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Stress Technetium-99m Tetrofosmin Myocardial Scintigraphy: A New One-hour Protocol for the Detection of Coronary Artery Disease

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Abstract

A one-hour protocol for stress myocardial scintigraphy using technetium-99m (^{99m}Tc) tetrofosmin was compared with scintigraphy using thallium-201 (^{201}Tl) for the detection of coronary artery disease in 43 consecutive patients who underwent stress ^{201}Tl and ^{99m}Tc-tetrofosmin myocardial scintigraphy, and coronary arteriography within 1 week.

For the stress ^{99m}Tc-tetrofosmin test, rest imaging data were acquired 20 min after intravenous injection of 5–7 mCi ^{99m}Tc-tetrofosmin, using a 3-head gamma camera collecting 20-sec views over 360°. After dobutamine infusion or bicycle ergometer exercise, 20–25 mCi of ^{99m}Tc-tetrofosmin was additionally injected at peak stress. The stress images were acquired 15 min after the second injection with 5-sec views over 360°. All patients also underwent ^{201}Tl exercise and redistribution (4-hour) imaging following a standard protocol.

The overall sensitivity for detecting coronary artery disease was 96.0%, with an overall specificity of 93.3% for both types of scintigraphy. Qualitative analyses of 21 conventionally divided left ventricular segments showed that the overall segmental concordance between the ^{99m}Tc-tetrofosmin and ^{201}Tl imagings was 85.2% on the rest images and 82.1% on the stress images. The segmental concordance of the rest images was 87.0% in patients with neither significant stenosis nor myocardial infarction, 86.2% in patients with significant stenosis without myocardial infarction, and 82.9% in patients with significant stenosis and myocardial infarction, and the concordance values of the stress images were 85.4%, 87.5% and 75.6%, respectively.

These preliminary results suggest that stress myocardial scintigraphy using the present new protocol is a promising approach for the detection of coronary artery disease, with diagnostic sensitivity and specificity comparable to those of stress ^{201}Tl scintigraphy.

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Key Words

■ **Coronary artery disease** ■ **Radionuclide imaging (^{99m}Tc-tetrofosmin, one-hour protocol)**
■ **Diagnostic techniques**

INTRODUCTION

Stress thallium-201 (^{201}Tl) myocardial scintigraphy is an established modality for diagnosing coronary artery disease, with sensitivity and specificity of 85% and 76%, respectively[1]. Several standardized protocols are available for stress ^{201}Tl scintigraphy. However, 4 hours to 2 days are required to

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obtain both rest and stress images with this method, which is rather disadvantageous in clinical practice[2,3]. Technetium-99 m (^{99m}Tc)-based agents have recently been introduced for myocardial perfusion imaging. A shorter half-life is characteristic of ^{99m}Tc-based agents, which allows the administration of an imaging agent with a higher specific activity, resulting in better counting statistics in a shorter period of time.

Since stress images can be obtained in less time with the use of ^{99m}Tc-tetrofosmin, we designed a one-hour protocol for stress myocardial scintigraphy using ^{99m}Tc-tetrofosmin and assessed its utility for clinical practice in terms of the sensitivity and specificity to detect coronary artery disease. In this preliminary evaluation, stress myocardial scintigraphy under the present new protocol was found to be a promising approach for the detection of coronary artery disease, with a diagnostic sensitivity and specificity comparable to those of stress ^{201}Tl scintigraphy.

METHODS

Patient population

This study included 43 consecutive patients who underwent both stress ^{201}Tl and ^{99m}Tc-tetrofosmin myocardial scintigraphy as well as coronary arteriography within 7 days. Twenty-seven patients were male and 16 were female, with a mean age of 60.7 ± 11.5 years (range 32 to 79 years). Selective coronary arteriography was performed in multiple views by the Sones or Judkins technique. All patients gave informed consent for all procedures.

