Myocardial Tomography with Technetium-99m-Tetrofosmin During Intravenous Infusion of Adenosine Triphosphate

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The purpose of this study was to determine the biodistribution of ^{99m}Tc-tetrofosmin during intravenous infusion of adenosine triphosphate (ATP) and to evaluate the potential diagnostic value of myocardial tomography with ^{99m}Tc-tetrofosmin during ATP infusion for the detection of coronary artery disease. **Methods:** Myocardial ^{99m}Tc-tetrofosmin imaging with ATP infusion and coronary arteriography were performed on 65 patients with suspected coronary artery disease. ATP was infused intravenously at a rate of 0.16 mg/kg/min for 5 min, and 370 MBq of ^{99m}Tc-tetrofosmin was injected 3 min after the start of ATP infusion. Myocardial SPECT imags were obtained 60 min later. Then, 740 MBq of ^{99m}Tc-tetrofosmin was administered at rest, and myocardial SPECT was repeated. Regional uptakes of ^{99m}Tc-tetrofosmin were scored from 4, normal, to 0, no activity. Serial 5-min planar images were obtained in the anterior projection at 15, 30, 45 and 60 min after the ^{99m}Tc-tetrofosmin injection in 10 patients. Heart-to-lung and heart-to-liver count ratios were defined from the serial planar images. **Results:** Adverse effects of ATP infusion were mild and transient. A heart-to-lung ratio after ATP infusion was high even at 15 min (3.40 ± 0.33) and gradually increased with time. A heart-to-liver ratio after ATP was 0.53 ± 0.40 at 15 min and increased with time. A heart-to-liver ratio reached 0.99 ± 0.25 ($p < 0.01$) after 45 min and 1.32 ± 0.36 ($p < 0.01$) after 60 min. The sensitivity and specificity for detecting coronary artery disease by myocardial SPECT with ATP were 89% (39/44) and 86% (18/21), respectively. **Conclusion:** This study shows the favorable biodistribution of ^{99m}Tc-tetrofosmin after intravenous infusion of ATP. A one-day imaging protocol of ^{99m}Tc-tetrofosmin tomography with ATP is feasible and has high diagnostic accuracy for coronary artery disease.

Key Words: technetium-99m-tetrofosmin; adenosine triphosphate; coronary artery disease

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Thallium-201 myocardial perfusion imaging during intravenous adenosine infusion has been used as a pharmacological stress test (*1*). Its safety and potential usefulness have been confirmed in clinical trials (*2–6*). Both adenosine and adenosine triphosphate (ATP) are potent coronary vasodilators with a short half-life (*7,8*). Recently, Kinoshita et al. (*9*) and Miyagawa et al. (*10*). have reported the potential diagnostic value of ^{201}Tl myocardial tomography with intravenous infusion of ATP in coronary artery disease. They show that myocardial ^{201}Tl perfusion imaging with ATP has diagnostic accuracy similar to that with adenosine, and intravenous infusion of ATP has fewer side effects than adenosine.

Technetium-99m-tetrofosmin is a new myocardial perfusion imaging agent (*11*). Because of the higher physical energy of ^{99m}Tc, myocardial images with ^{99m}Tc-tetrofosmin have better image quality with less soft-tissue attenuation than ^{201}Tl (*12*). It has been reported that ^{99m}Tc-tetrofosmin with dynamic exercise has a high diagnostic value comparable to ^{201}Tl for the detection of coronary artery disease (*13–15*). However, the feasibility of ^{99m}Tc-tetrofosmin tomography with intravenous ATP infusion has not been evaluated. In addition, the organ distribution of ^{99m}Tc-tetrofosmin during intravenous infusion of adenosine or ATP has not been examined.

The purpose of this study was to assess the feasibility and diagnostic value of myocardial ^{99m}Tc-tetrofosmin tomography with ATP in patients with coronary artery disease and to examine the organ distribution of ^{99m}Tc-tetrofosmin after intravenous ATP infusion.

