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Correlation Between Myocardial Uptake of Technetium-99m-Sestamibi and Pressure-Derived Myocardial Fractional Flow Reserve

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Abstract

Objectives. Development of the coronary pressure wire has facilitated the measurement of fractional flow reserve (FFR) to assess the functional severity of coronary artery stenoses.

Methods. This study evaluated the correlations between FFR and myocardial direct counts of technetium-99m (^{99m}Tc)-sestamibi in 20 patients (16 men, 4 women, mean age 66 ± 8 years) who underwent ^{99m}Tc-sestamibi single-photon emission computed tomography (SPECT) with the 2-day protocol using 740 MBq of ^{99m}Tc-sestamibi each day. Visual assessment of myocardial imaging and quantitative analysis with the measurement of percent uptake and direct count of ^{99m}Tc-sestamibi were performed.

Results. Visual assessment of myocardial imaging revealed that reversibility of ^{99m}Tc-sestamibi perfusion defects was correlated with FFR of < 0.75, which is regarded as functionally important stenosis (17/20 vs 3/20, $\kappa = 0.71$, $p < 0.002$). Regional reversibility score did not correlate with FFR ($r = -0.40$, $p =$ NS). Quantitative analysis revealed that the change in ^{99m}Tc-sestamibi percent uptake with pharmacologic stress using adenosine triphosphate disodium (ATP) also did not correlate with FFR ($r = 0.35$, $p =$ NS). In contrast, percent increase in ^{99m}Tc direct counts with ATP was lower in patients with FFR of < 0.75 than in those with FFR of ≥ 0.75 ($-4 \pm 16\%$ vs $24 \pm 30\%$, $p < 0.01$). In addition, a significant correlation ($r = 0.70$, $p < 0.001$) was observed between percent increase in ^{99m}Tc direct counts with ATP and FFR.

Conclusions. These results suggest that quantitative analysis of ^{99m}Tc-sestamibi scintigraphy enables the assessment of the magnitude of functional significance of coronary stenosis.

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Key Words

■**Coronary circulation (fractional flow reserve)** ■**Ischemia**
■**Radionuclide imaging (^{99m}Tc-SPECT)** ■**Diagnostic techniques**

INTRODUCTION

With advances in coronary interventional techniques, a more appropriate quantitative evaluation of the reduction in coronary blood flow is needed in addition to anatomical assessment of the coronary artery. In addition to visual assessment of coronary blood flow using coronary angiography, myocardial fractional flow reserve (FFR) has been established as a lesion-specific index of the functional severity of coronary artery stenoses that can be obtained invasively by intracoronary pressure measurements using a pressure wire[1−6]. Myocardial scintigraphy is a noninvasive method widely employed for qual-

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itative and/or semi-quantitative assessment of coronary artery stenoses in the clinical setting[3−7]. The present study tried to measure myocardial blood flow by technetium-99m(^{99m}Tc)-sestamibi myocardial scintigraphy using a 2-day protocol, as well as correlating the myocardial blood flow measured by quantitative ^{99m}Tc-sestamibi myocardial scintigraphy and coronary pressure-derived FFR.

SUBJECTS AND METHODS

Subjects

Twenty consecutive patients with suspected coronary artery disease, in whom coronary angiography revealed at least one intermediate lesion, underwent cardiac catheterization for coronary pressure measurements and ^{99m}Tc-sestamibi single-photon emission computed tomography (SPECT). The patients were 16 men and 4 women with a mean age of 66 ± 8 years. Four patients had angina pectoris and 16 had a previous myocardial infarction, of whom 12 had undergone percutaneous coronary intervention during the acute phase of myocardial infarction. Four patients had single-vessel disease, 4 had multivessel disease, and 12 had insignificant stenoses (**Table 1**). Intracoronary pressure measurements were performed in intermediate lesions as assessed visually: left anterior descending artery in 11 patients, left circumflex artery in 1, and right coronary artery in 8. The coronary risk factors included hypertension in 18 patients (90%), hypercholesterolemia in 11 (55%), diabetes mellitus in 10 (50%), and current smoking in 14 (70%). Written informed consents were obtained from all participants.