Stress test protocol

All patients underwent symptom-limited bicycle ergometer exercise or received dobutamine infusion. The initial work load of 50 W of the bicycle ergometer was increased by 25 W every 2 min. In the dobutamine infusion protocol, the initial infusion rate of 10 μg/kg/min was increased by 10 μg/kg/min every 2 min up to 40 μg/kg. Both bicycle ergometer exercise and dobutamine infusion were stopped if chest pain, fatigue, significant dyspnea, significant ventricular arrhythmia or hypotension occurred. The radiotracers were injected intravenously at peak exercise or dobutamine infusion, and the exercise or dobutamine infusion was continued for an additional 60 sec. Each patient underwent the same single test and same level of stress in the 2 scintigraphic studies.

Selected abbreviations and acronyms

^{99m}Tc = technetium-99 m
^{201}Tl = thallium-201

Scintigraphic protocol

^{99m}Tc-tetrofosmin study

Rest imaging was begun 20 min after ^{99m}Tc-tetrofosmin injection (5–7 mCi; 1/5 vial). The patient then underwent the stress test. ^{99m}Tc-tetrofosmin (20–25 mCi; 4/5 vial) was additionally administered at the peak stress time point. Stress imaging was begun 15 min after the second ^{99m}Tc-tetrofosmin injection. The rest images were obtained using a rotational 3-head gamma camera collecting 20-sec views over 360°. The stress images were collected as 5-sec views over 360°. The total acquisition times of the rest and stress images were about 10 and 3 min, respectively (**Fig. 1**).

^{201}Tl study

The patient received 3 mCi of ^{201}Tl at peak stress. Image acquisition was started within 5 min for the stress images, and after 4 hours for the rest images. The stress and rest images were collected as 30- and 40-sec views over 360°, respectively. The total acquisition times for the stress and rest images were about 14 and 18 min, respectively (**Fig. 1**).

Image analyses

The projection data were smoothed using a low-pass filter with a cutoff frequency of 0.3 cycles per pixel, and a series of 2.61 mm thick transverse slices was reconstructed using filtered backprojection with a ramp filter.

The left ventricular myocardium was divided into 21 segments (**Fig. 2**). The ^{201}Tl and ^{99m}Tc-tetrofosmin images were interpreted separately in a blinded manner, and the uptake of the tracer in each segment was scored using a 3-point grading system (0 = normal, 1 = hypoperfusion, 2 = defect).

Statistical analysis

Data are expressed as mean ± SD. Differences between the ^{99m}Tc-tetrofosmin and ^{201}Tl studies were compared using the κ statistic (κ value)[4] for discrete variables and the paired t-test for continuous variables. A p value less than 0.05 was considered significant.

RESULTS

Image quality of ^{99m}Tc-tetrofosmin

The stress and rest perfusion ^{99m}Tc-tetrofosmin tomograms were superior in quality to the ^{201}Tl tomograms in 11 patients (25.6%) and 6 patients (14.0%), equal in 28 (65.1%) and 21 (48.8%), and inferior in 4 (9.3%) and 16 (37.2%), respectively. No image was unusable in any patient. Thus, the image quality was generally good.

Coronary arteriographic findings

Twenty-five patients had significant (>75% luminal diameter) stenosis in one vessel, 2 in 2 vessels, and one in the left main trunk.

The complete series of 43 patients was divided into 3 groups on the basis of the presence or absence of diseased vessel(s) and whether the perfused area via the diseased vessels was associated with myocardial infarction. Group I included 15 patients who had neither significant stenosis (<50%) nor prior myocardial infarction, of whom 8 had vasospastic angina. Group II included 11 patients who had significant stenosis(es) but no myocardial infarction. Group III included 17 patients who had both significant stenosis(es) and prior myocardial infarction (>21 days after onset, **Table 1**).

