Quantitative Assessment of Regional Myocardial Flow Reserve Using Tc-99m-Sestamibi Imaging

— Comparison With Results of O-15 Water PET —

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Background The aims of this study were to develop a method for quantitative estimation of the myocardial blood flow index (MBFI) and myocardial flow reserve (MFR) of the whole left ventricle using ^{99m}technetium (Tc-99m)-sestamibi imaging.

Methods and Results Twenty-two patients with suspected coronary artery disease and 7 controls underwent both Tc-99m-sestamibi imaging and O-15 water positron emission tomography (PET). The global MBFI was calculated on the basis of the microsphere model from the ratio of the myocardial count to the area under the time–activity curve on the aortic arch. The regional MBFI was calculated from the relative distributions of Tc-99m-sestamibi uptake values. The regional MBFI and MFR (Tc-MFR) obtained using single-photon emission computed tomography were compared with the myocardial blood flow (MBF) and MFR (PET-MFR) obtained using PET as the gold standard. Regional MBFI significantly correlated with the MBF obtained using PET. Regional Tc-MFR also correlated with the regional PET-MFR, with some underestimation.

Conclusion These results indicate that regional MBF and MFR may be estimated by dynamic Tc-99m-sestamibi imaging and can be used for the early detection and estimation of the functional severity of coronary lesions without the need for a PET camera. (*Circ J* 2005; 69: 188–193)

Key Words: Coronary artery disease; Emission computed tomography; Myocardial flow reserve; Tc-99m-sestamibi

Techniques for evaluating myocardial blood flow (MBF) are important in the identification of patients with coronary artery disease (CAD) and for estimating its severity. Positron emission tomography (PET) using O-15 water or N-13 ammonia enables estimation of myocardial flow reserve (MFR) and evaluation of the physiologic significance of coronary lesions,^{1,2} but it is not used clinically because of limited availability of PET systems and in-house cyclotrons. Recently, quantitative assessment of MFR by dynamic acquisition following the administration of a ^{99m}technetium (Tc-99m) perfusion agent has been attempted^{3,4} and we also have developed a new method for the quantitative estimation of the MBF index (MBFI) and MFR using single-photon emission computed tomography (SPECT) and Tc-99m-sestamibi.⁵ Although the MBFI and MFR measured by this method exhibited good linear correlation with those obtained by O-15 water PET, these parameters were measured in the whole left ventricle. The aim of this study was to develop a method for measuring regional MBFI and MFR on the basis of coronary territories, and to compare these parameters obtained using our new method developed with those obtained using O-15 water PET.

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Methods

Study Patients

We enrolled 22 patients (17 men, 5 women; mean age: 64.0±10.0 years, Table 1) with suspected CAD and 7 normal volunteers (all men; mean age: 33.4±4.5 years). All the patients underwent coronary angiography; 8 of them had a previous myocardial infarction: 4 had undergone previous coronary revascularization, 2 had had angioplasty and 2 had had coronary artery bypass grafting (CABG).

All the study participants underwent Tc-99m-sestamibi myocardial perfusion SPECT and O-15 water PET, both performed within 2 weeks. No clinical events or change in medication occurred between the 2 studies. Subjects were instructed to refrain from caffeine intake for 24h before the

Table 1 Clinical Characteristics of the 22 Patients With Suspected Coronary Artery Disease

Age (years)	64.0±10.0
M/F	17/5
No. of diseased vessel	
0	6 (27%)
1	5 (23%)
2	9 (41%)
3	2 (9%)
Coronary risk factors	
Hypertension	12 (55%)
Hyperlipidemia	13 (59%)
Diabetes mellitus	9 (41%)
Smoking	12 (55%)

Fig 1. Two day study protocol in the Tc-99m-sestamibi study at rest and ATP pharmacological stress.

imaging studies. All gave written informed consent and the study was approved by the Ethics Committee of Hokkaido University Hospital.

Coronary Angiography

All the patients underwent Tc-99m-sestamibi coronary angiography using a computerized quantitative coronary angiography analysis system (CAASII System; Pie Medical Imaging, The Netherlands) to assess coronary stenosis severity. We defined a significant stenosis as more than 50% stenosis in the main branch.