Table 1 Clinical and angiographic characteristics in the patients

Number of patients	20
Age (yr, mean ± SD)	66 ± 8
Sex (men/women)	16/4
Clinical presentation	
Angina pectoris	4
Previous myocardial infarction	16
Coronary risk factors	
Hypertension	18 (90%)
Hyperlipidemia	11 (55%)
Diabetes mellitus	10 (50%)
Smoking	14 (70%)
Angiographic findings	
Patients with	
Single-vessel disease	4
Multivessel disease	4
No significant lesion	12
Vessel investigated (n = 20)	
Left anterior descending coronary artery	11
Left circumflex coronary artery	1
Right coronary artery	8

Stress technetium-99m-sestamibi myocardial scintigraphy: 2-day protocol

Stress ^{99m}Tc myocardial scintigraphy was performed within 1 month before coronary angiography. The mean time interval between scintigraphy and catheterization was 9.1 ± 7.6 days. In all patients, adenosine triphosphate disodium (ATP) loading myocardial scintigraphy with ^{99m}Tc-sestamibi was performed using the 2-day method[8]. ATP (0.16 mg/kg/min) was administered intravenously for 6 min[9]. Three min after the start of ATP administration, ^{99m}Tc-sestamibi (740 MBq precisely) was administered intravenously. Image acquisition was commenced 30 min after the administration. On the following day, the patients were given ^{99m}Tc-sestamibi (740 MBq precisely) while at rest. Great care was taken to avoid leakage of ^{99m}Tc-sestamibi during each infusion by using an intravenous cannula or a butterfly needle. Thirty min later, SPECT images were acquired. On the second day, absence of ^{99m}Tc-sestamibi accumulation in the heart was confirmed before the study.

Data was acquired with a 3-detector gamma camera (Prism 3000XP, Picker) for 360-degree arcs (in 6-degree-wide directions, taking 30 sec/direction), using a low-energy high-resolution parallel multi-hole collimator. The maximum matrix size was 64 × 64. SPECT images were reconstructed from the data using a data processor (Odyssey VP, Picker) combined with a Butterworth filter (order 8; cutoff frequency 0.25) and a Ramp filter. According to the method reported elsewhere, each SPECT image was divided into 20 segments[10], with segments 1−3, 7−9, 13−14, and 19−20 corresponding to the areas perfused by the left anterior descending coronary artery, segments 4, 10, and 15−16 corresponding to the areas perfused by the right coronary artery, and segments 5−6, 11−12, and 17−18 corresponding to the areas perfused by the left circumflex coronary artery (**Fig. 1**). The radioactivity accumulation in the myocardium was visually evaluated by three cardiologists unaware

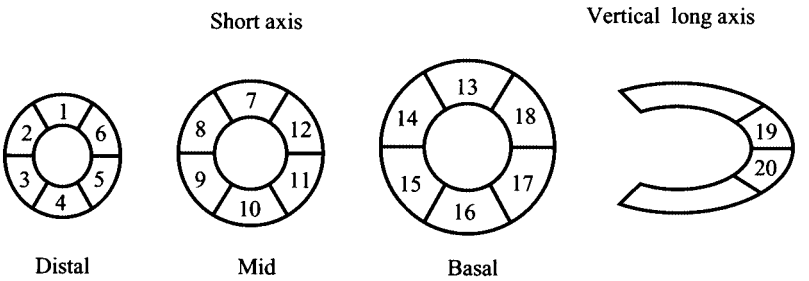

Fig. 1 Assignment of myocardial regions for scoring of single-photon emission computed tomography images

of any clinical information using a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake) or 4 (absence of radioactive uptake). Disagreements were resolved by consensus. The total of the scores for all segments during ATP loading and at rest was designated the summed stress scores (SS) and the summed rest scores (RS), respectively. Summed SS minus summed RS was defined as the summed difference score (DS). The radioactivity scores in each area perfused by different coronary arteries were defined as the regional SS, regional RS and regional DS. For each coronary artery, the regional SS, RS and DS values were calculated and divided by the number of segments involved, to yield the mean regional SS, RS and DS.

