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The Feasibility of Quantitative Assessment of Myocardial Perfusion Using Single Photon Emission Computed Tomography Imaging: Current Status and Future Challenges

Keisuke Kiso, MD, PhD, Emi Tateishi, MD, PhD, Akira Imoto, RT, Yusuke Terakawa, RT, Keizo Murakawa, RT and Tetsuya Fukuda, MD, PhD

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Abstract

Assessment of physiological ischemia is recently essential for the indication of coronary revascularization; such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) in patients with coronary artery disease. Moreover, quantitative assessment of myocardial flow reserve (MFR) is also getting important role for the evaluation of prognosis of heart diseases including non-ischemic cardiomyopathy.

In the field of nuclear cardiology, positron emission tomography (PET) has been the only modality for the quantitative assessment of myocardial blood flow (MBF) and MFR. However, since availability of PET is much less than that of single photon emission computed tomography (SPECT) imaging, quantitative MBF/MFR assessment has been limited.

Recently, high sensitivity gamma camera which equipped semiconductor detectors has been developed. It is reported that its image quality and spatial resolution are much superior to conventional Anger-type gamma camera. Moreover, since high sensitivity gamma camera consists of plural detectors, it can evaluate whole heart perfusion simultaneously. These advances make quantitative MBF/MFR analysis feasible like PET imaging. Although quantitative assessment with high sensitivity gamma camera is getting useful in clinical practice, several points; such as acquisition protocol and analysis methods, are immature compared to PET. Therefore, we have to investigate the solutions for these issues in near future for diagnostic certainty.

Keywords: CZT, Myocardial blood flow, Myocardial flow reserve, PET, Quantitative assessment, SPECT

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Usefulness of positron emission tomography (PET) myocardial perfusion imaging (MPI) is broadly recognized. Compared to single photon emission computed tomography (SPECT) MPI, excellent image quality which is derived from better spatial resolution and less influence from attenuation artifact, yields superior diagnostic accuracy of myocardial ischemia.

Moreover, one of the most prominent advantages of PET MPI is the ability of quantitative assessment of myocardial blood flow (MBF) and myocardial flow reserve (MFR). These quantitative MBF and MFR measurements allow to diagnose the severity of myocardial ischemia more accurately, especially in patients with multi-vessel coronary artery disease, which is difficult to evaluate with SPECT MPI.

In addition, MFR is also reported as one of the strongest prognostic factors in patients with non-ischemic cardiomyopathy, not only with ischemic cardiomyopathy (1).

As mentioned above, importance of quantitative MBF/MFR assessment by PET MPI has been increasing. American Society of Nuclear Cardiology and Society of Nuclear Medicine and Molecular Imaging stated joint position statement on the clinical indications for PET MPI in 2016,

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Keisuke Kiso, Emi Tateishi, Akira Imoto, Yusuke Terakawa, Keizo Murakawa and Tetsuya Fukuda
Department of Radiology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
E-mail: kkeisuke@ncvc.go.jp