MATERIALS AND METHODS

Subjects and Study Protocol

The subjects consisted of 65 consecutive patients (36 men, 29 women; mean age 67 yr) with suspected coronary artery disease who were admitted to the Yamagata University Hospital for the diagnosis of coronary artery disease. The exclusion criteria consisted of previous coronary arteriography, percutaneous transluminal coronary angioplasty or coronary-aorto bypass grafting and refused consent. Myocardial perfusion imaging with ^{99m}Tc-tetrofosmin was performed during ATP infusion and at resting state using a one-day protocol. Coronary arteriography was performed in all patients within 1 wk after the ^{99m}Tc-tetrofosmin imaging. Significant coronary stenosis was defined as a 50% or greater diameter narrowing in either main epicardial coronary arteries or their major branches. There were 23 patients with single-vessel disease, 12 patients with double-vessel disease, nine patients with triple-vessel disease and 21 patients without significant coronary artery stenosis.

The study protocol was approved by the Committee of Human Research of Yamagata University Hospital. Written informed consent was obtained from all patients.

Myocardial Perfusion Imaging with Technetium-99m-Tetrofosmin

ATP Infusion Protocol. Myocardial perfusion imaging with ^{99m}Tc-tetrofosmin during intravenous infusion of ATP (KOWA Co. Ltd., Tokyo, Japan) and at rest was performed using a one-day protocol (Fig. 1). All cardiovascular medications were discontinued at least 24 hr before the test. Blood pressure was measured every minute in the left arm by the cuff method, and electrocardiograms were constantly monitored during the test. ATP was infused intravenously at a rate of 0.16 mg/kg/min for 5 min using an infusion pump (*10*). Three minutes after the start of ATP infusion, a dose of 370 MBq ^{99m}Tc-tetrofosmin (Nihon-Medi-Physics, Tokyo, Japan) was administered into a separate vein. Myocardial perfusion imaging was begun 60 min after the ^{99m}Tc-tetrofosmin injection. Then, a dose of 740 MBq ^{99m}Tc-tetrofosmin was administered at rest, and myocardial imaging was repeated 60 min later.

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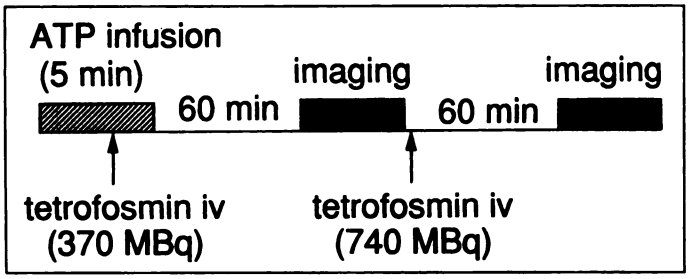

FIGURE 1. A one-day protocol of myocardial perfusion imaging with ^{99m}Tc-tetrofosmin during intravenous ATP infusion.

Data Acquisition and Processing. All images were obtained on a rotating gamma camera (MULTISPECT 3, Siemens Medical Systems, Chicago, IL) equipped with a parallel-hole, high-resolution collimator as described previously (*16*). Seventy-two images were obtained over a 360° arc. Energy discrimination was provided by a 15% window centered at 140 keV. Each image was accumulated for 40 sec. The data were stored on a 64 × 64 matrix. Data processing was performed on a nuclear medicine computer system (ICON, Siemens Medical Systems, Chicago, IL). A series of contiguous transaxial images of 6-mm thickness were reconstructed by a filtered backprojection algorithm without attenuation correction. These transaxial images were then reoriented in the short-axis, vertical long-axis and horizontal long-axis of the left ventricle.

Serial 5-min planar images were obtained in the standard anterior projection at 15, 30, 45 and 60 min after the injection of ^{99m}Tc-tetrofosmin in 10 patients. The same gamma camera was used for planar studies. In these patients, ^{99m}Tc-tetrofosmin imaging during ATP infusion and at rest was performed on a separate day.