To quantitatively assess myocardial uptake of ^{99m}Tc-sestamibi, a bull's eye coordinate map was used. ^{99m}Tc-sestamibi uptake in the left ventricle was measured in five separate areas: the anterior, septal and apical areas corresponding to the territory perfused by the left anterior descending coronary artery, the inferior area corresponding to the territory perfused by the right coronary artery, and the lateral area to the territory perfused by the left circumflex coronary artery (**Fig. 2**). To measure relative uptake of ^{99m}Tc-sestamibi, ^{99m}Tc counts in each pixel was divided by the maximal counts in the left ventricle, whereas counts in each pixel was calculated without standardization for the ^{99m}Tc-sestamibi direct count. The change in ^{99m}Tc-sestamibi percent uptake was defined as percent uptake of ^{99m}Tc-sestamibi in a given area during ATP infusion minus percent uptake of ^{99m}Tc-sestamibi at rest in the same area. Similarly, ^{99m}Tc-sestamibi direct count was represented as the two indexes: the difference of ^{99m}Tc direct counts and percent increase in ^{99m}Tc direct counts. The difference of ^{99m}Tc direct counts was defined as ^{99m}Tc direct counts in a given area during ATP infusion minus ^{99m}Tc direct counts at rest. Percent increase in ^{99m}Tc direct counts was obtained by dividing the difference of ^{99m}Tc direct counts by ^{99m}Tc direct counts at rest (**Fig. 2**). The scintigraphic quantification was performed using a perfusion increase computer program (Shimazu).

Coronary angiography and fractional flow reserve

For all cases, multi-directional coronary angiography was performed according to Judkins' method. Severity of coronary artery stenosis was analyzed using a quantitative angiographic system (QCA Analyzer System CMS, Medical Imaging Systems), and diameter narrowing of $>50\%$ was considered to represent significant stenosis[11]. Intracoronary pressure was measured for the vessels that were angiographically suspected to induce myocardial ischemia. A 0.014-inch guidewire with a mounted pressure sensor (PressureWire™, Radi Medical Systems) was placed across the lesion. To induce a maximal hyperemic vascular response, 8 and 12 mg papaverine hydrochloride as a vasodilator of resistance vessels was injected into the left coronary artery and the right coronary artery, respectively. Under maximal hyperemia, the pressure distal to the stenosis at the guidewire and the pressure proximal to the stenosis at the tip of the catheter were measured, and the calculated gradient ratio was expressed as the FFR (**Fig. 3**)[6].

Statistical analysis

Results are expressed as mean $\pm$ standard deviation. Student's *t*-test was used to compare the means of the continuous variables, and contingency tables were analyzed using the chi-square test. The paired *t*-test was used to compare the changes of each variable before and after ATP infusion. A *p* value of <0.05 was regarded as denoting statistical significance. The computations were performed using the StatView computer program (Version 5.0J; SAS Institute Inc.)

