

A new method to evaluate ischemic heart disease: Combined use of rest thallium-201 myocardial SPECT and Tc-99m exercise tetrofosmin first pass and myocardial SPECT

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We developed a new diagnostic method for simultaneously evaluating myocardial ischemia, myocardial viability and ventricular function in less than 90 minutes by combined use of rest thallium-201 (Tl) SPECT and exercise Tc-99m tetrofosmin (TF) first pass and SPECT. The subjects were 9 healthy controls, 19 angina pectoris patients, and 19 old myocardial infarction patients, in all of whom coronary angiography had been performed. Rest Tl myocardial SPECT was performed first, and was followed by exercise TF myocardial SPECT. We also performed first pass radionuclide angiography by TF during maximum exercise on a bicycle ergometer to assess the left ventricular ejection fraction (LVEF). The total examination time was less than 90 minutes. SPECT diagnosis was performed by semi-quantitative analysis. LVEF below 55% was regarded as abnormal. In the patients with angina pectoris, analysis according to the coronary artery showed that the diagnostic accuracy of SPECT was 85.0% for ischemia in the region of the left anterior descending branch (LAD), 87.5% for the left circumflex branch (LCX) and 77.8% for the right coronary artery (RCA). The accuracy of diagnosis for angina pectoris was 82.1%, as determined by SPECT alone, and rose to 89.3% when the LVEF levels were also taken into consideration. In the patients with old myocardial infarction, the diagnostic accuracy of SPECT was 84.2% for the LAD, 92.3% for the LCX and 85.0% for the RCA. Analysis by patients showed that the accuracy of diagnosis for myocardial infarction was 85.7%, as determined by SPECT alone. The diagnostic accuracy, however, rose to 89.3% when the LVEF levels also were taken into consideration. In conclusion, it was demonstrated that this combined diagnostic method was highly reliable for evaluating ischemic heart disease within a short time.

Key words: ^{201}Tl , $^{99\text{m}}\text{Tc}$ -tetrofosmin, myocardial SPECT, exercise radionuclide angiography

INTRODUCTION

^{201}Tl is quite useful for detecting myocardial ischemia and for evaluating myocardial viability,^{1,2} but is affected by absorption and scattering because of low gamma-ray

energy spectrum. In addition, the maximal dose is limited because of the relatively long half decay time.

$^{99\text{m}}\text{Tc}$ -labeled myocardial agents that provide better SPECT images have recently been developed.³⁻⁶ $^{99\text{m}}\text{Tc}$ -tetrofosmin (Tetrofosmin) has shown promise in a variety of clinical applications because of lower accumulation in the liver than other $^{99\text{m}}\text{Tc}$ -labeled compounds, easy preparation at room temperature, a high labeling rate of more than 95% over 6 hours after preparation and the absence of adverse effects such as metallic taste.⁷⁻¹⁰ The phase 1 through phase 3 clinical studies in Japan have also demonstrated that Tetrofosmin provides excellent SPECT

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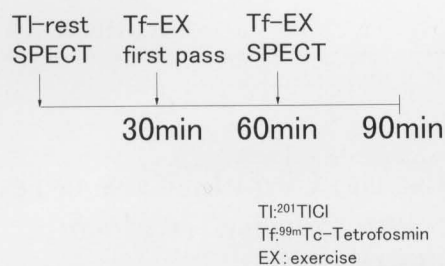


Fig. 1 Diagram illustrating a new diagnostic method for simultaneously evaluating myocardial perfusion, myocardial viability and ventricular function in less than 90 minutes by combined use of rest ^{201}Tl SPECT and exercise $^{99\text{m}}\text{Tc}$ -Tetrofosmin first pass and SPECT.

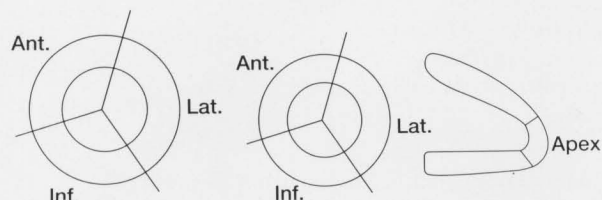


Fig. 2 Schematic representation of a short-axis view and vertical long-axis view of the left ventricle. Ant = Anterior wall, Lat = Lateral wall, Inf = Inferior wall

images, similar sensitivity in detection of ischemic heart disease¹¹⁻¹⁴ and higher specificity than ^{201}Tl .⁷⁻¹⁶ Tetrofosmin, however, needs to be administered both at rest and after exercise, because there is no redistribution.^{17,18} Berman et al. have developed new approaches to rapid evaluation of ischemic heart disease in a short time by using both ^{201}Tl and $^{99\text{m}}\text{Tc}$ -labeled tracers.¹⁹⁻²²

