CONCLUSION

Glucose-loading ^{201}Tl SPECT protocol represents a significant improvement in identification of viable myocardium over traditional ^{201}Tl imaging, with results similar to those obtained using ^{18}F-FDG PET.

REFERENCES

1. Schoeder H, Friedrich M, Topp H. Myocardial viability: what do we need? *Eur J Nucl Med* 1993;20:792–803.
2. Lui P, Keiss MC, Okada RD, et al. The persistent defect on exercise thallium imaging and its fate after myocardial revascularization: does it represent scar or ischemia? *Am Heart J* 1985;110:996–1001.
3. Cloninger KG, DePuey EG, Garcia EV, et al. Incomplete redistribution delayed thallium-201 single-photon emission computed tomographic images: an overestimation of myocardial scarring. *J Am Coll Cardiol* 1988;12:955–963.
4. Kiat H, Berman DS, Maddashi J, et al. Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability. *J Am Coll Cardiol* 1988;12:1456–1463.
5. Yang LD, Berman DS, Kiat H, et al. The frequency of late reversibility in SPECT thallium-201 stress-redistribution studies. *J Am Coll Cardiol* 1990;15:334–340.
6. Rocco TP, Dilsizian V, McKusick KA, Fishman AJ, Boucher CA, Strauss HW. Comparison of thallium redistribution with rest "reinjection" imaging for the detection of viable myocardium. *Am J Cardiol* 1990;66:158–163.
7. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after the stress-redistribution imaging. *N Engl J Med* 1990;323:141–146.
8. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. Comparison of thallium scintigraphy with reinjection and PET imaging with ^{18}F-fluorodeoxyglucose. *Circulation* 1991;83:26–37.
9. Mori T, Minamiji K, Kurogane H, Ogawa K, Yoshida Y. Rest-injected thallium-201 imaging for assessing viability of severe asynergic regions. *J Nucl Med* 1991;32:1718–1724.
10. Dilsizian V, Perrone-Filardi P, Arrighi JA, et al. Concordance and disconcordance between stress-redistribution-reinjection and rest-redistribution thallium imaging for assessing viable myocardium. Comparison with metabolic activity by positron emission tomography. *Circulation* 1993;88:941–952.
11. Lomboy CT, Schulman DS, Grill HP, Flores AR, Orie JE, Granato JE. Rest-redistribution thallium-201 scintigraphy to determine myocardial viability early after myocardial infarction. *J Am Coll Cardiol* 1995;25:210–217.
12. Sawada SG, Allman KC, Muzik O, et al. Positron emission tomography detects evidence of viability in rest technetium-99m-sestamibi defects. *J Am Coll Cardiol* 1994;23:92–98.
13. Omatsu-Kanbe M, Kitasato H. Insulin stimulates the translocation of Na^+/K^+-dependent ATPase molecules from intracellular stores to the plasma membrane in frog skeletal muscle. *Biochem J* 1990;272:727–733.
14. Hundal HS, Marette A, Mitsumoto Y, Ramlal T, Blostein R, Klip A. Insulin induces translocation of the alpha 2 and beta 1 subunits of the Na^+/K^+-ATPase from intracellular compartments to the plasma membrane in mammalian skeletal muscle. *J Biol Chem* 1922;267:5040–5043.
15. Gehring PJ, Hammond PB. The inter-relationship between thallium and potassium in animals. *J Pharmacol Exper Ther* 1967;155:187–201.
16. McCall D, Zimmer LJ, Katz AM. Kinetics of thallium exchange in metabolic factors on thallium exchange in cultured rat myocardial cells. *Circ Res* 1985;56:370–376.
17. Kusuoka H, Hashimoto K, Fukuchi K, Nishimura T. Kinetics of a putative hypoxic tissue marker, technetium-99m-nitroimidazole (BMS181321) in normoxic, hypoxic, ischemic and stunned myocardium. *J Nucl Med* 1994;35:1371–1376.
18. Ishii Y, MacIntyre WJ, Pritchard WH, Eckstein RW. Measurement of total myocardial blood flow in dogs with ^{43}K and the scintillation camera. *Circ Res* 1973;33:113–122.
19. Erlij D, Grinstein S. The number of sodium ion pumping sites in skeletal muscle and its modification by insulin. *J Physiol (London)* 1976;259:13–31.
20. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernation myocardium." *J Am Coll Cardiol* 1986;8:1467–1470.
21. Rahimtoola SH. The hibernating myocardium. *Am Heart J* 1989;117:211–222.
22. Ritchie JL, Albro PC, Caldwell JH, Trobaugh GB, Hamilton GW. Thallium-201 myocardial imaging: a comparison of the redistribution and rest images. *J Nucl Med* 1979;20:477–483.
23. Rozanski A, Berman DS, Gray R, et al. Use of thallium-201 redistribution scintigraphy in the preoperative differentiation of reversible and nonreversible myocardial asynergy. *Circulation* 1981;64:936–944.
24. He ZX, Darcourt J, Guignier A, et al. Nitrates improve detection of ischemic but viable myocardium by thallium-201 reinjection SPECT. *J Nucl Med* 1993;34:1472–1477.
25. Bisi G, Sciagr 66 R, Santoro GM, Zerauschek F, Fazzini PF. Sublingual isosorbide dinitrate to improve technetium-99m-teboroxime perfusion defect reversibility. *J Nucl Med* 1994;35:1274–1278.
26. Bisi G, Sciagr R, Santoro GM, Fazzini PF. Rest technetium-99m-sestamibi tomography in combination with short-term administration of nitrates: feasibility and reliability for prediction of postrevascularization outcome of asynergic territories. *J Am Coll Cardiol* 1994;24:1282–1289.
27. Maurea S, Cuocolo A, Soricelli A, et al. Enhanced detection of viable myocardium by technetium-99m-MIBI imaging after nitrate administration in chronic coronary artery disease. *J Nucl Med* 1995;36:1945–1952.
28. Brunken RC, Schwaiger M, Grower-McKay M, Phelps M, Tillisch J, Schelbert H. Positron emission tomography detects tissue metabolic activity in myocardial segments of patients with persistent thallium perfusion defects. *J Am Coll Cardiol* 1987;10:557–567.
29. Schelbert HR. Euglycemic hyperinsulinemic clamp and oral glucose load: stimulating myocardial glucose utilization during positron emission tomography? *J Nucl Med* 1992;33:1263–1266.
30. Tamaki N, Yonekura Y, Konishi J. Myocardial FDG PET studies with fasting, oral glucose-loading or insulin clamp methods. *J Nucl Med* 1992;33:1263–1268.
31. Tartagni F, Fallani F, Corbelli C, et al. Detecting hibernated myocardium with SPECT and thallium-glucose-insulin infusion. *J Nucl Med* 1995;36:1377–1383.
32. Wilson RA, Okada RD, Strauss HW, Pohost GM. Effect of glucose-insulin-potassium infusion on thallium myocardial clearance. *Circulation* 1983;68:203–209.
33. Tamaki N, Ohtani H, Yamashita K, et al. Metabolic activity in the areas of new fill-in after thallium-201 reinjection: comparison with positron emission tomography using fluorine-18-deoxyglucose. *J Nucl Med* 1991;32:673–678.

