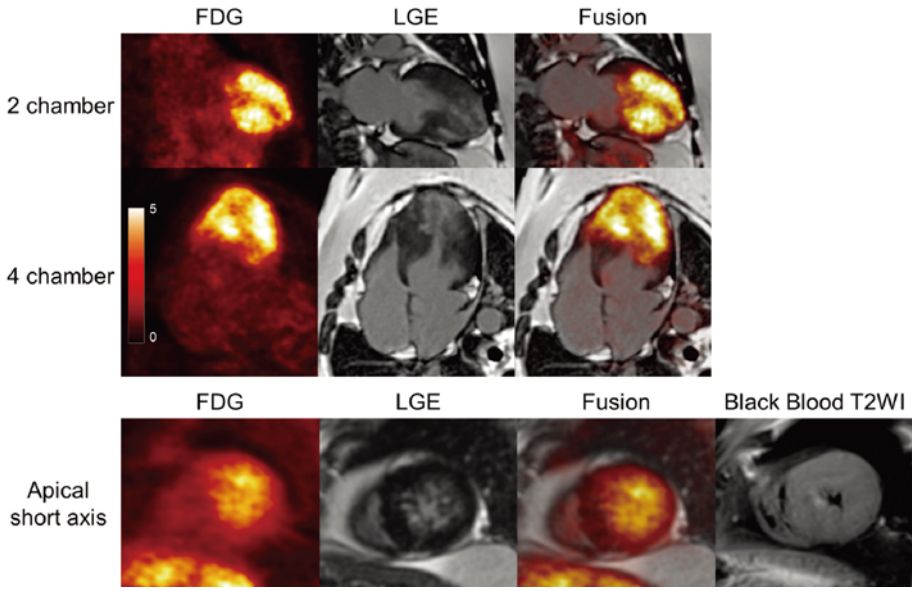

Fig. 2 ^{18}F-fluorodeoxyglucose PET/MR images of hypertrophic cardiomyopathy.
Intense ^{18}F-fluorodeoxyglucose (FDG) uptake was observed on the mid-wall in the left ventricular myocardium. Late gadolinium enhancement (LGE) was detected on the apex. Fused images clearly showed a markedly increased FDG uptake in the hypertrophied myocardial regions. However, there was no high-intensity region in the black blood T2WI in the apex, indicating that FDG uptake means a metabolic shift in the hypertrophied region rather than active inflammation.
FDG: ^{18}F-fluorodeoxyglucose, LGE: late gadolinium enhancement, T2WI: T2 weighted image

evaluated using the transmural extent of LGE. A non-viable myocardium is indicated when the transmural extent of LGE penetrates more than 50% of the left ventricular wall (31). LGE-MR imaging has a high sensitivity (83%) and a moderate specificity (63%) for the diagnosis of myocardial viability (29).

These pathological findings can be obtained through FDG PET/MR simultaneously. Although the association between FDG uptake and the extent of LGE is not fully understood, and the clinical application of PET/MR for viability evaluation has yet to be investigated, simultaneous assessment by PET/MR provides a lot of information regarding myocardial metabolism and tissue characterization.

3. Cardiomyopathy and myocarditis

FDG PET is used to evaluate myocardial metabolic changes in patients with cardiomyopathy (32). FDG PET images of hypertrophic cardiomyopathy showed remarkable FDG uptake in the apical region of the left ventricular wall, which may indicate a metabolic shift from fatty acid metabolism to glucose metabolism in the hypertrophied myocardium (Fig. 2). PET/MR may provide various pathological findings for evaluating cardiomyopathies; however, further investigation is required for clinical application.

The inflammatory process of myocarditis may be detected by PET/MR (33). To date, the inflammatory findings of myocardial biopsy have been used to confirm the diagnosis of myocarditis. Using FDG PET/MR, we can determine the range and extent of the inflammation noninvasively. However, there are several disadvantages to the PET/MR evaluation of myocarditis. Patients with severe conditions are unable to stay still for the long period of time that is needed in order to acquire the images, and patients in the acute phase of disease have to wait until their conditions become stable before PET/MR is performed. Although several implantable devices are available for MR scans in the present day (34), MR cannot generally be performed on patients with mechanical devices such as a temporary pacemaker. Therefore, the disease stage and presence of contraindications should be taken into consideration when performing PET/MR in patients with myocarditis.

Suppression of myocardial physiological uptake is necessary for evaluating cardiomyopathy and myocarditis, as well as cardiac sarcoidosis. There is no recommendation of diet modification for this indication; however, extended fasting and carbohydrate restriction may prove to be effective (33).