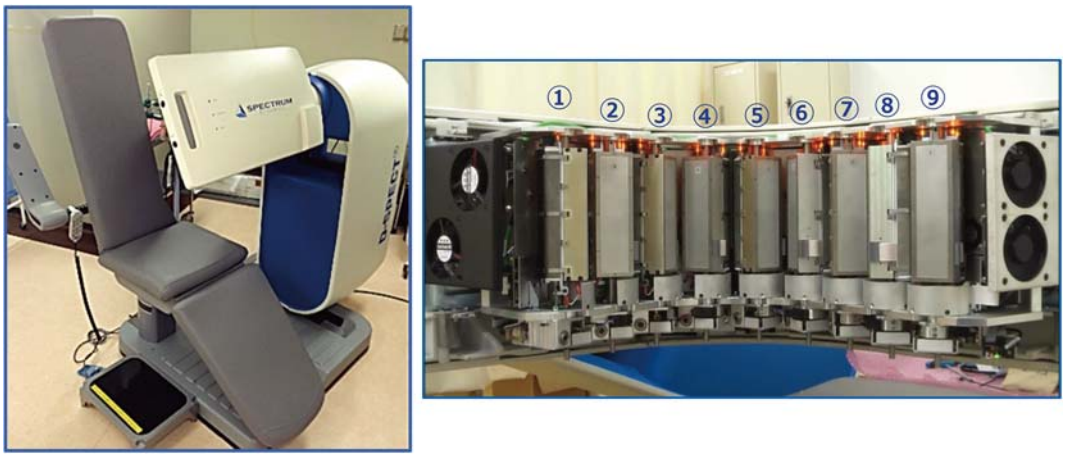


Fig. 1 Appearance and detectors arrangement of "D-SPECT"
(Left) Appearance of D-SPECT
(Right) Detectors arrangement. D-SPECT consists of nine CZT detectors (①-⑨).

which highlight the usefulness of PET MPI based on its important properties, such as high-quality images, quantification of MBF, low radiation exposure dose, and so on (2).

However, availability of PET MPI is so limited in Japan. Although more than 250 sites are available for PET MPI in USA, just only 10 sites are available in Japan.

On the contrary, SPECT MPI is performed in more than 800 sites in Japan. Therefore, needs for quantitative MBF/MFR assessment by "SPECT MPI" has been increasing, and several attempts with conventional Anger-type gamma cameras have been already reported (3-10).

In this review, we would address the feasibility of quantitative assessment of MBF and MFR with SPECT MPI based on previous and ongoing studies, including our investigation.

Quantitative MBF/MFR assessment by SPECT/CT system with conventional Anger-type gamma cameras

SPECT/CT system with conventional Anger-type detectors is available for CT attenuation correction like PET imaging. Several investigators have demonstrated the feasibility of measuring MBF/MFR by SPECT/CT system with dynamic scan (= data acquisition is started at the time of tracer injection) (8-10). However, compared to quantitative assessment by PET MPI, MFR by SPECT approach showed only moderate correlation and the accuracy to distinguish regions of normal and abnormal appeared to be low (8).

Several reasons for difficulty of quantitative MBF/MFR assessment with conventional Anger-type gamma cameras have been clarified (11). Firstly, these conventional SPECT systems consist of slowly rotating and large detectors. Moreover, the detectors' orbit is limited by mechanical as well as safety factors. These aspects are resulting in blurred images and possible bias in the estimated kinetic parameters. In addition, temporal resolution of conventional detector crystals is limited, which is insufficient for collection of adequate numbers of counts when tracer concentrations are rapidly changing, such as in dynamic acquisitions.

Quantitative MBF/MFR assessment with SPECT MPI with CZT semiconductor gamma camera

Recently, high sensitivity and high resolution gamma cameras equipped with cadmium zinc telluride (CZT) semiconductor detectors, which is dedicated to cardiac scan, have been developed by several manufacturers. CZT detectors have several advantages compared to conventional Anger-type gamma cameras with NaI scintillators. One of the most excellent advantages is "direct detection system", which is resulting in dramatic improvement of systemic sensitivity and spatial resolution, in contrast with Anger-type detectors which have "indirect detection system".

Two types of CZT gamma cameras are available in Japan; the one is "D-SPECT" manufactured by Spectrum Dynamics Medical Co. and the other is "Discovery NM 530c" manufactured by General Electronics Co. Our hospital has "D-SPECT", hence its appearance and detectors arrangement are shown in Fig. 1. Those CZT cameras have been already installed in more than 20 facilities, which numbers has been already more than the numbers of facilities of PET MPI.

From the perspective of quantitative analysis, CZT cameras have several advantages to improve measurement accuracy, compared to Anger-type cameras. The one is higher sensitivity (8-10 times better) which enable to response to the rapid change of RI counts during dynamic scan, and the other is multiple detectors which enable to acquire projection data of whole heart simultaneously.