Image Interpretation. The myocardial distribution of ^{99m}Tc-tetrofosmin was analyzed in the three standard orthogonal tomographic imaging planes as follows: the anterior, septal, inferior and lateral regions in the short-axis view; the anterior, apical and inferior regions in the vertical long-axis view; and the septal, apical and lateral regions in the horizontal long-axis view. The left ventricle was divided into 10 segments by splitting the anterior, septal, inferior and lateral wall in basal and middle segments, including two extra segments for the apex (*17*). Each segment was assigned to the vascular territories of the three major coronary arteries as follows: the anterior, septal and apical segments were corresponded to the left anterior descending artery, the inferior to the right coronary artery and the lateral to the left circumflex artery. The image was interpreted by two independent observers who were unaware of the clinical history and angiographic findings of the patients. A five-point scoring system was used for evaluating the regional myocardial tracer uptakes (*17*): 4 = normal, 3 = slightly reduced, 2 = moderately reduced, 1 = severely reduced, 0 = no activity. An uptake score in each segment was obtained by consensus. An increase of more than 1 of the segmental score in the rest image was considered as an ischemic response.

Data Analysis. For evaluation of ^{99m}Tc-tetrofosmin organ distribution and biokinetics, regions of interest (ROIs) were defined on the anterior planar image including the entire visualized heart, liver and left lung (*18,19*). The average counts per pixel in each ROI were determined in the serial images and normalized to the initial count density in the heart at 15 min postinjection (*18,19*).

For analysis of organ count ratios, square ROIs were defined for areas of the left ventricular myocardium, the left upper lung field and the upper part of the right liver lobe, as described previously (*20*). Heart-to-lung and heart-to-liver count ratios were calculated as a fraction of the mean counts per pixel in the heart divided by those in the lung and the liver, respectively (*20*).

Coronary Arteriography

Selective coronary arteriography was performed in multiple projection using the standard Judkins' technique. After visual inspection of the coronary angiograms in all views, the frame of optimal clarity was selected, showing a lesion at the maximal narrowing and arterial silhouette in sharpest focus. The images were analyzed by an experienced cardiologist blinded to the patients' clinical data and scintigraphic results. The severity of coronary stenosis was measured with caliper and expressed as percent of luminal diameter reduction. Significant coronary stenosis was defined as a 50% or greater diameter narrowing in either main epicardial coronary arteries or their major branches.

Statistical Analysis

Data are reported as mean ± 1 s.d. Statistical analysis was performed by the analysis of variance (Bonferroni test) and Student's t-test. A p value < 0.05 was considered significant.

RESULTS

Case Presentation

Figure 2 shows myocardial tomograms with ^{99m}Tc-tetrofosmin during ATP infusion and at rest. This patient had a coronary stenosis of 90% in the left circumflex artery. Transient ischemic abnormality was clearly seen in the posterolateral region of the left ventricle.