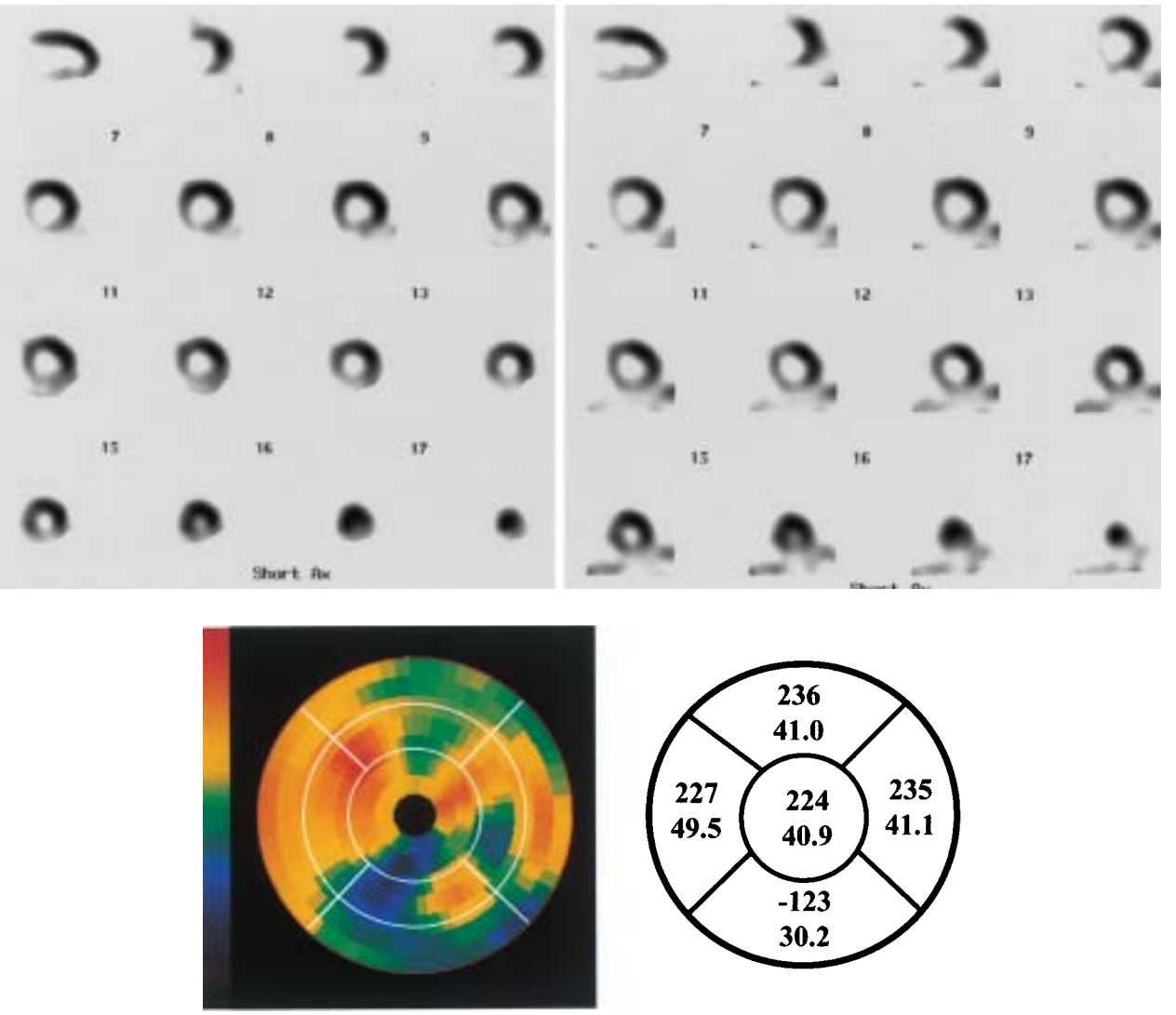

Fig. 2 Quantitative assessment of myocardial technetium-99m-sestamibi uptake
Using a bull's eye coordinate map, the left ventricle was divided into five areas: anterior, septal, inferior, lateral and apical areas. Relative uptake and direct counts of technetium-99m-sestamibi in each myocardial area were automatically calculated. Direct counts are shown (*upper line*) and relative uptake (*lower line*).

RESULTS

Visual assessment of perfusion defects in the coronary region of interest

The summed SS was 20 ± 8, the summed RS was 17 ± 9, and the summed DS was 3 ± 3. The average regional SS, RS, and DS were 3.0 ± 2.0, 2.6 ± 1.9, and 0.39 ± 0.46, respectively, in the area supplied by the coronary artery in which intracoronary pressure measurements were conducted. The mean regional RS was greater in the infarct-related arteries than in the non-infarct related arteries (3.4 ± 1.8 vs 1.2 ± 1.0, $p = 0.01$), whereas the mean regional DS was similar (0.5 ± 0.6 vs 0.3 ± 0.4, $p =$ NS). In the areas supplied by the coronary arteries in which intracoronary pressure measurements were conducted, the average regional DS was greater in regions where a reversible defect was observed by visual assessment than in regions where no such change was observed (0.98 ± 0.40 vs 0.25 ± 0.72, $p < 0.002$). In addition, a significant change in ^{99m}Tc-sestamibi percent uptake was noted in regions in which a reversible defect was noted by visual assessment than in regions showing no reversible defect ($-4.5 \pm 2.4\%$ vs $1.9 \pm 4.7\%$, $p < 0.02$). The mean FFR value was 0.68 ± 0.19 in