Stress test results

The exercise duration, peak heart rate and pressure rate products during the ^{99m}Tc-tetrofosmin study and the ^{201}Tl study are shown in **Table 1**. The exercise workload and duration were not significantly different in each group. Angina occurred in 5 patients, ischemic ST-segment depression in 9, and significant ventricular arrhythmia in 8 during both stress ^{99m}Tc-tetrofosmin and ^{201}Tl tests.

Scintigraphic and coronary arteriographic findings

Among the 28 patients with significant coronary artery disease (Groups II and III), stress ^{201}Tl and ^{99m}Tc-tetrofosmin imagings revealed abnormal findings in 27 patients. The overall sensitivity for detecting coronary artery disease was 96.0% (27/28) for both ^{99m}Tc-tetrofosmin and ^{201}Tl studies.

Among the 15 patients with no significant coronary stenosis (Group I), stress ^{99m}Tc-tetrofosmin and ^{201}Tl imagings revealed normal perfusion in the same 14 patients. Thus, the overall specificity was 93.3% (14/15) for both ^{99m}Tc-tetrofosmin and ^{201}Tl studies.

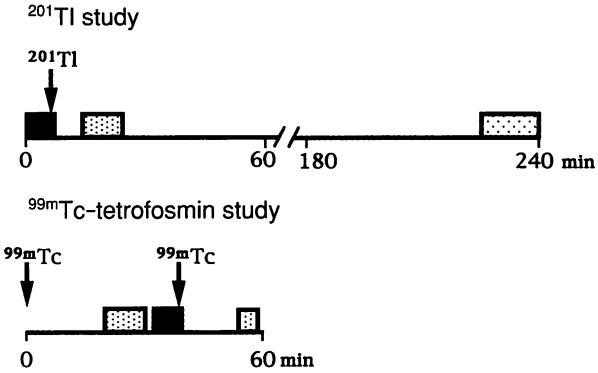

Fig. 1 Protocol of stress myocardial scintigraphy
In the stress thallium-201 (^{201}Tl) study, the patient received 3 mCi at peak stress. The image acquisition was then begun 5 min and 4 hours for the stress and resting imagings, respectively (*upper*). In the stress technetium-99m (^{99m}Tc) tetrofosmin study, the resting imaging was begun 20 min after a 5–7 mCi injection; the patient then underwent stress and received an additional 20–25 mCi at peak stress. The stress imaging was begun 15 min after the second injection (*lower*).
▨: Single photon emission computed tomography (SPECT).
■: Stress test.

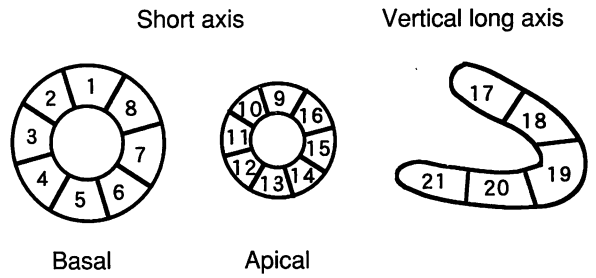

Fig. 2 Schematic presentation of 2 short-axis slices and mid-ventricular vertical long-axis slice displaying 21 myocardial segments

Qualitative analyses of ^{99m}Tc-tetrofosmin and ^{201}Tl images

A total of 903 myocardial segments were examined. Stress ^{99m}Tc-tetrofosmin imaging classified 579 (64.1%) as normal, 263 (29.1%) with hypoperfusion and 61 (6.8%) with a defect. Stress ^{201}Tl imaging classified 565 (62.6%) as normal, 286 (31.7%) with hypoperfusion, and 52 (5.7%) with a defect. ^{99m}Tc-tetrofosmin imaging classified 71 (7.9%) myocardial segments with transient hypo-

