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Tc-99m tetrofosmin myocardial perfusion SPECT after dipyridamole combined with low-level exercise in the diagnosis of coronary artery disease

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Tc-99m tetrofosmin is a lipophilic, cationic perfusion imaging agent that changes to Tl-201 in detecting coronary artery disease during exercise testing. The purpose of this study is to evaluate the usefulness of Tc-99m tetrofosmin dipyridamole stress imaging combined with low level exercise for the detection of coronary artery disease. We examined 42 patients and 10 normal volunteers who also underwent coronary angiography. A one-day protocol was used: in the stress study, 296 MBq of tetrofosmin was injected and in the rest study 888 MBq was injected. After intravenous administration of dipyridamole (0.142 mg/kg/min for 4 minutes), the patient was exercised on a bicycle ergometer for 3 min (25 Watts). Tetrofosmin was injected 2 minutes after dipyridamole infusion during the exercise. Single photon emission computed tomographic images were obtained 30 minutes after the tracer injection. Images were interpreted as abnormal in 36 of 42 patients with coronary artery disease, and normal in all of 10 normal volunteers. The overall sensitivity of detection of coronary artery disease was 83.3% and the normalcy rate was 100%. The diagnostic values for the detection of significant stenosis in the three major arteries were: LAD sensitivity 83%, specificity 92%; LCX sensitivity 47%, specificity 91%; RCA sensitivity 75%, specificity 83%. Of the 66 arteries with more than 50% stenosis, 48 arteries were correctly identified. Of the 36 with more than 70% stenosis, 31 were identified. Scintigraphic evidence of multivessel disease was found in only 9 patients (50%).

A protocol of Tc-99m tetrofosmin SPECT combined with low level exercise after dipyridamole is therefore useful for the detection of the coronary artery disease.

Key words: Tc-99m tetrofosmin, dipyridamole, coronary artery disease, single photon emission computed tomography

INTRODUCTION

THE CLINICAL USE of thallium-201 (Tl-201) as a myocardial perfusion agent has been well-established for almost 20 years. Stress and redistribution myocardial imaging is an excellent method for the detection of coronary artery disease,[1–3] but dipyridamole Tl-201 scintigraphy is also an accepted alternate to exercise stress Tl-201 scintigraphy for diagnosis in patients who are unable to exercise as a result of peripheral vascular disease, severe arthritis or other orthopedic conditions.[4–8]

Nevertheless, the physical characteristics of Tl-201 are far from ideal. The 68–80 KeV energy level is suboptimal and its long half-life of 73 hours results in suboptimal dosimetry. Since the introduction of Tl-201, attempts have been made to develop a perfusion agent labeled with technetium-99m (Tc-99m). Tc-99m has an energy level of 140 KeV and a half-life of 6 hours making it an ideal radionuclide for gamma camera imaging. Amersham International, plc has developed a diphosphine-Tc complex, tetrofosmin, for myocardial perfusion imaging.[9–11] Recent studies have shown that it has a fast clearance from the blood with excellent cardiac uptake and relatively slow clearance from the heart. There appears to be no significant myocardial redistribution 3–4 hours

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postinjection. The general availability of Tc-99m tetrofosmin stimulated studies to assess its safety and diagnostic accuracy for cardiac ischemia.[12-14] Furthermore, pharmacological stress agents such as dipyridamole are becoming more and more important because large patient groups are not able to perform conventional exercise stress testing adequately. Low level bicycle exercise is able to be added to the dipyridamole infusion protocol because of the lower incidence of non-cardiac side effects.[7,8] As the overall efficacy of Tc-99m tetrofosmin SPECT after dipyridamole infusion combined with low level exercise is not well defined, the aim of this study is to determine the clinical value for myocardial perfusion Tc-99m tetrofosmin imaging after dipyridamole combined with low-level exercise in the diagnosis of coronary artery disease.