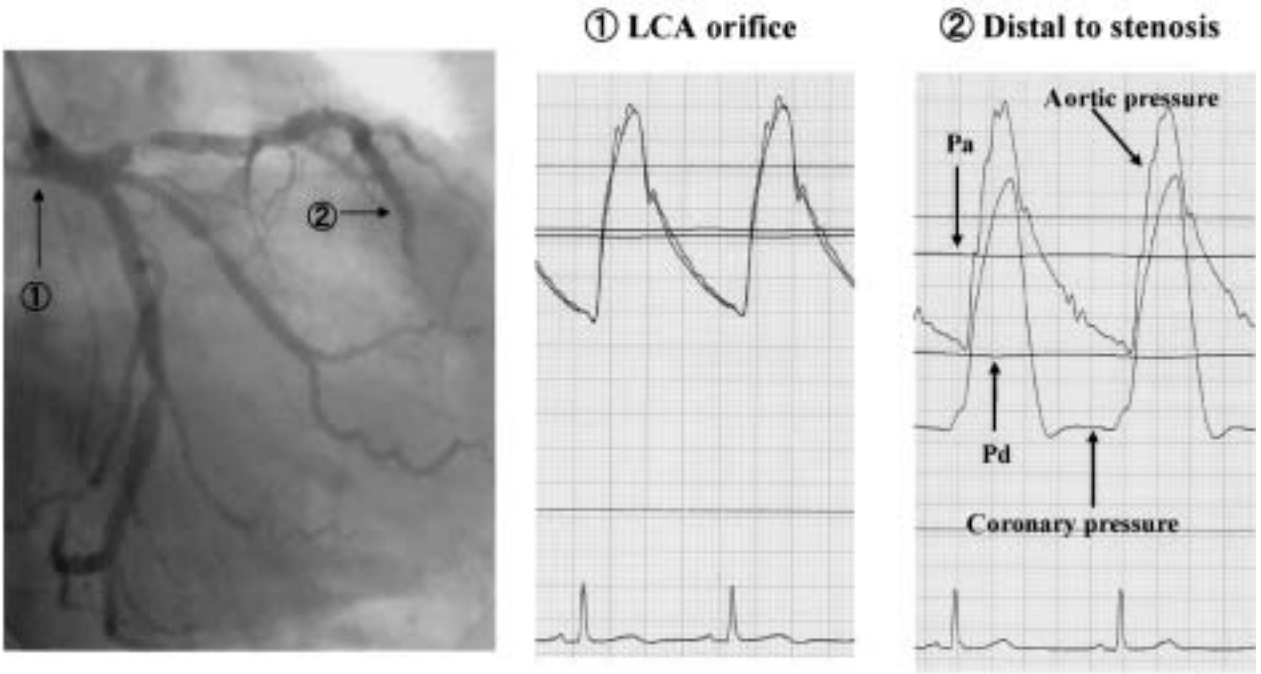

Fig. 3 Measurements of fractional flow reserve

Angiogram (*left*) showing the vessels of interest, ① = orifice of the left coronary artery; ② = left anterior descending artery distal to a stenosis. Mean coronary pressure was lower than aortic pressure in the site distal to the stenotic lesion at the baseline. During the hyperemic state, further reduction of the distal coronary artery pressure occurred, and the FFR is calculated by the formula: FFR = (Pa − Pv)/(Pd − Pv) Pa/Pd. FFR = fractional flow reserve; LCA = left coronary artery; Pa = mean aortic pressure as measured at the coronary ostium during maximal hyperemia; Pd = mean distal coronary pressure during maximal hyperemia; Pv = mean central venous pressure.

the 20 coronary arteries in which intracoronary pressure measurements was made. When the cutoff value for physiological myocardial ischemia was defined as 0.75, based on previous studies[4,6], visual assessment of myocardial imaging revealed that reversibility of ^{99m}Tc-sestamibi perfusion defects was correlated with a FFR of < 0.75, which is regarded as functionally important stenosis (17/20 vs 3/20, $\kappa = 0.71$, $p < 0.002$).

Quantitative analysis of technetium-99m-sestamibi uptake

Quantitative analysis revealed that the myocardial territories supplied by coronary arteries, in which intracoronary pressure measurements were made, showed decreased change in ^{99m}Tc-sestamibi percent uptake and reduced percent increase in ^{99m}Tc direct counts in regions with a reversible defect compared to those without a reversible defect ($-4.5 \pm 2.4\%$ vs $1.9 \pm 4.7\%$, $p < 0.02$, $-15 \pm 15\%$ vs $16 \pm 26\%$, $p < 0.05$, respectively), whereas the difference in ^{99m}Tc direct counts was similar (177 ± 362 vs -131 ± 216, $p =$ NS). In contrast, the FFR values showed a significant decrease in regions with a reversible defect compared to that in regions not showing a reversible defect (0.38 ± 0.11 vs 0.76 ± 0.12, $p < 0.0001$).