Table 1 Clinical profile and hemodynamic parameters during maximum stress

		Group I	Group II	Group III
Male : female		7 : 8	7 : 4	13 : 4
Age (yr)		64.3±11	64.3±10	55.8±12
Lesion				
Single-vessel disease		0	10	15
2-vessel disease		0	0	3
Left main trunk disease		0	1	0
Stress profile				
Double product (beat/min · mmHg)	TF	21,916±9,275	24,344±5,380	2,6402±6,760
	Tl	23,903±6,656	23,531±5,954	23,721±7,870
Peak heart rate (beat/min)	TF	119±27	122±22	136±22
	Tl	127±21	123±22	134±23
Exercise time (min)	TF	6.3±1.7	7.2±1.3	6.9±2.3
	Tl	6.7±1.9	6.5±1.4	6.7±2.1

Group I: patients without significant stenosis (<50%), Group II: patients with significant stenosis and without myocardial infarction, Group III: patients with significant stenosis and prior myocardial infarction.
TF=technetium-99m tetrofosmin.

Table 2 Concordance of perfusion images in each segment between ^{99m}Tc-tetrofosmin and ^{201}Tl imagings

Segment	Group I		Group II		Group III	
	Rest (%)	Stress (%)	Rest (%)	Stress (%)	Rest (%)	Stress (%)
1	87	93	73	82	100	82
2	87	73	91	91	76	82
3	73	60	91	100	88	76
4	73	67	82	100	88	59
5	67	73	82	82	88	65
6	87	100	91	82	71	59
7	100	100	91	100	100	100
8	100	100	100	73	88	88
9	100	93	91	91	94	76
10	100	87	91	91	82	65
11	80	73	82	91	88	82
12	80	73	73	73	65	53
13	67	53	55	64	71	71
14	100	100	91	100	94	76
15	100	100	100	100	82	71
16	100	100	91	91	94	76
17	93	100	91	82	88	88
18	100	100	100	100	82	88
19	80	67	82	91	71	65
20	73	93	82	82	71	53
21	80	87	82	73	82	88

Explanation of the groups as in Table 1.

perfusion by qualitative analysis of the standard redistribution on the ^{201}Tl images. The overall segmental concordance between the ^{99m}Tc-tetrofosmin and ^{201}Tl studies was 85.2% on the rest images and 82.1% on the stress images. The segmental concordance of rest imaging was 87.0% ($\kappa = 0.49$) in Group I, 86.2% ($\kappa = 0.51$) in Group II and 82.9% ($\kappa = 0.71$) in Group III; and for stress imaging was 85.4% ($\kappa = 0.51$), 87.5% ($\kappa = 0.74$), 75.6% ($\kappa = 0.60$), respectively (**Fig. 3**). The concordances of perfusion images in each segment are summarized in **Table 2**. The concordance of the inferoposterior segments was lower than those of other segments in Groups I and II. The anteroseptal segments also had lower concordance in Group III. A representative case is shown in **Fig. 4**.

Thus, both rest and stress imagings with ^{99m}Tc-tetrofosmin clearly demonstrated the presence of significant stenosis without being affected by the presence or absence of myocardial infarction, and achieved a similar accuracy to ^{201}Tl imaging.

DISCUSSION

^{201}Tl stress myocardial scintigraphy is useful in the diagnosis of coronary artery disease, and the mean sensitivity and specificity of the qualitative analysis by single photon emission computed tomography are 89% and 76%, respectively[1]. However, the commonly used standard redistribution study or reinjection study of stress ^{201}Tl scintigraphy are associated with some disadvan-