MATERIALS AND METHODS

Patient selection: Forty-two patients with stable coronary disease and 10 normal volunteers were studied. Patients had both clinical symptoms suggestive of coronary artery disease and more than 50% stenosis of at least one major coronary artery by coronary angiographs. Not of patients were able to undergo adequate conventional exercise stress testing for various reasons (Table 1). Patients with well-demonstrated previous myocardial infarction, left bundle branch block, significant valvular disease, unstable angina and cardiomyopathies were excluded. Whenever possible, patients stopped their routine medication for at least 24 hours prior to the tests.

Radiopharmaceutical preparation: Tetrofosmin was supplied by Amersham Japan, plc in freeze-dried vials. Each vial was reconstituted at room temperature with 4–8 m*l* of sterile sodium [Tc-99m]pertechnetate, containing no more than 1110 MBq/m*l* of Tc-99m. The vial was shaken to ensure adequate mixing and then allowed to stand at room temperature for 15 min. Radiochemical purity was determined by thin-layer chromatography and only doses with 90% labeling were used within 8 hours of preparation.

Tetrofosmin scintigraphy: In each of the 42 patients and 10 normal volunteers, tetrofosmin SPECT with combined dipyridamole and exercise stress was performed. Dipyridamole (0.56 mg/kg) was infused over 4 minutes and it was followed by 3 minutes of low level (25 Watts) bicycle ergometer exercise. A 12-lead electrocardiogram was recorded, the heart rate and blood pressure were determined at the baseline and each minute of dipyridamole infusion and exercise. Two minutes after the start of the exercise, 296 MBq of tetrofosmin was injected intravenously and the patients were encouraged to continue the exercise for another minute. Infusion of dipyridamole or exercise was discontinued when significant ST depression, typical chest pain or exertional hypotension appeared. Tetrofosmin SPECT was started approximately

Table 1 Characteristics of the patient population

	Patients	Volunteers
N	42	10
Age (yr)	62.4 ± 2.8	38.6 ± 2.4
Male (%)	71	70
No. of MVD	43	—
Reason for not performing conventional stress test (n)		
Intermittent claudication	12	—
Lumbago	8	—
Arthritis	6	—
Hemiplegia	4	—
Cannot ride ergometry	8	—
Others	4	—

MVD: multivessel disease

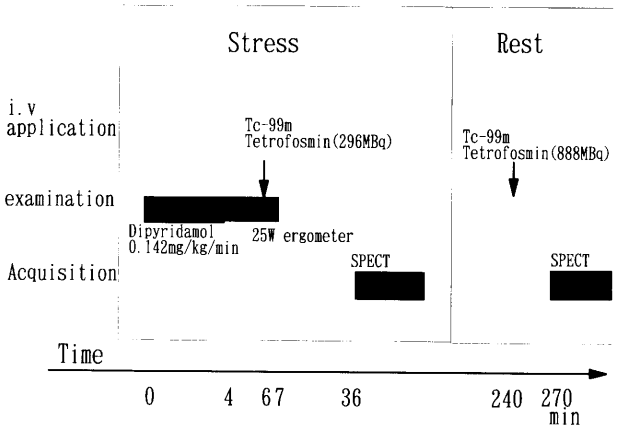

Fig. 1 Schema of examination protocol.

30 minutes after the injection. Four hours after stress imaging, each patient received a repeat injection of 888 MBq of tetrofosmin and underwent rest tetrofosmin SPECT imaging (Fig. 1). In each stress and rest imaging, the energy window was set at 140 KeV with a 20% window. Images were acquired with a large field of view gamma camera equipped with a low energy general purpose collimator that was rotated around the patients over 180 degrees at intervals of 6 degrees for 30 seconds/image.