Studies of quantitative MBF/MFR analysis with each CZT camera have been already reported, and those reports showed

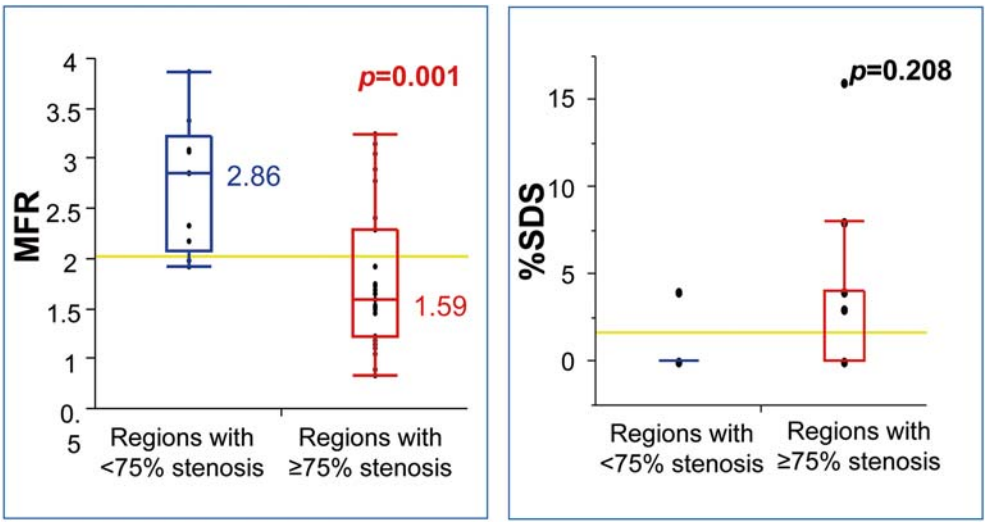


Fig. 2 Comparison of MFR, %SDS between regions with significant coronary stenosis and those without
Although there was no significant difference in % SDS between two groups (right graph), MFR in regions with coronary artery with ≥75% stenosis was significantly lower (left graph).

significant MFR differences between subjects of normal, single vessel disease, and multi-vessel disease (12, 13). However, even in normal subjects, average MFR showed less than 2.0, which was much lower than the normal limit of MFR evaluated by PET MPI. The reason of this difference is estimated to be derived from lower extraction fraction of SPECT tracers (^{201}Tl, ^{99m}Tc-agents) compared to PET tracers.

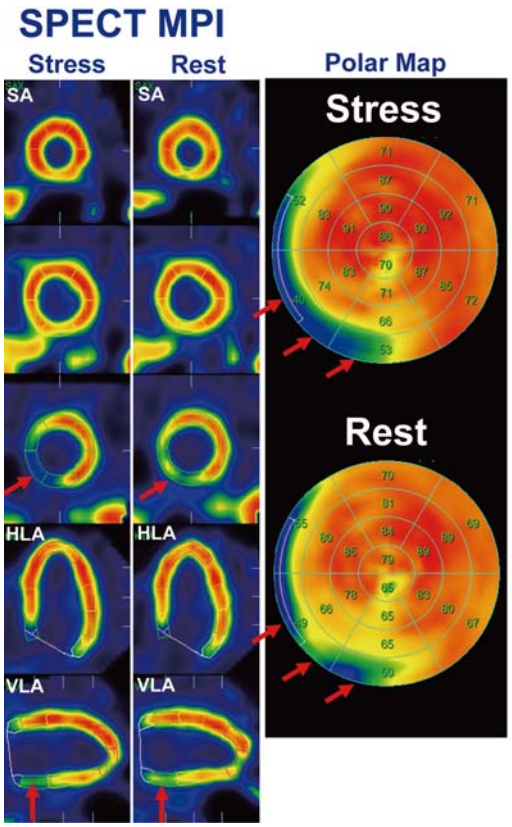
Recently, MBF/MFR calculation software dedicated to CZT cameras with correction of extraction fraction of ^{99m}Tc-MIBI, which name is “Corridor 4DM-SPECT (INVIA LLC. USA)”, has been released.

We reported the usefulness of quantitative MBF/MFR assessment in patients with MVD evaluated by D-SPECT and 4DM-SPECT at the 81st annual scientific meeting of the Japanese Circulation Society. We evaluated 12 patients with suspected multi-vessel CAD (with more than two coronary arteries with ≥50% stenosis) and compared MFR between regions with significant stenosis (≥75%) and those without. Then we observed that MFR showed significantly lower in region with significant stenosis. On the contrary, regional % summed difference score: SDS, which is the semi-quantitative index of visual assessment, showed no differences between two groups (Fig. 2). Moreover, ROC analysis showed that MFR had better specificity for the detection of significant coronary stenosis than conventional semi-quantitative assessment of myocardial perfusion (%SDS: Optimal cut off=3, Sensitivity=33.3%, Specificity=88.9%, AUC=0.62, p=0.117, MFR: Optimal cut off=1.91, Sensitivity=70.4%, Specificity=100%, AUC=0.85, p=0.002).