Noting the special properties of Tetrofosmin, which also can be used to evaluate ventricular function,²³ we developed a new diagnostic method for simultaneously evaluating myocardial perfusion and ventricular function within 90 minutes by using both ^{201}Tl and Tetrofosmin.

SUBJECTS AND METHODS

Subjects

The subjects were 9 normal controls (5 men and 4 women, the average age; 64.8 ± 9.4 years old) and 38 patients with ischemic heart disease (29 men and 9 women; average age: 66.0 ± 9.4 years old). Nineteen of the patients had angina pectoris (AP) and the remaining 19 had old myocardial infarction (OMI). In AP, culprit lesions were 11 in LAD, 7 in LCX and 9 in RCA, respectively. There were 2 triple vessels disease, 4 double vessels disease and 13 single vessel disease. In OMI culprit lesions were 9 in LAD, 4 in LCX and 11 in RCA. There were 2 triple vessels disease, 1 double vessels disease and 16 single vessel disease.

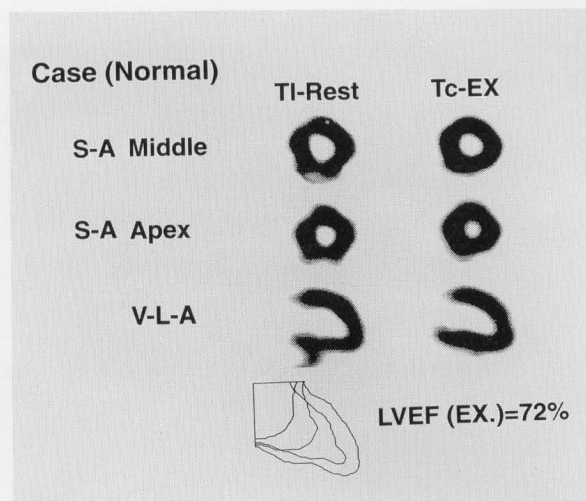


Fig. 3 A normal case.

Protocols

As shown in Figure 1, ^{201}Tl myocardial SPECT at rest was performed first, immediately thereafter the subjects performed maximal exercise on a bicycle ergometer and a Tetrofosmin first pass study was performed to evaluate the left ventricular ejection fraction (LVEF). This was followed by Tetrofosmin myocardial SPECT. The time required to complete the examination was less than 90 minutes.

Data acquisition

^{201}Tl myocardial SPECT

Data acquisition was started 20 minutes after 111 MBq of ^{201}Tl was injected at rest. The SPECT images were obtained at 30 seconds per step, rotating 180 degrees between the positions of 45°-LPO and 45°-RAO. A large field of view gamma camera with a parallel-hole high-resolution collimator (GCA901A/HG, Toshiba, Tokyo, Japan) was used in this study. The data obtained were stored on a 64×64 matrix and analyzed by means of a dedicated nuclear medicine computer (GMS5500A, Toshiba, Tokyo, Japan). Scatter correction was performed by using a triple-energy window method. Attenuation correction was not applied. The main window was placed at 71 ± 24 keV, and a sub-window was set at 4% in front and behind the main window. A low-pass (Butterworth) filter was used for the projection imagings, and a ramp filter for back-projection. Tomographic slices (approximately 5.3 mm thick) were reconstructed relative to the anatomical axis of the left ventricle. Vertical and horizontal long-axis slices and short-axis slices were generated.