Tc-99m-Sestamibi Imaging Protocol and Data Analysis

Both Tc-99m-sestamibi angiography and SPECT were performed using a 2-day rest–stress imaging protocol (Fig 1). SPECT used a dual-head gamma camera system equipped with high-resolution collimators (Vertex; ADAC Laboratories, Milpitas, CA, USA). Planar dynamic images were used to estimate myocardial counts and dynamic counts of blood pool activities, whereas SPECT images were used to estimate the left ventricular mass and relative distributions of Tc-99m-sestamibi uptake. The details of the SPECT examination are in our previous report⁵. Pharmacological stress was induced by infusion of adenosine triphosphate (ATP) at a rate of $0.16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 5 min through the left antecubital vein.^{6,7}

The myocardial count (Cm counts per min (cpm)) for 1 min was obtained from the planar static image 5 min after Tc-99m-sestamibi injection. First-pass angiographic data were analyzed to obtain the time integral of the first-pass Tc-99m-sestamibi counts for the aorta. On the summed image (3- to 4-s duration) of the aortic phase of the first-pass images, a 2×2 pixel region of interest (ROI) was fixed on the aortic arch. The time integral of the first-pass Tc-99m-sestamibi counts was obtained as an area under the gamma-variate-fitted aortic time-activity curve (aorta ACU, counts/cm²) for the aortic ROI⁸. The same aortic ROI was used for measurement of the time integral of the aortic counts during ATP stress. The left ventricular myocardium was delineated automatically by the edge where the count was 40–50% of the left ventricular myocardium peak count. The weight of the left ventricular myocardium (M, g) was calculated from the volume of the left ventricular myocardium, having fixed myocardial gravity at 1.05. The MBFI was obtained using $\text{MBFI} = \text{Cm/Aorta ACU} \times 100/\text{M}$.

Because the baseline myocardial blood flow is closely associated with the rate–pressure product (RPP), MBFI at rest was corrected by RPP, an index of myocardial oxygen

Fig 2. Schematic presentation of each coronary territory on the SPECT polar map display. The tracer distribution of the cardiac base was excluded from the study.

consumption, using:

corrected MBFI = $\text{MBFI} \times (\text{mean RPP at rest in PET study} / \text{individual RPP at rest in MIBI study})^{0.9,10}$

MFR measured by Tc-99m-sestamibi imaging was calculated as the ratio of MBFI during ATP infusion to MBFI at rest.

Regional Analyses of MBFI and MFR

The relative distributions of Tc-99m-sestamibi uptake in the SPECT images were divided into 3 regions on the basis of coronary areas (ie, left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA)) on the SPECT polar map (Fig 2). The distribution at the cardiac base was excluded. The regional MBFI was calculated as:

regional MBFI = $\text{MBFI} \times (\text{mean Tc-99m-sestamibi uptake of one coronary area} / \text{mean uptake of the whole left ventricle})$.

Regional MFR (Tc-MFR) was calculated as the ratio of regional MBFI during ATP infusion to that at rest.

PET Protocol and Data Analysis

The PET examination was performed as previously described^{5,11}. MBFs at rest and during ATP infusion were calculated by O-15 water PET (Fig 3). All PET scans were obtained with an ECAT EXACT HR+ (Siemens/CTI).

A transmission scan was performed to correct photon attenuation for 6 min with a germanium-68 source. Next,

Fig 3. Study protocol in the O-15 water PET study.

Table 2 Hemodynamic Data at Rest and During ATP Infusion in the Sestamibi SPECT and PET Studies

	<i>PET (rest)</i>	<i>PET (ATP)</i>	<i>MIBI (rest)</i>	<i>MIBI (ATP)</i>
<i>SBP (mmHg)</i>	117.9±16.9	107.3±11.2*	123.6±11.7	113.6±12.9*,**
<i>HR (/min)</i>	65.1±11.2	79.1±11.7*	67.2±10.9	79.3±11.2*
<i>RPP</i>	7,680.0±1,729.9	8,496.4±1,548.6*	8,278.9±1,373.5	8,986.9±1,507.2*,**

ATP, adenosine triphosphate; SBP, systolic blood pressure; HR, heart rate; RPP, rate-pressure product.

* $p < 0.01$ vs rest, ** $p < 0.01$ vs PET.

Fig 4. Correlation between the regional MBFI measured by sestamibi and MBF measured by PET in the all segments (Left) and in the 3 coronary territories (Right).

the subject inhaled O-15 CO for 1 min to obtain the blood volume image. The total inhaled dose was 2,000 MBq. Then 1,000 MBq O-15 water was infused into an antecubital vein to obtain the blood flow image and 12 min later, the ATP was infused intravenously ($0.16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) until the end of the second PET scan. Heart rate (HR), blood pressure (BP), and 12-lead ECG were recorded at rest and at 1-min intervals during and after ATP administration.

All emission sinograms were reconstructed with filtered back projection using a Hann filter (cut-off frequency, 0.3 cycles/pixel). The in-plane resolution was 4.5 mm full width at half-maximum in images reconstructed into a 128×128 matrix. All data were corrected for dead time, decay, and measured photon attenuation.