Radionuclide processing: Processing was performed on a Scintipack 24000 nuclear medicine computer (Shimadzu, Kyoto). After acquisition, the cardiac volume was reconstructed by filtered back projection with a Ramp filter. Short-axis, horizontal and vertical axis slices were obtained by re-orienting the cardiac volume. Each slices was divided into the myocardial segments and matched according to the coronary artery redistribution as follows: septal and anterior segments corresponded to the left anterior descending artery (LAD), inferior segments to the right coronary artery (RCA), and lateral and posterior segments to the left circumflex artery (LCX). No isolated apical perfusion was assigned to any of three particular flow regions. An image was considered abnormal if there was a decrease on visual inspection of Tc-99m Tetrofosmin

uptake in any of the segments listed previously in at least two consecutive slices, and matching images of stress and rest images were displayed side by side for comparison. The reversibility of the perfusion abnormality was evaluated by consensus of three investigators who had no knowledge of coronary angiographic findings.

Coronary angiography: Selective coronary arteriography was carried out several days before tetrofosmin scintigraphy. The stenosis was measured by an automated edge detection method, and the greatest diameter reduction in any projection was recorded.

Data analysis: The relation between the scintigraphic data and the angiographic findings is given in terms of sensitivity and specificity, positive predictive value, negative predictive value and accuracy. Data are presented as the mean ± standard deviation. The statistical significance of difference was determined by Student's t-test for paired and unpaired values. Comparisons of categorical variables were analyzed by the chi-square test. Values for p lower than 0.05 were considered significant.

RESULTS

Hemodynamic response: The hemodynamic changes during dipyridamole infusion and exercise are listed in Table 2. During dipyridamole infusion, the heart rate increased and the systolic blood pressure decreased slightly. Chest pain was reported in 7 patients (13.5%) and ischemic horizontal ST segment depression were found in 6 patients (11.1%). No one was given aminophylline intravenously and two patients also received nitroglycerine sublingually. Side effects such as headache and nausea were noted in 4 cases (7.8%).

Comparison of detectability of patients with coronary artery disease: Good image quality was obtained with Tc-99m tetrofosmin in all of the 52 patients studied. Table 3 shows a comparison of detectability of patients with coronary artery disease. In patients with coronary artery disease, the perfusion abnormality was detected in 35 patients (Sensitivity 83.3%). In normal volunteers, all 10 showed normal images (Normalcy rate 100%). Diagnostic accuracy in predicting significant stenosis in the three major coronary arteries, in terms of sensitivity, specificity, and accuracy is shown in Table 4.

Comparison of sensitivity in percent lesion stenosis: Figure 2 shows comparison of sensitivity in percent stenosis of coronary lesions. Of the 66 diseased arteries with more than 50% stenosis, 48 vessels were correctly identified (Sensitivity 72.7%). Of the 36 diseased arteries with more than 70% stenosis, 31 arteries were identified (Sensitivity 86.1%).

Prediction of extent of coronary artery: The comparison of the number of jeopardized flow regions as detected by tetrofosmin SPECT with the number of diseased vessels is shown in Table 5. There were 4 false negative results in single vessel disease. Of 12 patients

Table 2 Hemodynamic changes during dipyridamole infusion and exercise

Heart rate at rest (bpm)	68 ± 14
Heart rate after dipyridamole infusion (bpm)	82 ± 12*
Heart rate at injection of tetrofosmin (bpm)	101 ± 16*
SBP at rest (mmHg)	152 ± 30
SBP after dipyridamole infusion (mmHg)	128 ± 32**
SBP at injection of tetrofosmin (mmHg)	164 ± 38

SBP: systolic blood pressure
*,**$p < 0.05$ vs. rest value

Table 3 SPECT imaging result

	Sensitivity of tetrofosmin SPECT
All CAD patients	35/42 (83.3%)
Single vessel disease	20/24 (83.3%)
Double vessel disease	10/12 (83.3%)
Triple vessel disease	5/6 (83.3%)
Normalcy rate	10/10 (100%)

Table 4 Diagnostic accuracy of Tc-99m tetrofosmin for the detection of stenosis in the three major coronary arteries

PV-negative	LAD	LCX	RCA
Sensitivity	83%	47%	75%
Specificity	92%	88%	91%
PV-positive	96%	73%	89%
PV-negative	71%	71%	83%
Accuracy	86%	72%	83%

LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, PV: predictive value

Table 5 Prediction of extent coronary artery disease

No. of stenosed arteries	No. of abnormal SPECT flow regions				
	0	1	2	3	Total
0	10	0	0	0	10
1	4	17	3	0	24
2	2	3	7	0	12
3	1	1	2	2	6

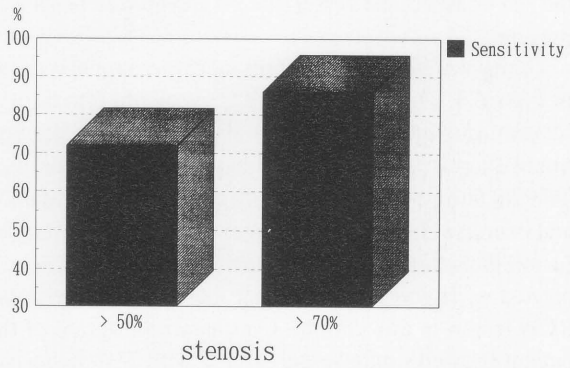

Fig. 2 Comparison of sensitivity in percent lesion stenosis.

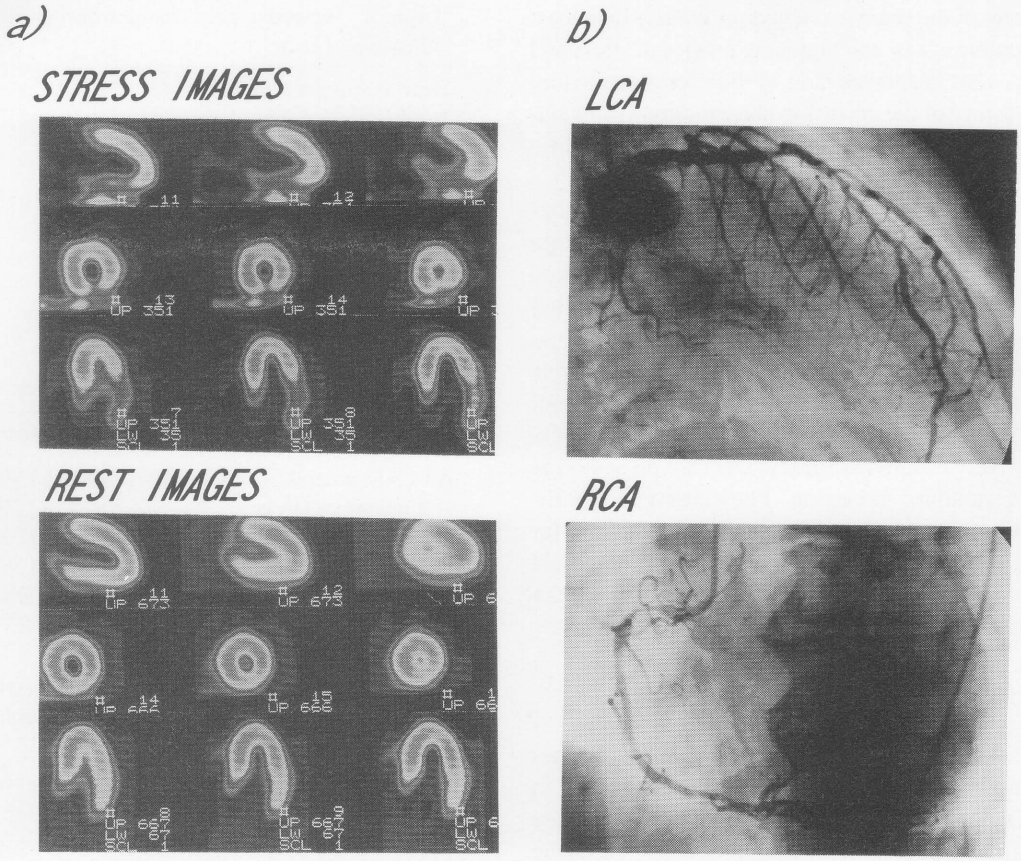

Fig. 3 Representative example of tetrofosmin dipyridamole stress SPECT. a) Stress images showed decrease of tetrofosmin uptake in inferior region. Rest images showed normal perfusion. b) Coronary angiogram showed single vessel disease with 78% stenosis in right coronary artery.