Correlation between quantitative measurements technetium-99m-sestamibi SPECT and fractional flow reserve

Percent increase in ^{99m}Tc direct counts was significantly reduced in regions in which the value was < 0.75, as compared to that in regions in which the value was ≥ 0.75 ($-4 \pm 16\%$ vs $24 \pm 30\%$, $p < 0.01$), whereas the change in ^{99m}Tc-sestamibi percent uptake and the difference in ^{99m}Tc direct counts were similar ($-1.0 \pm 4.8\%$ vs $2.3 \pm 5.0\%$, $p =$ NS, -22 ± 187 vs 254 ± 436, $p =$ NS, respectively; **Fig. 4**). Linear regression analysis showed no significant correlation between the FFR and the regional DS, or between the FFR and the change in ^{99m}Tc-sestamibi percent uptake in areas supplied by coronary arteries in which intracoro-

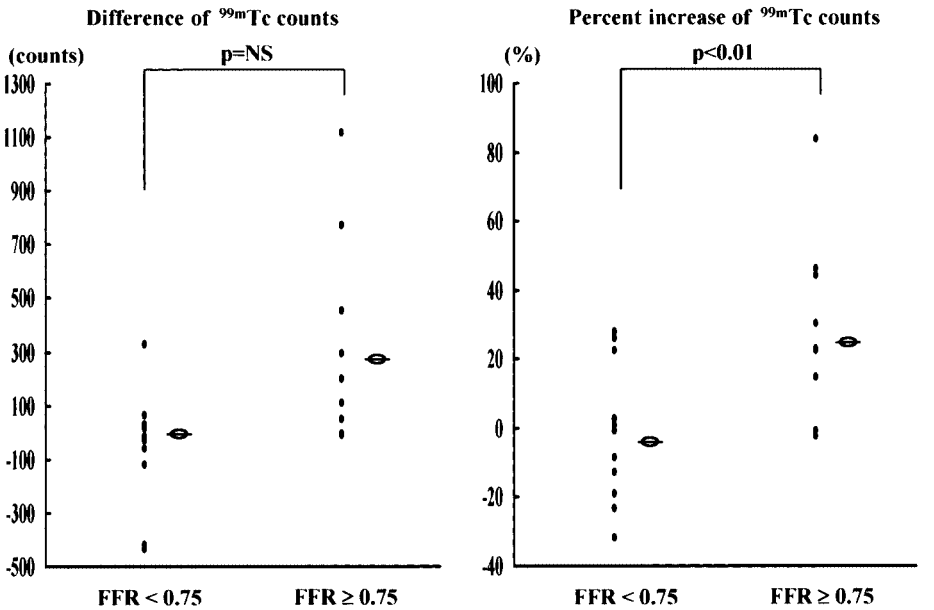

Fig. 4 Difference of technetium-99m direct counts (*left*) with adenosine triphosphate disodium infusion and percent increase of technetium-99m direct counts (*right*) correlated with fractional flow reserve of 0.75
^{99m}Tc = technetium-99m. Other abbreviation as in Fig. 3.

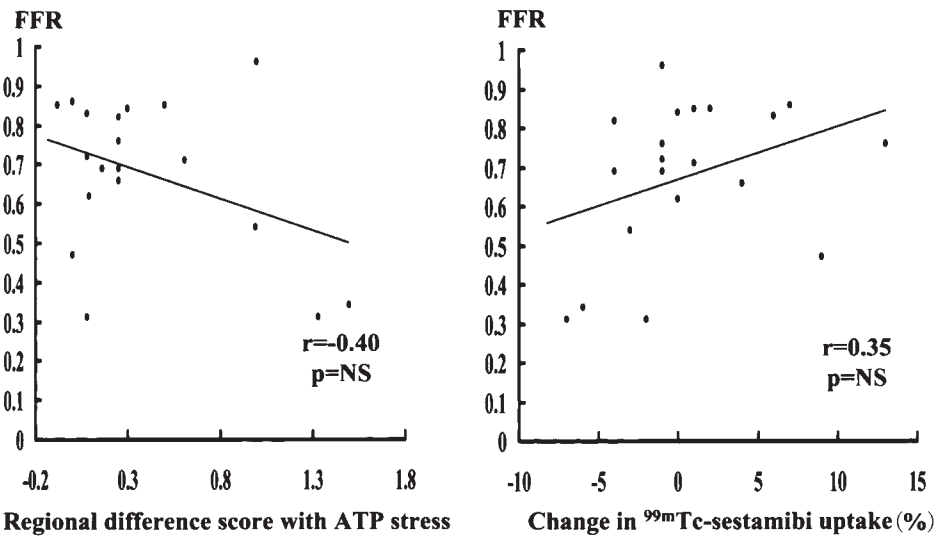

Fig. 5 Correlation between fractional flow reserve and regional difference score (*left*) or the change in technetium-99m-sestamibi percent uptake (*right*) with adenosine triphosphate disodium
ATP = adenosine triphosphate disodium. Other abbreviations as in Figs. 3, 4.

nary pressure measurements were made ($r = -0.40$, p = NS, $r = 0.35$, p = NS, respectively; **Fig. 5**). On the other hand, a significant correlation was found between the FFR and the percent increase in ^{99m}Tc direct counts ($r = 0.70$, $p < 0.001$; **Fig. 6**).