MBF was quantified using the single tissue compartment model developed by Katoh et al.^{12,13} Regional MBF was calculated on the basis of the same coronary areas as used in the Tc-99m-sestamibi study. Regional MFR (PET-MFR) was calculated as the ratio of regional MBF during ATP infusion to regional MBF at rest. Three experienced doctors who were unaware of the patients' clinical data analyzed all PET data.⁵

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD, and

hemodynamic parameters were compared by paired t-test. The MFRs in normal subjects and patients, and in the regions with and without significant stenosis, were compared by unpaired t-test. A p -value < 0.05 was considered statistically significant.

Results

Hemodynamic Response

Hemodynamic data are summarized in Table 2. Under ATP stress, significant increases in HR and RPP were observed, with a significant decrease in systolic BP in the Tc-99m-sestamibi and PET studies. No significant differences in HR between the Tc-99m-sestamibi and PET studies under ATP stress were noted, although systolic BP and the RPP were slightly higher in the sestamibi study.

Relationship Between Regional MBFI Measured by Tc-99m-Sestamibi Imaging and MBF Measured by PET

The regional MBFI measured by Tc-99m-sestamibi imaging showed a good linear correlation with MBF measured by PET ($MBFI = 10.95 \times MBF + 14.06$, $R = 0.792$, $p < 0.0001$) (Fig 4). Regional MBFI in the LAD area correlated well with the regional MBF in the same area ($MBFI = 10.93 \times MBF + 12.92$, $R = 0.874$, $p < 0.0001$). Although the

Fig5. Correlation between the regional Tc-MFR measured by sestamibi and PET-MFR measured by PET in the all segments (Left) and in the 3 coronary territories (Right).

Fig6. The regional MFR estimated by PET Tc-sestamibi in the patients suspected with CAD and in the normal subjects.

Fig7. The regional MFR estimated by PET Tc-sestamibi in the areas with and without significant (>50%) stenosis on quantitative coronary angiography (QCA).

regional MBFI in the LCX and RCA areas correlated with the regional MBF in the same areas (LCX: $\text{MBFI} = 11.67 \times \text{MBF} + 15.78$, $R = 0.745$, $p < 0.0001$; RCA: $\text{MBFI} = 10.10 \times \text{MBF} + 13.64$, $R = 0.796$, $p < 0.0001$), the regional MBFI in the LCX area was slightly overestimated, whereas that in the RCA area was slightly underestimated. When regional MBFI and MBF at rest were corrected by RPP, the coefficient of correlation between MBFI and MBF slightly increased (corrected $\text{MBFI} = 11.86 \times \text{MBF} + 10.83$, $R = 0.814$, $p < 0.0001$).

Relationship Between Tc-MFR and PET-MFR

The regional MFR measured by sestamibi imaging showed a good linear correlation with the regional MFR measured by PET ($\text{Tc-MFR} = 0.30 \times \text{PET-MFR} + 0.94$, $R = 0.838$, $p < 0.0001$) (Fig 5). Generally, Tc-MFR values were underestimated compared with PET-MFR values. When MBFI and MBF at rest were corrected by RPP, a high correlation was also obtained (corrected $\text{Tc-MFR} = 0.40 \times \text{corrected PET-MFR} + 0.94$, $R = 0.819$, $p < 0.0001$). In each coronary area, Tc-MFR correlated well with PET-MFR

(LAD: $\text{Tc-MFR} = 0.29 \times \text{PET-MFR} + 0.99$, $R = 0.904$; LCX: $\text{Tc-MFR} = 0.33 \times \text{PET-MFR} + 0.82$, $R = 0.826$; RCA: $\text{Tc-MFR} = 0.28 \times \text{PET-MFR} + 0.98$, $R = 0.795$, each $p < 0.0001$).

Comparison of Regional MFR in Normal Subjects and in Patients

The PET-MFR in the patients with suspected CAD was significantly lower than that in the control subjects (2.12 ± 0.92 vs 3.82 ± 0.82 , $p < 0.0001$) (Fig 6). Similarly, the Tc-MFR was significantly lower in the patients than in the control subjects (1.54 ± 0.35 vs 2.12 ± 0.21 , $p < 0.0001$) (Fig 6).

Relationship Between Regional MFR and Coronary Stenosis

The PET-MFR in the areas with significant coronary artery stenosis (>50%) was lower than in the areas without significant stenosis (1.76 ± 0.59 vs 2.50 ± 1.06 , $p < 0.0001$) (Fig 7). Similarly, the Tc-MFR in the areas with significant stenosis was lower than in the areas without significant stenosis (1.44 ± 0.26 vs 1.65 ± 0.41 , $p < 0.05$) (Fig 7).