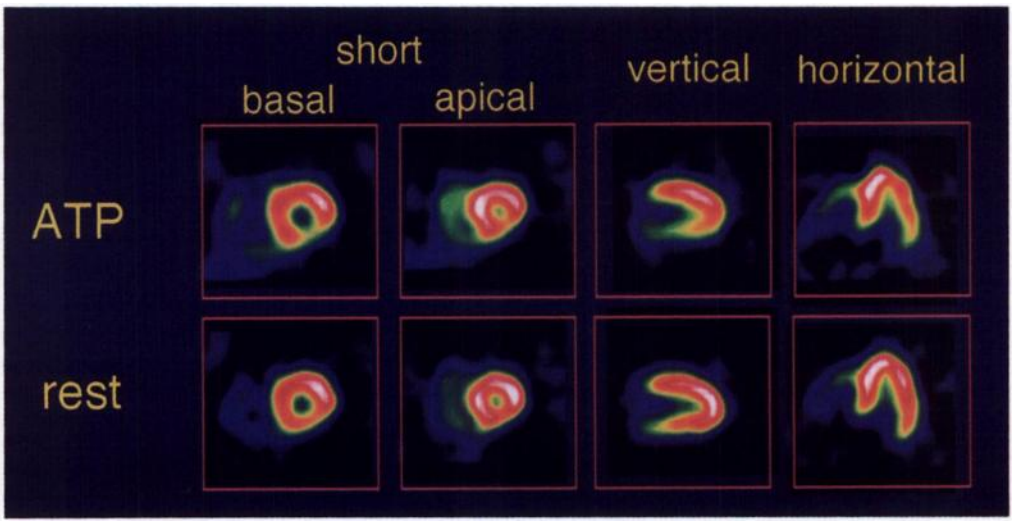

FIGURE 2. Myocardial tomographic images of ^{99m}Tc-tetrofosmin from a patient with angina pectoris. This patient had a severe coronary stenosis in the left circumflex artery. Transient ischemic abnormality was seen in the posterolateral region of the left ventricle.

TABLE 1
Hemodynamic Changes After ATP Infusion

	Basal	ATP Infusion
Heart rate (bpm)	68 ± 12	80 ± 13*
Systolic blood pressure (mmHg)	142 ± 19	126 ± 24*
Diastolic blood pressure (mmHg)	81 ± 13	71 ± 15*
Rate pressure products (bpm × mmHg)	9544 ± 2341	9976 ± 2456

*$p < 0.01$ versus basal value.

Hemodynamic Changes and Adverse Effects During Intravenous ATP Infusion

Hemodynamic changes during intravenous infusion of ATP are summarized in Table 1. ATP infusion caused an increase in heart rate and a decrease in systolic and diastolic blood pressures. Rate-pressure products increased slightly. Side effects including electrocardiographic changes are shown in Table 2. Headache and nausea were the most frequent side effects. Nineteen patients (29%) experienced chest pain, and ischemic ST depression, defined as horizontal or down-sloping ST depression of greater than or equal to 1 mm, was observed in 17 (26%) patients. Transient prolongation of the PR interval (first-degree atrioventricular block) was observed in two (3%) patients. Transient second-degree atrioventricular block developed in two (3%) patients. All symptoms and hemodynamic changes were tolerated well and disappeared within 1 or 2 min after discontinuing ATP infusion. No patient required intravenous infusion of aminophylline to reverse the side effects of ATP.

Organ Distribution of Technetium-99m-Tetrofosmin During ATP Infusion

Serial anterior planar images of ^{99m}Tc-tetrofosmin after ATP infusion are shown in Figure 3. Liver uptake of ^{99m}Tc-tetrofosmin was markedly high at 15 min but decreased promptly with time. Myocardial uptake was relatively constant and had the highest activity at 60 min.

The average organ activity of ^{99m}Tc-tetrofosmin was plotted against time after injection (Fig. 4). Initially, the highest ^{99m}Tc-tetrofosmin concentration after ATP was in the liver followed by the heart and lung. However, ^{99m}Tc-tetrofosmin cleared rapidly from the liver: 200% ± 57% at 15 min, 143% ± 50% at 30 min ($p < 0.01$ versus 15 min), 98% ± 33% at 45 min ($p < 0.01$ versus 15 min and $p < 0.05$ versus 30 min), and 70% ± 22% at 60 min ($p < 0.01$ versus 15 min and 30 min). Technetium-99m-tetrofosmin activity in the heart remained relatively stable: (92% ± 5% at 45 min ($p < 0.01$ versus 15 min), 89% ± 6% at 45 min ($p < 0.01$ versus 15 min) and 85% ± 5% at 60 min ($p < 0.01$ versus 15 min and 30 min). At 60 min postinjection, the heart had highest activity.