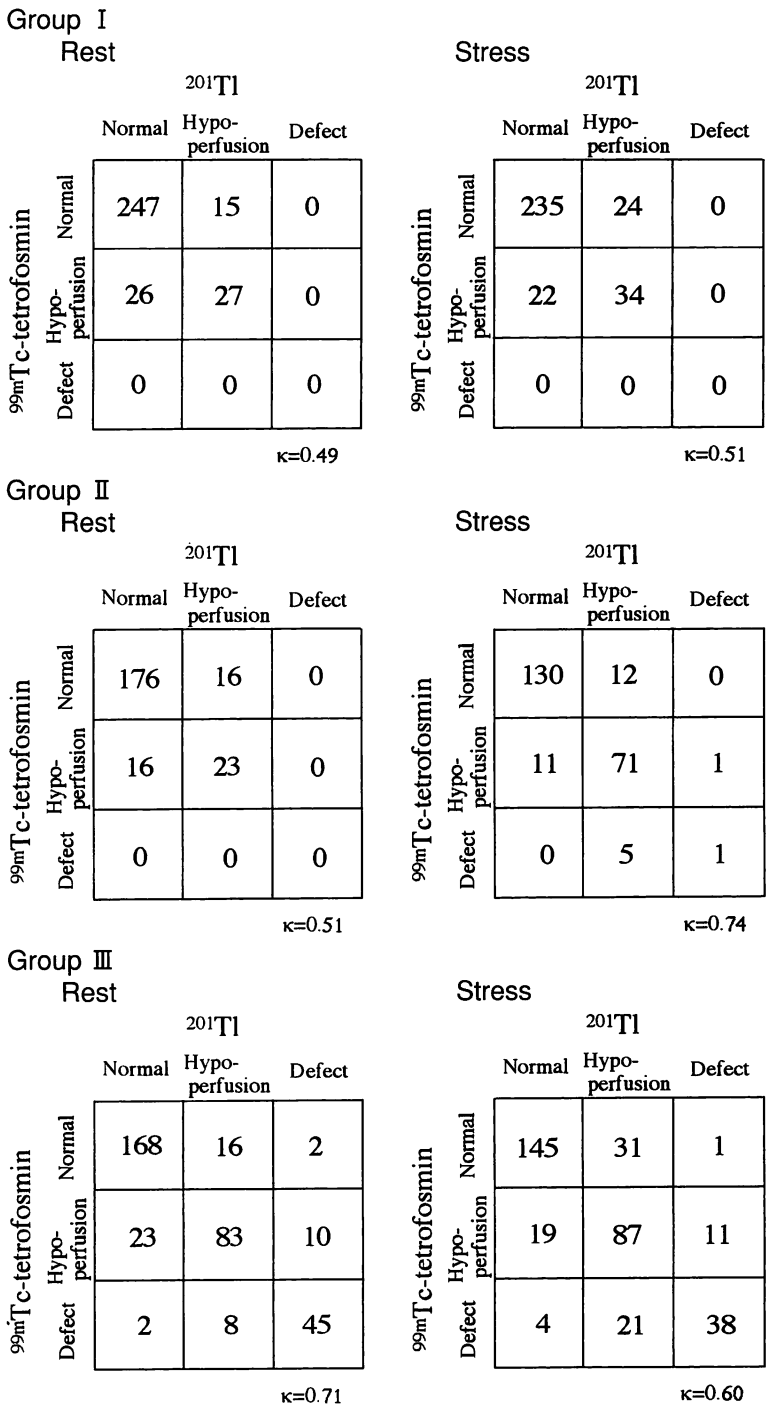

Fig. 3 Correlation between stress ^{99m}Tc-tetrofosmin and ^{201}Tl images in all segments
Explanation of the groups as in Table 1.

tages in clinical practice, such as 4 hours to 2 days required for the detection of myocardial ischemia; the scheduling examination needed because of the preparation of ^{201}Tl; and the patient must fast for about 6 hours before and after the stress test.

^{99m}Tc-based agents were recently introduced for myocardial perfusion imaging. The half-life of ^{99m}Tc is shorter than that of ^{201}Tl, and the agents have more favorable characteristics for imaging, such as higher emission energy and less scattered radiation. Phase I and II studies of ^{99m}Tc-tetrofosmin have shown good myocardial uptake with rapid