Tetrofosmin first-pass study and myocardial SPECT

The subject performed bicycle ergometer exercise with 25-watts increases every two minutes in the modified supine position, the patient's body was raised 45°, and the legs were lowered 45°. When the maximal level of exer-

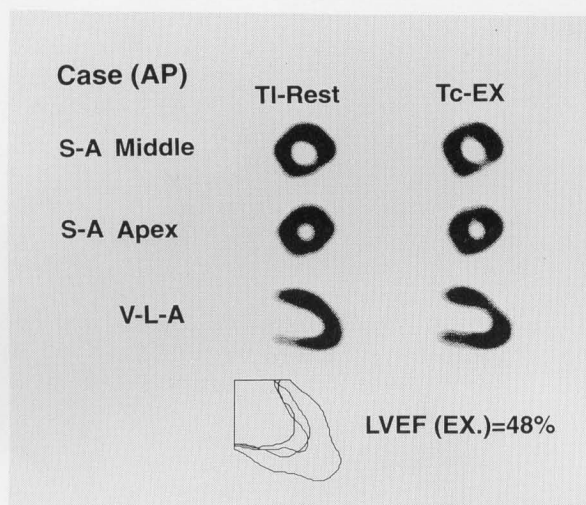


Fig. 4 A case of angina pectoris with coronary arterial stenosis in both the LAD (segment 7 = 90%, segment 9 = 99%) and the LCX (segment 13 = 99%). Although the Tetrofosmin SPECT images on exercise revealed mild perfusion defects in the anterior and lateral wall, the patient could not be clearly diagnosed as having myocardial ischemia on the basis of the SPECT study alone. However, this patient was confirmed to have ischemia, because the LVEF was low, 48%.

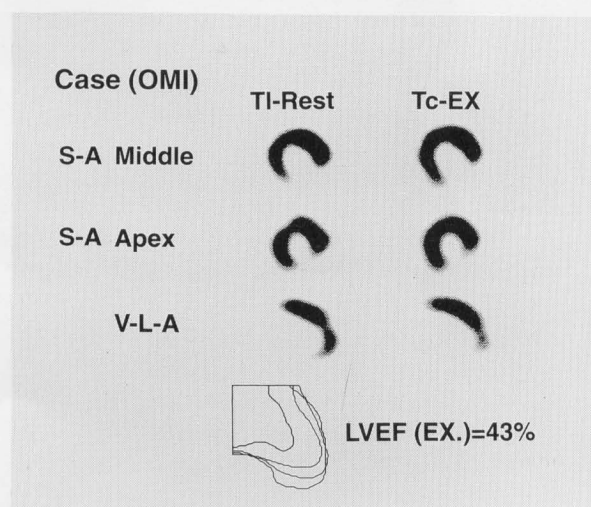


Fig. 5 A case with inferior old myocardial infarction (OMI). The study revealed a perfusion defect in the inferior wall and low LVEF value of 43%.

cise was reached, the patient was positioned close to the gamma camera (GCA 401, Toshiba, Tokyo, Japan) and exercise was stopped. A bolus of 925 MBq of ^{99m}Tc -tetrofosmin was administered to perform the first pass study within a few seconds after exercise, so that no apparent motion artifacts occurred. The first pass study was performed at the 30°-RAO position by the list mode method. In each case in a nuclear medicine computer (GMS 55U, Toshiba, Tokyo, Japan), the frame rate was calculated in 16 segments, which divided the R-R interval

of 2 or 3 heart beats in an electric cardiograph. Tetrofosmin SPECT images were obtained 30 minutes after the exercise, taking 20 seconds per step and rotating 180 degrees between the 45°-LPO and 45°-RAO positions. The images were collected with the main window set at 140 ± 24 keV, and a sub-window set at 3% in front and behind the main window. Other conditions were the same as used in ^{201}Tl myocardial SPECT study.

Data analysis

Radionuclide study

As shown in Figure 2, the representative myocardial SPECT images along the short and vertical long axis were divided into three segments: anterior wall, lateral wall, and inferior wall, as territories of left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA), respectively. The subjects were diagnosed as "normal," "ischemia" or "infarction (scar)" based on visual comparison of the rest TI and exercise Tetrofosmin SPECT images by three physicians in conference who had no knowledge of the patients' background. Reversible hypoperfusion was diagnosed as ischemia, and fixed perfusion defect as infarction. LVEF obtained in the first pass study during exercise was determined to be abnormal when the value was below the mean - 2SD of the healthy controls (LVEF < 55%).

Coronary angiography and left ventriculography

Coronary angiography and left ventriculography in the 30°-RAO position were performed on all the subjects within a week before performance of the radionuclide study.

When there was more than 75% coronary artery stenosis, it was considered as positive in accordance with the AHA classification. The left ventriculogram obtained in the 30°-RAO position was divided into 5 parts: anterobasal, anterolateral, apical, inferior and inferobasal. The left ventricular regional wall motion was evaluated by the centerline method, and was determined to be abnormal when the value was below the mean - 2SD of the healthy controls. Old myocardial infarction was defined according to wall motion abnormality.