TABLE 2
Side Effects of ATP Infusion

Effect	No. of patients
Chest pain	19 (29%)
Headache	8 (12%)
Nausea	4 (6%)
Flushing	3 (5%)
Abdominal discomfort	2 (3%)
Dyspnea	1 (2%)
ST depression	17 (26%)
Atrioventricular block	
First degree	2 (3%)
Second degree	2 (3%)

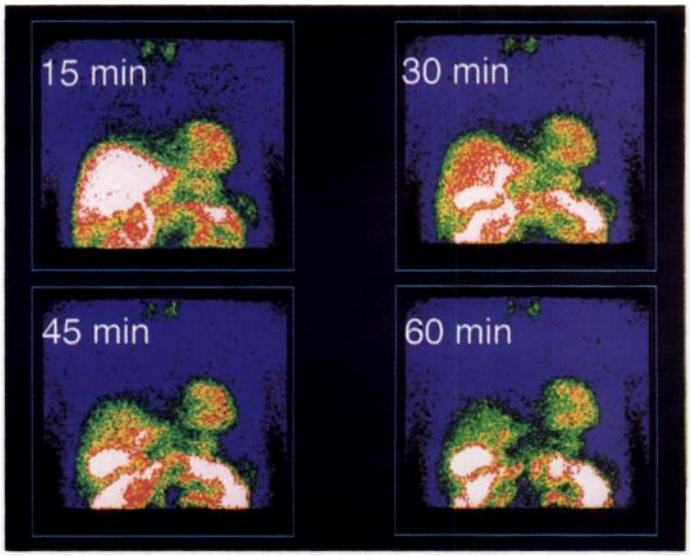

FIGURE 3. Serial anterior planar images after intravenous ATP infusion. Images were obtained at 15, 30, 45 and 60 min after the ^{99m}Tc-tetrofosmin injection.

Heart-to-lung and heart-to-liver count ratios are shown in Table 3. A heart-to-lung ratio was high even at 15 min for both ATP and rest studies (ATP: 3.40 ± 0.33 and rest: 3.39 ± 0.33) and gradually increased with time. A heart-to-liver ratio after ATP was 0.53 ± 0.40 at 15 min and increased with time. A heart-to-liver ratio reached 0.99 ± 0.25 ($p < 0.01$ versus 15 min) at 45 min and 1.32 ± 0.36 ($p < 0.01$ versus 15 min) at 60 min.

Comparison with Coronary Arteriographic Findings

The presence of a perfusion abnormality in ^{99m}Tc-tetrofosmin imaging was compared with the angiographic findings (Table 4). The sensitivity and specificity for the detection of patients with significant coronary stenosis (greater than 50%) were 89% (39/44) and 81% (17/21), respectively. The sensitivity in patients without prior myocardial infarction was 85% (28/33). The sensitivity for individual coronary stenosis was 79% (27/34) for left anterior descending artery, 83% (20/24) for right coronary artery and 63% (10/16) for left circumflex artery.

DISCUSSION

Technetium-99m-Tetrofosmin

Recently, ^{99m}Tc-tetrofosmin has become commercially available as a myocardial perfusion imaging agent. It has been demonstrated that ^{99m}Tc-tetrofosmin has high myocardial uptake and rapid clearance from the blood (*11*). These favorable biokinetic characteristics provide good quality of myocardial images (*12*). Preliminary clinical studies report that exercise ^{99m}Tc-tetrofosmin imaging shows similar diagnostic accuracy to ^{201}Tl for the detection of coronary artery disease (*13–15*). Compared with ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin appears to have some advantages: more convenient labeling procedure at room temperature and more rapid clearance from the liver (*11*). The clearance of tracer from the liver has an important clinical implication for myocardial image interpretation, because it has been reported that hepatic accumulation of the perfusion tracer is higher in pharmacological vasodilation, including dipyridamole, adenosine and ATP, than in dynamic exercise stress (*20*). Flamen et al. (*21*) have shown that a heart-to-liver activity ratio after dipyridamole infusion was significantly higher for tetrofosmin than for sestamibi. However, the biodistribution of ^{99m}Tc-tetrofosmin during adenosine or ATP infusion has not been previously examined. In the present ^{99m}Tc-tetrofosmin