Representative case, which indicates the usefulness quantitative assessment by D-SPECT and 4DM-SPECT, is shown in Fig. 3. From the visual assessment, only slight myocardial ischemia was observed in inferoseptal region. However, each MFR in 3 coronary territories showed significantly low, which indicated severe 3-vessel disease. Coronary angiography of this patient showed significant stenosis in 3 main coronary arteries (#2=75%, #3=100%, #7=75%, #13=75%). This is the good example for indicating the importance of quantitative assessment with D-SPECT and 4D-MSPECT in patients with balanced ischemia of multi-vessel disease.

As mentioned above, quantitative assessment with D-SPECT ant 4D-MSPECT is thought to be applicable to clinical practice, however, we are not sure about the accuracy of MBF/MFR values, compared to PET MPI. In 29th Annual Congress of the European Association of Nuclear Medicine (EANM 2016), Agostini D. et al. reported the comparison data between D-SPECT and ^{15}O-Water PET MPI (data has not been published as journal paper yet). Although global MBF by D-SPECT was significantly lower than that of PET, global MFR was slightly higher. Moreover, regional MFR of RCA was significantly lower than that of PET, and the reasons of this result was speculated to be the influence of attenuation artifact. Thinking from these results, accuracy of quantitative MBF/MFR assessment by D-SPECT and 4DM-SPECT might not be the same as PET MPI.

Furthermore, several limitations of quantitative assessment with D-SPECT are pointed out. In the context of protocol, one of the limitations is that available RI tracer is restricted to ^{99m}Tc-MIBI. Since correction of extraction fraction has been completed only in ^{99m}Tc-MIBI, other tracers, such as ^{201}Tl and ^{99m}Tc tetrofosmin, have not been available. Other limitation is that optimal acquisition protocol has not been established. For example, in Japan, sequential and short time protocol of rest and stress scans, which total scan time is about 60 min., is usually performed. On the other hand, in European countries, long protocol which interval between rest and stress



MBF/MFR

Region	Stress MBF	Rest MBF	MFR
LAD	3.09	1.78	**1.74**
LCX	3.01	1.96	**1.53**
RCA	2.01	1.26	**1.59**
Total	2.75	1.67	**1.65**

Fig. 3 Representative case of quantitative MBF/MFR assessment with D-SPECT and 4D-MSPECT
(Left) SPECT MPI: From the visual assessment, inferoseptal non-transmural myocardial infarction with slight ischemia was observed (red arrows).
(Right) MBF (ml/min/g) and MFR calculated by 4D-MSPECT: MFR in 3 coronary territories showed significantly low, which indicated severe 3-vessel disease.
SA: short axis, HLA: horizontal long axis, VLA: vertical long axis, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery

is more than 90 min. is usually applied. Furthermore, in association with calculation software: 4D-MSPECT, location and size of ROI for input function in LV cavity influences to MBF/MFR values. In addition, optimal analysis model, such as NET retention model, one-tissue compartment model, etc. has not been established.

For the improvement of measurement accuracy, we have to investigate the solutions for these issues.

Summary and future direction

In this review, we described the feasibility of quantitative assessment of MBF/MFR evaluated by SPECT MPI. CZT cameras enable quantitative assessment of MBF/MFR in daily clinical situations, compared to conventional Anger-type gamma cameras. In addition, several reports have already published about the usefulness for diagnosis of severity of myocardial ischemia and selection of optimal therapy. Moreover, availability has been already superior to PET MPI. However, accuracy of quantitative MBF/MFR assessment might be inferior to that of PET MPI. For improvement the measurement accuracy, there are several challenges, such as optimal acquisition protocol and calculation software, etc.

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Conflict of interests

None.

Reprint requests and correspondence:
Keisuke Kiso, MD, PhD
Department of Radiology, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka, 565-8565, Japan
E-mail: kkeisuke@ncvc.go.jp

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