Statistical analysis

All the values are expressed as the means \pm SD. Differences among the three groups were statistically analyzed by one-way analysis of variance. A value of $p < 0.05$ was considered significant.

RESULTS

Case presentation

A normal case is shown in Figure 3. Myocardial perfusion is normal, and LVEF during exercise is well maintained at 72%. Figure 4 represents an angina pectoris patient with coronary artery stenosis in both the LAD (segment 7 =

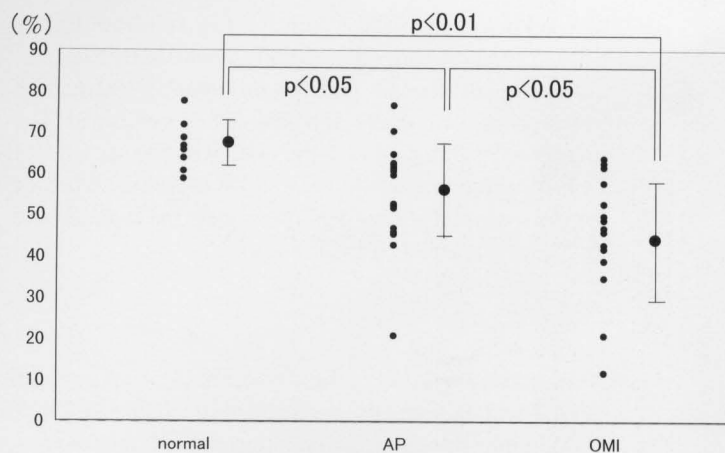


Fig. 6 Significant differences in the LVEF were observed among the controls ($67.2 \pm 5.7\%$), AP patients ($55.8 \pm 12.3\%$), and OMI patients ($43.1 \pm 15.3\%$).

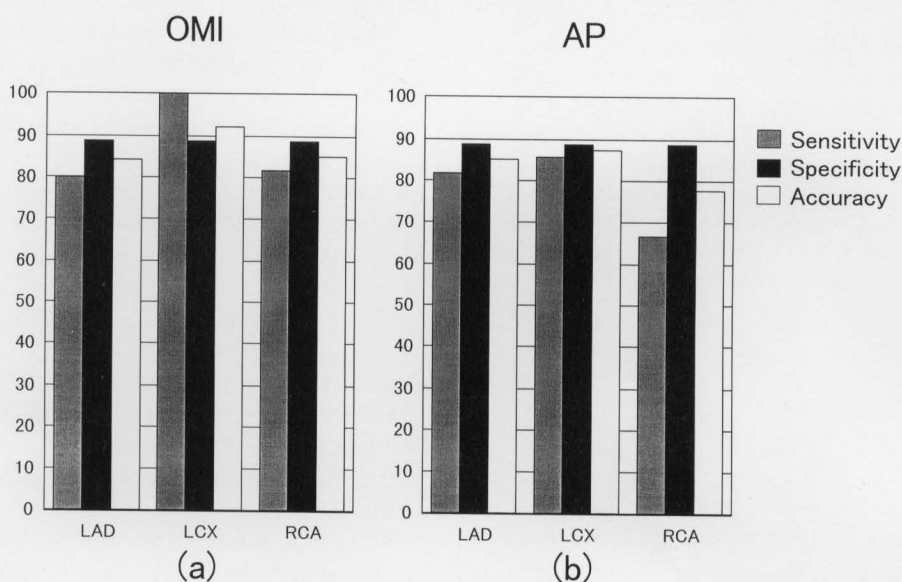


Fig. 7 (a) On analysis according to each coronary artery, the diagnostic sensitivity was 80%, specificity 88.9%, and accuracy 84.2% in the patients with OMI in the LAD region, 100%, 88.9%, and 92.3%, respectively, for the LCX region and 81.8%, 88.9% and 85.0%, respectively, for the RCA region. (b) Diagnostic sensitivity for myocardial ischemia in angina pectoris was 81.8%, specificity 88.9% and accuracy 85% in the patients with the stenosis of the LAD, 85.7%, 88.9%, and 87.5%, respectively, for the LCX and, 66.7%, 88.9%, and 77.8% for the RCA.