Discussion

Based on our method for estimating global MBFI and MFR,⁵ we developed a new method for analyzing regional MBFI and MFR using dynamic Tc-99m-sestamibi imaging. The regional MBFI and MFR values obtained by Tc-99m-sestamibi imaging correlated well with those from O-15 water PET, although there was a slight but significant underestimate. Regardless of this, the regional MFR in the areas with significant stenosis was significantly lower than in the areas without significant stenosis. Thus, this method of quantitative assessment may have add diagnostic value to SPECT imaging.

Our new method is based on the microsphere model, which assumes that Tc-99m-sestamibi is taken up by the myocardial tissue according to blood flow.¹⁴ Based on the principle of Sapirstein¹⁵ and Stewart-Hamilton, MBF is calculated as the ratio of the count in the tissue to the integral of the arterial concentration of the tracer up to the time of imaging.

There have been several recent attempts to estimate MFR using SPECT tracers,^{3,4,16,17} but none measured the absolute value of MBF. The present model can estimate the regional MBFI and MFR using dynamic Tc-99m-sestamibi imaging and a gamma camera without the need for a PET system. For the measurement of absolute MBF, arterial input function should also be measured, but we measured the activity in the ascending aorta. Because the thickness of the ROI on the aortic arch was not measured by planar imaging, the actual activity per milliliter could not be obtained. However, the MBFI had a good linear correlation with MBF obtained by PET and accordingly could be substituted for the MBF. The advantage of the current method is that it is simple and can be performed using a 2-min planar dynamic acquisition without arterial blood sampling.

The value of MFR measurement has been well recognized. The concept of coronary flow reserve (CFR) was introduced by Coffman and Gregg¹⁸ and has been developed by other investigators to estimate myocardial ischemia. Gould et al originally recognized the importance of measuring CFR in clinical practice,^{19,20} and Schelbert et al first demonstrated the clinical value of PET perfusion imaging for the accurate detection of CAD.²¹ Uren et al first reported PET data that described the relationship between MFR and the severity of coronary stenosis.²² MFR also decreased in patients with coronary risk factors, such as diabetes mellitus, hypertension and hypercholesterolemia.^{23–25} Those results suggested that reduced MFR may be caused by an abnormality in the regulation of coronary flow and preclinical atherosclerosis. Therefore, MFR measurement is useful for assessing the functional significance of coronary artery stenosis and in predicting coronary atherosclerosis and microvascular dysfunction. An invasive method for measuring CFR is the intravascular Doppler ultrasound transducer technique;²⁶ PET with O-15 water or N-13 ammonia is noninvasive method.^{12,27,28} However, both these techniques have limited applicability for routine clinical use because of their high cost and complicated procedures, including the production of ultra-short-lived positron tracers. It is possible to measure CFR using transthoracic Doppler echocardiography;^{29–32} but that technique can estimate CFR in the LAD only. Therefore, the simple non-invasive method of assessing MFR by Tc-99m-sestamibi imaging may be clinically useful.

In patients with multivessel disease, perfusion SPECT may not detect stress-induced ischemia, because of the diffused reduction in coronary flow, and A quantitative estimate of MFR may overcome that limitation. The current method distinctly showed a reduction in regional MBFI and Tc-MFR in the patients with suspected CAD compared with the normal controls. In addition, these values may be significantly decreased in the stenosed areas. Thus, this method has potential application to the diagnosis of multivessel disease or microvascular disease.

A number of physical factors limit the accurate estimates of myocardial count, arterial count and relative uptake value based on images, such as attenuation, scatter, and partial volume effects. The inferior and septal wall segments are represented by a significantly decreased relative count caused by photon attenuation by the diaphragm. The counts of the anterior wall are also attenuated by the breast tissue in women. Therefore, the relative uptake values are particularly decreased in such areas. Thus, the MBFI in the LCX area tended to be higher than in the other areas. An accurate correction of attenuation and scatter may minimize regional differences in the MBFI. On the other hand, most of these factors may be canceled out by calculating the MFR, which did not change among the various coronary areas.

One of the major limitations of this study was the underestimation of MFR. In canine experimental models, the initial distribution of Tc-99m-sestamibi under basal conditions correlated closely with regional blood flow, but when Tc-99m-sestamibi was administered at a flow rate $>2\text{--}3\text{ ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$, its uptake or retention reached a plateau.^{14,33,34} In humans, Taki et al³ reported that the increase in myocardial Tc-99m-sestamibi uptake underestimates the increase in blood flow, particularly at higher flow rates, because of a significant reduction in the extraction fraction in the high-flow range for SPECT perfusion tracers compared with that for O-15 water.

Conclusion

We have developed a new method for quantitative estimation of regional MBFI and MFR using Tc-99m-sestamibi imaging. The MBFI and MFR obtained by this method showed good linear correlation with those obtained by PET, albeit with a slight underestimation. However, despite this, we believe that these values have clinical use in SPECT imaging for predicting diffuse coronary atherosclerosis and preclinical microvascular dysfunction.

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