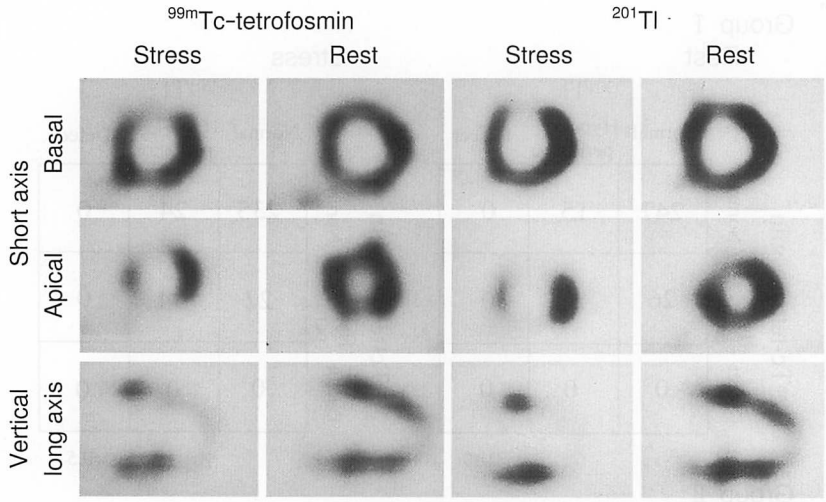

Fig. 4 ^{99m}Tc-tetrofosmin and ^{201}Tl myocardial single photon emission computed tomography scans from a 55-year-old man without prior myocardial infarction
Coronary arteriography showed 90% stenosis of the proximal left anterior descending artery. Both ^{99m}Tc-tetrofosmin and ^{201}Tl imagings showed transient hypoperfusion in the anteroseptal and apical walls.

clearance from background organs (blood, liver and lung)[5-7]. In recent clinical studies, ^{99m}Tc-tetrofosmin achieved high diagnostic accuracy comparable to that of ^{201}Tl for detecting coronary artery disease[7-13]. Because of the introduction of new ^{99m}Tc-based agents, imaging protocols have recently been modified considerably. One-day protocols including 4- to 5-hour[10,13-15] and 2-hour[16] protocols, a 2-day protocol[14,15], and a dual isotope protocol[17,18] have been reported. However, these protocols have disadvantages in clinical practice, including the 2 hours to 2 days required for the determination of myocardial ischemia, so the cost of scintigraphic examination with these protocols is higher than that with ^{201}Tl. ^{99m}Tc-based agents must be administered twice, requiring 2 vials of the agents. To reduce cost, we used one vial of tetrofosmin for the collection of the images, with the ^{99m}Tc-tetrofosmin divided into 2 different volumes (1/5 vial for rest imaging and 4/5 vial for stress imaging).

Our preliminary evaluation of the utility of the present one-hour protocol for stress myocardial scintigraphy using ^{99m}Tc-tetrofosmin compared the detection of coronary artery disease with that of stress scintigraphy using ^{201}Tl. The evaluation of a limited number of patients (43 patients) found the overall sensitivity and specificity of the new method were comparable to those of scintigraphy with ^{201}Tl, with the overall segmental concordance at the same level in the ^{99m}Tc-tetrofosmin and ^{201}Tl studies in the qualitative analyses. Thus, this new protocol is promising and has the following clinical benefits: The scintigraphic study is completed within one hour; the diagnostic sensitivity and specificity are comparable to those of ^{201}Tl scintigraphy; ^{99m}Tc-tetrofosmin is easily prepared from a kit at room temperature, allowing immediate preparation; in hospitals with a standing injection generator for ^{99m}Tc, the examination can be performed at any time; oral intake of the patients is not restricted, and scintigraphic study under the present protocol can be conducted for outpatients, even in patients receiving treatment for diabetes mellitus with medicine or insulin; the cost for the imaging agent is lower than that for previous protocols (except for the ^{201}Tl stress test with a single administration).

However, some issues remain to be examined. The sensitivity and specificity values for detecting coronary artery disease obtained in the present study were somewhat higher than those in previous reports[3]. This may be because 25 of the 28 patients in Groups II and III had more than 90% luminal stenosis on only one vessel, and because many patients in Group I were without stenosis, although the series was comprised of consecutive patients.