90%, segment 9 = 99%) and the LCX (segment 13 = 99%). Although exercise Tetrofosmin SPECT images showed mild perfusion defects in the anterior and lateral walls, the patient could not be clearly diagnosed as having myocardial ischemia on the basis of the SPECT study alone. It was confirmed, however, that the patient had ischemia, since the LVEF was a low 48%. Figure 5 shows a patient with old inferior myocardial infarction. The study revealed a perfusion defect in the inferior wall and a low LVEF of 43%.

Radionuclide study

As shown in Figure 6, significant differences in exercise LVEF were observed among the controls ($67.2 \pm 5.7\%$),

AP patients ($55.8 \pm 12.3\%$), and OMI patients ($43.1 \pm 15.3\%$). Analysis of the diagnostic reliability of SPECT according to each coronary artery showed 80% sensitivity, 88.9% specificity and 84.2% accuracy in the patients with OMI caused by occlusion of the LAD. Similarly, analysis of the reliability of SPECT alone showed 100% sensitivity, 88.9% specificity and 92.3% accuracy for the LCX, and 81.8% sensitivity, 88.9% specificity and 85.0% accuracy for the RCA (Fig. 7a). Similar results were obtained in the AP patients. Analysis of diagnostic reliability of SPECT alone showed 81.8% sensitivity, 88.9% specificity and 85% accuracy in the patients with stenosis of the LAD, 85.7% sensitivity, 88.9% specificity and 87.5% accuracy for the LCX, and 66.7% sensitivity,

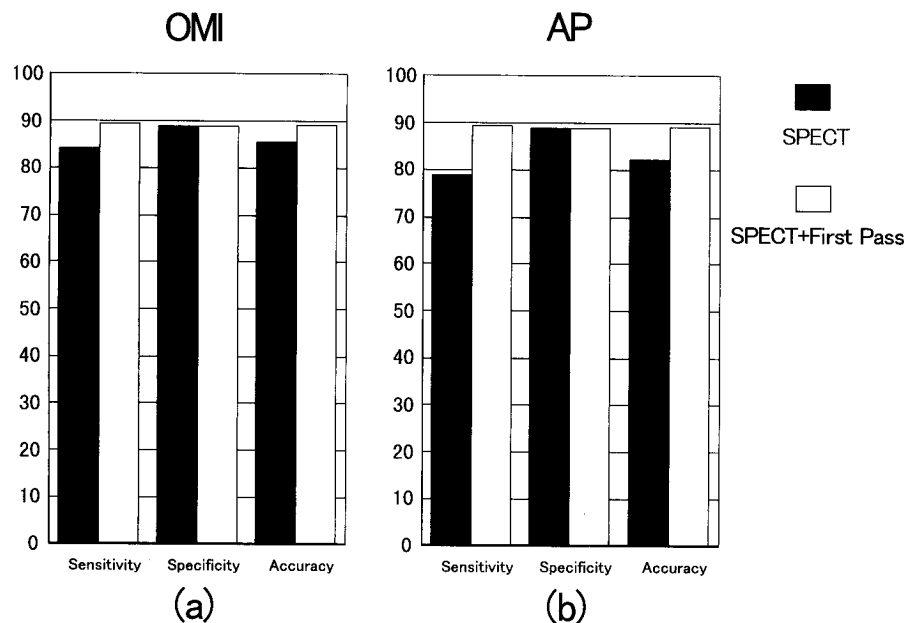


Fig. 8 (a) On analysis by patient, there was 84.2% sensitivity, 88.9% specificity, and 85.7% accuracy by the SPECT study alone in patients with OMI. Taking the LVEF on exercise into account, the reliability became higher, with 89.5% sensitivity and 89.3% accuracy. (b) On analysis by patient, there was 78.9% sensitivity, 88.9% specificity, and 82.1% accuracy by SPECT alone in the AP patients. Taking LVEF into account, the reliability of the diagnosis increased to 89.5% sensitivity and 89.3% accuracy.

88.9% specificity and 77.8% accuracy for the RCA (Fig. 7b).

The patients were diagnosed as having OMI with 84.2% sensitivity, 88.9% specificity and 85.7% accuracy by SPECT alone in the analysis by patients. When LVEF during exercise was taken into account, the reliability of the diagnosis increased to 89.5% sensitivity, 88.9% specificity and 89.3% accuracy (Fig. 8a). The AP patients were diagnosed as having ischemia with 78.9% sensitivity, 88.9% specificity and 82.1% accuracy, in the SPECT study. When the LVEF findings were taken into account, the reliability of the diagnosis increased to 89.5% sensitivity, 88.9% specificity and 89.3% accuracy (Fig. 8b).