with double vessel disease, 7 correctly showed perfusion defects corresponding to multiple vessel involvement, whereas in 3 patients single vessel disease was predicted, and in 2 cases no significant perfusion defects could be detected. In 3 of the last 5 cases there was distal vessel disease in LCX. Two other cases had mild stenosis in at least one coronary artery. Of 6 patients with triple vessel disease 5 had abnormal SPECT scans. But 3 patients had perfusion defects in segments corresponding to one or two of the three major coronary arteries. In one case no significant abnormalities were noticed on scintigram. In the last 4 cases distal vessel disease and mild stenosis were present.

Case presentation: A representative example is shown in Figure 3. This patient was a 65-year-old female with severe lumbago. She was not able to perform conventional exercise stress testing adequately. She underwent Tc-99m tetrofosmin SPECT with combined dipyridamole and exercise stress. Stress images showed abnormal perfusion in the inferior region. Rest images showed normal perfusion. It was predicted that there was single vessel RCA lesion in this patient. Coronary angiogram of this patient showed single vessel disease with 78% stenosis in RCA.

DISCUSSION

Since its introduction into clinical use in 1973, Tl-201 imaging has been widely accepted as a noninvasive diagnostic procedure for the detection of coronary artery disease. Dipyridamole thallium scintigraphy is an accepted alternative to exercise thallium scintigraphy for the diagnosis of coronary artery disease in patients who are unable to exercise.

The physical characteristics of Tl-201 are far from ideal. Since the introduction of Tl-201, attempts have been made to develop a perfusion agent labeled with Tc-99m. Recently tetrofosmin has been developed by Amersham International, plc. It can be labeled at room temperature with Tc-99m. The advantages of tetrofosmin are: ideal photon energy (140 KeV), a relatively short half-life of 6 hours and availability and suitability for gated acquisition to assess left ventricular function as well as myocardial perfusion. But a potential disadvantage is a lower extraction fraction of myocardium. The heart to liver uptake ratio of Tc-99m tetrofosmin is low in the rest image. We suggested that only dipyridamole infusion stress tetrofosmin scintigraphy had worse image quality due to this disadvantage. On the other hand, low level

bicycle exercise is added as a supplement to the dipyridamole infusion because of the lower incidence of non-cardiac side effects. Furthermore, the addition of low level exercise following dipyridamole infusion would be shown to improve image quality by increasing the extraction fraction of the myocardium and improving target-to-background uptake.[15,16]

The present study demonstrated that Tc-99m tetrofosmin scintigraphy by means of dipyridamole infusion in combination with low level bicycle exercise as the myocardial stress method is a sensitive and specific technique for the detection of coronary artery disease. This technique also provided promising results in the evaluation of individual coronary stenosis, and is in agreement with what nowadays may be expected from cardiac imaging techniques. Distal coronary artery disease, especially in left circumflex artery, was the main cause of the false negative test results. The detection rate for abnormal perfusion patterns in all three major coronary arteries was 33% in the case of triple vessel disease. It is inherent in the scintigraphic technique that in cases of multivessel disease severely hypoperfused and less perfused segments cannot be discriminated.[17] We suggest that more studies with tetrofosmin are necessary to improve this. Our results are comparable to reported results obtained with Tl-201 and physical or pharmacological stress methods. In this respect sensitivity in the diagnosis of coronary artery disease is in the 76 to 95% range, and specificity from 57 to 90% has been reported.[7,8]

We concluded that Tc-99m tetrofosmin SPECT, after dipyridamole infusion combined with low level bicycle exercise, is a valuable diagnostic tool for the evaluation of coronary artery disease. Dipyridamole infusion in combination with low level bicycle exercise is a patient-friendly and safe method of inducing perfusion abnormalities although the precise mechanism of action of combined dipyridamole and exercise stress on coronary blood flow is unknown.

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