4. Coronary artery atherosclerosis

PET/MR provides a lot of information that can be used in the evaluation of atherosclerotic plaques. FDG is one of the most frequently used tracers for such evaluations, as it accumulates on macrophage infiltration, and is associated with plaque vulnerability (35). Only a few studies have reported that FDG uptake might identify vulnerable plaque in patients with acute coronary syndrome (36). We previously investigated the association between FDG uptake and T1-weighted images on MR in common iliac arteries (37) (Fig. 3). The findings of that study can be utilized for the evaluation of

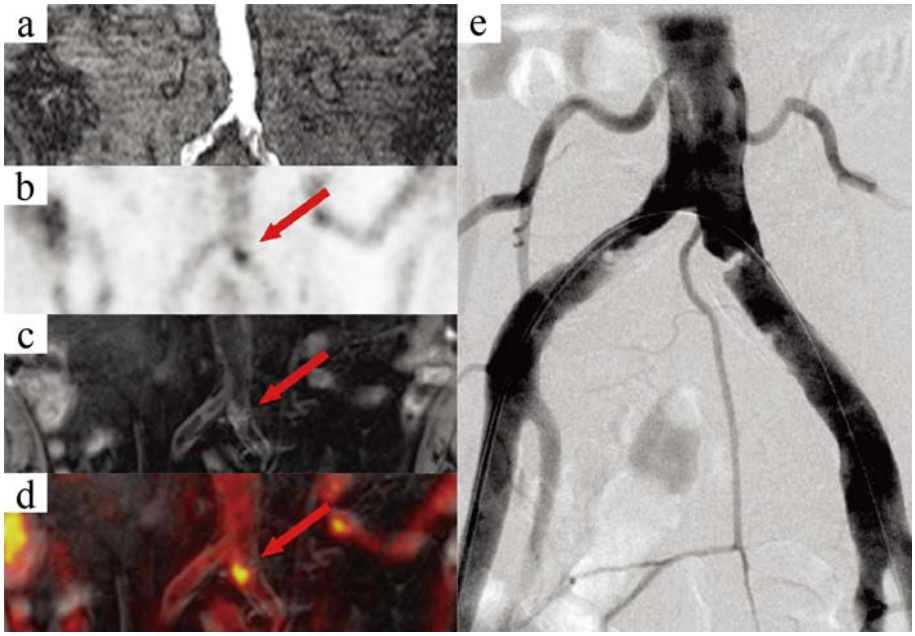

Fig. 3 ^{18}F-fluorodeoxyglucose PET/MR images.
Non-contrast enhanced MR angiography showed stenosis on the bilateral common iliac arteries (**a**). The left common iliac artery showed remarkable FDG uptake (**b, d**, red arrow). FDG uptake at level of stenosis revealed a high signal intensity on T1-weighted images (**c**, red arrow), suggesting that the lesion was a vulnerable plaque. On the right common iliac artery, no FDG uptake was observed, although there was significant stenosis. Arterial angiography revealed stenosis on both the left and right common iliac arteries (**e**).

coronary artery atherosclerosis in future.

In preparation for FDG PET image acquisition for evaluating coronary artery atherosclerosis, suppression of myocardial physiological uptake is necessary. Extended fasting, carbohydrate restriction, or combination of these methods may be effective.

^{18}F-NaF has also been used for the evaluation of vulnerable plaque activities showing accumulation on microcalcifications in the vulnerable plaques (38). Although physiological FDG uptake in the myocardium often interferes with the evaluation of FDG uptake on coronary arteries, ^{18}F-NaF does not show obstructive myocardial physiological uptake, and thus might be simple to apply for clinical use.

Although plaques in various arteries have been evaluated for vulnerability, the clinical application has not yet been thoroughly evaluated.

^{13}N-ammonia

Myocardial perfusion imaging is important for evaluating ischemic heart disease. Several PET tracers, including ^{15}O-water, ^{82}Rb, and ^{13}N-ammonia, have been used for evaluating ischemic heart disease. ^{13}N-ammonia has been used in the clinical setting, and is the only PET perfusion tracer approved in Japan. It provides superior image quality and accuracy for the quantitative analysis of MBF compared with SPECT (39). For the detection of myocardial ischemia, the sensitivity of perfusion PET is 83% and the specificity is 89%, while the sensitivity of SPECT is 61% and the specificity is 84% (40).

The combination of ^{13}N-ammonia PET and MR may provide interesting findings. Transient ischemic dilatation (TID) is one of the inportant finding of myocardial perfusion PET. TID is observed in patients with severe myocardial ischemia. Extensive subendocardial ischemia or dilatation of the left ventricular cavity due to an elevation of left ventricular end-diastolic pressure may be associated with TID, but the mechanism has yet to be fully understood (41). ^{13}N-ammonia PET/MR can be used to evaluate left ventricular wall motion by cine MR during pharmacologic stress. This technique may reveal the mechanism of TID. Furthermore, identifying associations between quantitative measurement of MBF and MR findings including LGE, T1 mapping, and extracellular volume map is important for evaluating various types of cardiac disease.

Conclusion

In this review article, we focused on the technical aspects of PET/MR and its clinical applications with cardiac diseases, and we presented our experience with PET/MR in the field of cardiology. Although there are several technical issues that have yet to be overcome, the clinical application of PET/MR to the cardiac diseases has a promising future.

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Conflicts of interest

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