DISCUSSION

Recent progress in percutaneous coronary intervention has shown an increasing need for an approach that would allow more appropriate selection of patients with coronary artery disease who are most likely to benefit from revascularization

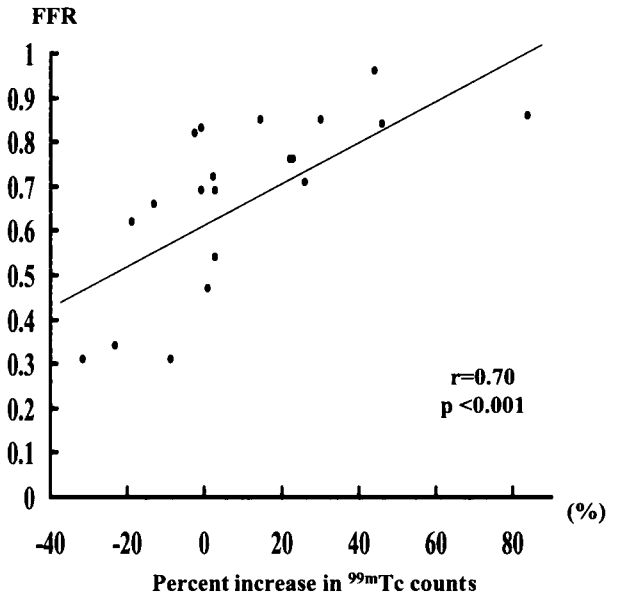

Fig. 6 Correlation between fractional flow reserve and percent increase in technetium-99m direct counts with adenosine triphosphate disodium infusion
Abbreviations as in Figs. 3, 4.

procedures[12,13]. Coronary angiography, an invasive procedure, has been used conventionally to evaluate arterial lesions from the anatomical standpoint. Recently, pressure-derived FFR and coronary flow reserve(CFR), which are obtained from the blood flow velocity, have been used as physiological parameters in the investigation of coronary artery disease[4,6,14–16]. These two parameters allow the cardiologist to make a more precise assessment of the severity of myocardial ischemia. However, stress myocardial scintigraphy has been applied widely in daily practice for the assessment of myocardial ischemia because this method is noninvasive[7,10,13,17]. Several studies have demonstrated the high sensitivity of myocardial scintigraphy for the detection of coronary artery stenoses[10,14,17]. Furthermore, FFR and CFR, the two physiological parameters of coronary stenoses determined by invasive methods, are also well correlated within the parameters of myocardial ischemia as measured by stress myocardial scintigraphy[14,16,18]. These studies have focused on determining the possible relationship between the defined cutoff values of FFR or CFR values, and the presence or absence of myocardial ischemia as determined qualitatively by myocardial scintigraphy. A direct comparison between FFR and ^{99m}Tc-sestamibi myocardial scintigraphy assessed the scintigraphic findings qualitatively[19].

In this study, the 2-day ^{99m}Tc-sestamibi myocardial scintigraphy protocol used allowed us to separately quantify myocardial perfusion at rest and during pharmacologic stress. We could also determine how myocardial perfusion was related to pressure-derived FFR, an index of the severity of myocardial ischemia. The results indicated that percent increase in ^{99m}Tc direct counts, based on an objective and quantitative method, were well correlated with FFR, the physiological parameter of coronary stenoses. A 1-day ^{99m}Tc-sestamibi myocardial SPECT protocol is useful for determining the relationship between coronary perfusion and the coronary flow reserve, but the scintigraphic imaging counts obtained under two conditions(rest and stress)are compared based on many assumptions that rely on complicated formulae[9,20,21]. In contrast, the 2-day myocardial scintigraphy protocol used in this study enables direct comparison between stress imaging counts and at rest in the patient under the same conditions. To use this to the greatest advantage, we used the intravenous cannula or butterfly needle with utmost care to avoid leakage of ^{99m}Tc-sestamibi during the two infusions. Applying this simple method, the value of coronary pressure-derived FFR can be estimated noninvasively with the use of ^{99m}Tc direct counts measurements. In particular, ^{99m}Tc direct counts increased by more than 20% with ATP in the coronary territory of FFR $\geq$ 0.75, whereas no increase in the uptake was observed in the territory of FFR $<$ 0.75.