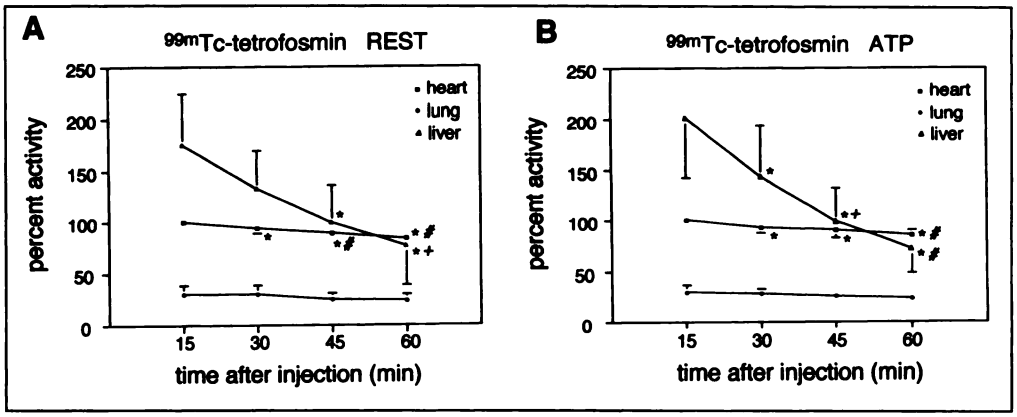

FIGURE 4. Percent organ activities over time after injection of ^{99m}Tc-tetrofosmin, at rest (A) and ATP infusion (B). Organ activity was normalized to the activity in the heart at 15 min postinjection. *p < 0.01 versus 15 min; # p < 0.01 versus 30 min and † p < 0.05 versus 30 min.

study, a heart-to-liver ratio was 1.43 ± 0.92 at 60 min on the rest image, which was higher than that in ^{99m}Tc-sestamibi study by Wackers et al. (*18*). Although hepatic accumulation was initially high, it was reduced rapidly with time, and heart-to-liver count ratios at 45 min and 60 min images were 0.99 ± 0.25 and 1.32 ± 0.36 after ATP and 1.07 ± 0.59 and 1.43 ± 0.92 at rest, respectively. From the present data, liver uptake of ^{99m}Tc-tetrofosmin did not interfere with the interpretation of myocardial images, when SPECT image was obtained 45–60 min after the tracer injection. In this study, the sensitivity and specificity of ^{99m}Tc-tetrofosmin tomography with ATP for detecting patients with coronary artery disease were 89% (39/44) and 86% (18/21), respectively.

Although a low myocardial extraction fraction of ^{99m}Tc-tetrofosmin at high flow rate has been obtained in animal studies (*22*), good clinical results of ^{99m}Tc-tetrofosmin tomography have been reported with dipyridamole (*23*) and adenosine (*24*). Our results with ATP were consistent with these studies. However, this limitation might have special importance in patients with mild to moderate coronary stenosis (*22*).

Technical Considerations

Although the use of a threefold difference between early and late imaging in a one-day protocol was reported, we used 370 MBq of ^{99m}Tc-tetrofosmin for ATP (early) images and 740 MBq for rest (late) images. We considered that, for the diagnosis of coronary artery disease, the presence or absence of a perfusion abnormality on the ATP (early) image was important. Although threefold difference of ^{99m}Tc-tetrofosmin for rest images might be advantageous for the assessment of myocardial viability (reversibility), the patients received more radiation exposure.

With a one-day protocol, a longer interval between the stress and the rest images might be more advantageous to allow for enhanced decay from the first administration. However, a longer interval between the stress and rest images needs more total time for the imaging protocol, and thus decreases the throughput of the study.

A lower extraction fraction in ^{99m}Tc-tetrofosmin than in ^{201}Tl may affect the detection of coronary artery stenoses. Thus, direct comparison between ^{99m}Tc-tetrofosmin and ^{201}Tl tomography in combination with ATP should be further examined in the same patients population.