In this study, the image quality using ^{99m}Tc-tetrofosmin was generally good. However, the resting images were of inferior quality compared to the images obtained with ^{201}Tl in 37.2% of patients.

The administration of small doses of ^{99m}Tc-tetrofosmin for the resting imaging may partly account for the image inferiority, but the poorer image quality did not interfere with the interpretation of the images. The concordance of the inferoposterior segments was lower than those of other segments in all Groups. These findings are compatible with those of previous studies[10,12]. Another possible explanation of these findings is that the count density in the inferoposterior wall was attenuated by the liver and abdominal background. In Group Ⅲ, the count density may also have been affected by the difference in gamma photopeak energy between ^{99m}Tc and ^{201}Tl in the infarcted myocardium. The distribution of ^{99m}Tc-tetrofosmin is slightly higher after stress than that of ^{201}Tl, indicating a lower defect contrast, especially in the area where ^{201}Tl redistributes after exercise[11]. The use of quantitative analysis by generating perfusion maps and the computer coding of abnormally perfused myocardium, relative to a composite map from normal subjects, could solve some of these problems.

The present study did not examine an adequate number of patients with various clinical features. Only a prospective study with a greater number of patients will provide more objective and definitive results concerning scintigraphy using ^{99m}Tc-tetrofosmin. To more accurately assess the diagnostic significance of the new protocol, a double-blind prospective evaluation is now underway.

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要　約

虚血性心疾患の診断における1時間法Technetium-99m Tetrofosmin負荷心筋シンチグラフィーの有用性：予備的検討

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Technetium-99m (^{99m}Tc) tetrofosminを用いた1時間プロトコルによる新しい負荷心筋シンチグラフィー(^{99m}Tc負荷心筋シンチグラフィー)を考案し，冠動脈病変の検出率を従来の標準的thallium-201 (^{201}Tl)負荷心筋シンチグラフィーのそれと比較した．

対象は^{99m}Tcと^{201}Tl負荷心筋シンチグラフィーの両者を施行し，更に1週間以内に冠動脈造影を得た連続43例で，これらの症例を冠動脈造影所見により，有意狭窄を伴わない群15例(Group Ⅰ)，有意狭窄を伴うが心筋梗塞の合併のない11例(Group Ⅱ)，有意狭窄を伴い梗塞も合併する17例(Group Ⅲ)に分類した．

^{99m}Tc負荷心筋シンチグラフィーでは，5−7 mCi (1/5 vial)の^{99m}Tc-tetrofosminを静注20分後に安静時像を三検出器型ガンマカメラを用い，5°ごとに20 sec/stepで360°収集した．撮像終了後，ただちにdobutamine投与，または自転車エルゴメーターによる多段階負荷を行い，最大負荷時に20−25 mCi (4/5 vial)を再度静注し，その後1分間負荷を継続した．静注15分後に負荷時像を5 sec/stepで360°収集した．^{201}Tl負荷心筋シンチグラフィーは負荷時像を収集した後，4時間安静後に再分布像を撮像した．^{99m}Tcと^{201}Tl負荷心筋シンチグラフィーの冠動脈病変の診断精度は，両者とも感度96.0%，特異度93.3%で同等であった．シンチグラムを21分節に分けた時の各分節の所見の一致率は安静時像では85.2%，負荷後像では82.1%であった．各群内における各分節の所見の一致率は，安静時像ではGroup Ⅰ 87.0%，Group Ⅱ 86.2%，Group Ⅲ 82.9%で，負荷後像ではそれぞれ85.4%，87.5%，75.6%であった．

新たに考案した1時間プロトコルによる^{99m}Tc負荷心筋シンチグラフィーは，従来の^{201}Tl負荷心筋シンチグラフィーと同等の精度の情報を短時間内に提供するので，臨床上有用であると考えられた．

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