Conventional SPECT images or the perfusion defect score on the SPECT images were normalized to the maximum count in each myocardial region. Thus, the presence or absence of a reversible perfusion defect determined by visual assessment was more significantly correlated with the DS obtained by visual semi-quantitative analysis or the change in ^{99m}Tc-sestamibi percent uptake, than with the percent increase in ^{99m}Tc direct counts as the former was derived from relative uptake of radioisotopes. However, no significant correlation was noted between the FFR and the RS or the change of ^{99m}Tc-sestamibi percent uptake, suggesting that scintigraphic analysis based on relative uptake of radioisotopes has limitations to assess the functional severity of myocardial ischemia. In contrast, measurements of ^{99m}Tc-sestamibi direct count were correlated significantly with both the visual mark-

ers of myocardial ischemia and the quantitative markers for functional severity of coronary-artery stenoses. These findings indicate that our quantitative analysis using ^{99m}Tc direct counts might be superior for the evaluation of the severity of myocardial ischemia to the conventional visual semi-quantitative method. Such parameters of relative values may be useful for the diagnosis of single-vessel disease or identification of the culprit lesion in multivessel disease, but the correct diagnosis of more severe disease such as triple-vessel disease is more difficult[22]. Thus, the two analytic methods of myocardial scintigraphy, relative uptake and direct counts of ^{99m}Tc-sestamibi, may be useful for the identification of myocardial ischemia and for improving the sensitivity of detection of multivessel disease that cannot be clearly detected by myocardial SPECT.

CONCLUSIONS

The present study suggests that quantitative analysis of ^{99m}Tc-sestamibi scintigraphy performed with the 2-day protocol enables the assessment of the magnitude of functional significance of coronary stenosis, which is far more important than the anatomic evaluation of the coronary lumen. ^{99m}Tc direct counts increased $>$ 20% with ATP in the coronary territory of FFR $\geq$ 0.75, whereas no increase in the uptake was observed in the territory of FFR $<$ 0.75.

要　　約

Technetium-99m-Sestamibi心筋取り込み率と冠血流予備量比との相関

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目　的: 近年，冠動脈狭窄の機能的重症度の評価指標である冠血流予備量比(FFR)の測定が重要になっているが，FFRと^{99m}Tc-sestamibi(MIBI)の直接測定値との比較に関する報告はない．心筋シンチグラフィーによる機能的心筋虚血を評価するために，心筋シンチグラフィーにより定量化した心筋虚血とFFRとの相関性について検討した．

方　法: 虚血性心疾患を疑い冠動脈造影とFFRを測定した症例の中で，アデノシン三リン酸(ATP)負荷心筋シンチグラフィーを実施した連続20例(男性16例，女性4例，平均年齢66±8歳)を対象とした．負荷シンチグラフィーはおのおの740 MBqずつを使用し，二日法のプロトコルで行った．視覚的評価ばかりでなく，^{99m}Tc-MIBIのカウントを用いた定量評価も行いFFRと比較検討を行った．

結　果: 視覚的に評価された^{99m}Tc-MIBIの灌流欠損は，機能的に重要な狭窄と考えられるFFR $<$ 0.75と良い相関をみた(17/20 vs 3/20，$\kappa = 0.71$，$p < 0.002$)．しかし，冠動脈領域における可逆性変化はFFRと相関がなかった($r = -0.40$，p = NS)．また，^{99m}Tc-MIBIのATP負荷における相対的摂取率もFFRと相関を認めなかった($r = 0.35$，p = NS)．これに対して，直接測定値のATP負荷による増加率はFFRが0.75未満の症例において，0.75以上の症例よりも有意に低値であった(−4±16% vs 24±30%，$p < 0.01$)．さらに，直接測定値のATP負荷による増加率がFFRと良い相関をみた($r = 0.70$，$p < 0.001$)．

結　論: ^{99m}Tc-MIBIシンチグラフィーの定量解析により冠動脈狭窄の機能的評価が可能であることが示唆された．

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