Adenosine Triphosphate

Dipyridamole prevents cellular uptake of adenosine and elevates the level of adenosine in the blood and tissue, thereby producing its vasodilatory effect (*25*). The vasodilatory effect of dipyridamole on coronary blood flow is thus indirect, and maximal coronary dilation cannot be achieved in a substantial number of patients with a standard intravenous injected dose of dipyridamole (*26*). Adenosine is a potent coronary vasodilator with a short half-life (less than 2 sec), and near-maximal coronary vasodilation can be achieved safely with intravenous infusion of adenosine (*7*). Thus, ^{201}Tl or ^{99m}Tc-sestamibi was used in combination with adenosine as an alternative to the exercise stress test (*1–6*). Recently, the feasibility and potential usefulness of ^{201}Tl tomography with ATP for detecting coronary artery disease have been reported by Kinoshita et al. (*9*) and Miyagawa et al. (*10*). Both adenosine and ATP are potent coronary vasodilators with a short half-life. ATP is rapidly metabolized to adenosine in plasma, and adenosine produces coronary vasodilation through the activation of adenosine receptors. Although the vasodilatory effect of ATP is mostly obtained by adenosine, direct stimulation of adenosine receptors by ATP is also suggested (*8–10*). Coronary perfusion reserve measured by the Doppler catheter during intravenous ATP infusion at a rate of 0.16 mg/kg is 4.2, which is significantly higher than that during dipyridamole infusion (*27*).

In addition, it has been reported that ATP has fewer side effects than adenosine (*10*). ATP is gradually degraded to adenosine from a peripheral vein to the coronary sinus, and its degradation product, adenosine, induces vasodilatory effects. Thus, it has been suggested that the possible reason for less side effects in ATP than in adenosine may be the breakdown time of ATP in plasma (*10*). However, direct comparison regarding the

TABLE 3
Heart-to-Organ Ratios of Technetium-99m-Tetrofosmin

	Heart-to-lung		Heart-to-liver	
	ATP	Rest	ATP	Rest
15 min	3.40 ± 0.33	3.39 ± 0.33	0.53 ± 0.40	0.60 ± 0.16
30 min	3.39 ± 0.75	3.44 ± 0.90	0.71 ± 0.18*	0.77 ± 0.29†
45 min	3.62 ± 0.86†	3.64 ± 0.92†	0.99 ± 0.25*	1.07 ± 0.59†
60 min	3.43 ± 0.85	3.71 ± 0.89†	1.32 ± 0.36*	1.43 ± 0.92†

*p < 0.01 and †p < 0.05 versus 15 min.

TABLE 4
Sensitivity and Specificity for Detecting Coronary Artery Disease

	Sensitivity	Specificity
All patients	89% (39/44)	86% (18/21)
No prior MI	85% (28/33)	
One-vessel disease	83% (19/23)	
Two-vessel disease	92% (11/12)	
Three-vessel disease	100% (9/9)	

MI = myocardial infarction.

vasodilatory effects, side effects, diagnostic accuracy of perfusion imaging between adenosine and ATP has not been reported. This should be further examined in the same patients population. In this study, 49% of patients experienced some adverse effects, but these were tolerated well and disappeared within 1 or 2 min after termination of ATP infusion. ATP infusion could be completed in all patients, and intravenous infusion of aminophylline was not used to reverse the side effects of ATP. Thus, myocardial perfusion imaging with ^{99m}Tc-tetrofosmin during ATP infusion may be a promising method as a pharmacological stress test for detecting coronary artery disease in patients unable to exercise.

CONCLUSION

Our results indicate that ^{99m}Tc-tetrofosmin offers favorable tracer biodistribution after intravenous ATP infusion. Technetium-99m-tetrofosmin tomography with ATP is a practical method for the noninvasive diagnosis of coronary artery disease.

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