DISCUSSION

^{99m}Tc -sestamibi (MIBI),²⁴⁻²⁶ ^{99m}Tc -tetrofosmin⁷⁻¹⁰ and ^{201}Tl have been used as myocardial flow tracers. Tetrofosmin provides excellent images even 30 minutes after intravenous injection, because it has lower liver activity. As with MIBI, however, Tetrofosmin needs to be injected twice, at rest and immediately after exercise, to detect myocardial ischemia and to evaluate myocardial viability,^{16,18} because it is hardly redistributed at all.¹⁷ Although diagnostic protocols for ^{201}Tl in combination with ^{99m}Tc -myocardial agents have been tried,¹⁹⁻²² many of them still need to be improved. Noting the properties of Tetrofosmin by which a relatively large dose enables

measurement of LVEF by the first pass method,²³ we have been able to develop a new diagnostic method for simultaneously evaluating myocardial perfusion and ventricular function in a short time.

Many reports on changes in LVEF during exercise have demonstrated that patients with ischemic heart disease exhibit little or no increase in LVEF immediately after exercise,³¹⁻³³ in contrast with a rapid increase in healthy controls.²⁷⁻³⁰ It was also demonstrated that decreasing LVEF values are correlated with the outcome of ischemic heart disease.^{34,35} The protocol we developed may therefore be useful in predicting outcome, because LVEF during exercise can be evaluated. In our protocol, however, LVEF cannot be obtained at rest and compared with LVEF during exercise. We therefore judged a patient to have myocardial ischemia if LVEF on exercise was smaller than the mean minus 2SD of the LVEF values of the healthy controls.

Our diagnostic protocol is cost-effective, since the examination can be completed in a short time, but whether our protocol functions more effectively than other protocols, in which ^{201}Tl alone is used, is a more important question.¹¹⁻¹⁴ We first identified affected sites in the coronary arteries of OMI and AP patients to assess the reliability of the protocol. In OMI, the reduced wall motion detected by left ventriculography was employed as the gold standard. The accuracy of diagnosis by SPECT was satisfactory: 84.2% for the LAD, 92.3% for the LCX

and 85.0% for the RCA, as shown in Figure 7a, and ^{201}Tl myocardial SPECT performed 24 hours later may be useful for evaluating myocardial viability as well. We next determined which coronary branch was responsible for AP. Coronary artery branches with more than 75% stenosis were considered as "positive" on coronary angiography, in accordance with the AHA classification. The diagnosis by SPECT was compared with that by the angiographic study to assess the reliability of the protocol. As shown in Figure 7b, the accuracy of the SPECT diagnosis was 85.0% for the LAD, 87.5% for the LCX and 77.8% for the RCA. In two patients with stenosis of the RCA who were in poor condition and could not perform maximal exercise, the sensitivity was a low 66.7%. This effect probably influenced the accuracy of RCA. When these two cases are excluded, the results appear consistent with the findings reported by Mahmood et al.²¹

We were able to confirm that our protocol is useful in identifying coronary arterial involvements as mentioned above. Another objective of this study was to demonstrate that our protocol is an appropriate screening examination that can be completed in a short time. Figure 8 shows the usefulness of our protocol for analysis by patients as a screening test for evaluating myocardial ischemia. The accuracy of the diagnosis by SPECT alone was 85.7% for OMI and 82.1% for AP, and is therefore satisfactory as a screening examination. Almost 90% accuracy was obtained when LVEF on exercise was taken into consideration. As limitations, the protocol we have presented here includes some complicated steps, such as measurement of LVEF on exercise, but it is evidently a very useful screening test for simultaneously evaluating myocardial perfusion and ventricular function within 90 minutes.

In conclusion, we developed a new diagnostic method that allows myocardial perfusion and ventricular function to be simultaneously evaluated within 90 minutes, and, if necessary, myocardial viability can be precisely evaluated by 24-hour ^{201}Tl imaging. Thus, The protocol was therefore demonstrated to be very reliable, and we expect it to occupy a secure place in the diagnosis of ischemic heart disease in the near future.

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