Comparison of Adenosine Triphosphate and Dipyridamole in Diagnosis by Thallium-201 Myocardial Scintigraphy

Kouki Watanabe, Michihito Sekiya, Shuntarou Ikeda, Masao Miyagawa, Masayuki Kinoshita and Seishi Kumano

Division of Cardiology, Minamiuwa Ehime Prefectural Hospital, Minamiuwa-gun; Division of Cardiology and Division of Radiology, Ehime National Hospital, Onsen-gun, Ehime, Japan

We examined whether ^{201}Tl myocardial scintigraphy with intravenous infusion of adenosine triphosphate (ATP) can be substituted for dipyridamole (DIP) in the diagnosis of coronary artery disease (CAD). **Methods:** The coronary flow reserve (CFR) during intravenous infusion of ATP (0.10–0.20 mg/kg/min) was compared with that during intravenous infusion of DIP (0.56 mg/kg) using a Doppler flow wire in 19 subjects with normal coronary arteries. The highest CFR level was found in the ATP dose range of 0.16–0.20 mg/kg/min. The CFR at the ATP dose of 0.16 mg/kg/min was significantly higher than that during DIP infusion (4.2 versus 3.6) ($p < 0.01$), for which reason we adopted this dose of ATP. Accordingly, ^{201}Tl SPECT in 140 patients with suspected CAD was performed after infusion of 0.16 mg/kg/min of ATP in 70 of them and 0.56 mg/kg of DIP in the 70 others. **Results:** ATP stress ^{201}Tl SPECT showed no significant difference in sensitivity and accuracy from DIP stress ^{201}Tl SPECT (87.0% versus 82.9, and 87.1% versus 78.6, respectively). Adverse effects occurred at higher frequency when ATP was used, but they were mild and disappeared rapidly after administration was stopped. **Conclusion:** ATP stress ^{201}Tl SPECT is accurate and safe. The optimal ATP regimen for this purpose is considered to be a 5-min infusion at 0.16 mg/kg/min. However, our data in CAD patients suggest that ATP stress ^{201}Tl SPECT is equivalent to DIP stress ^{201}Tl SPECT in the detection of CAD.

Key Words: thallium-201; adenosine triphosphate; dipyridamole; coronary artery disease; coronary flow reserve

J Nucl Med 1997; 38:577–581

Received May 20, 1996; revision accepted Aug. 14, 1996.

For correspondence or reprints contact: Kouki Watanabe, MD, Division of Cardiology, Minamiuwa Ehime Prefectural Hospital, Jouhen-cyo, Minamiuwa-gun, Ehime, 798-41, Japan.

TABLE 1
Clinical Characteristics of the Study Group

	ATP-Tl	DIP-Tl
Number	70	70
Age (yr)	62.3 ± 10.3	63.1 ± 11.2
Male/Female	43/27	47/23
Angina pectoris	61 (87.1%)	58 (82.9%)
Prior MI (by ECG)	13 (18.6%)	16 (22.9%)
Prior CABG surgery	6 (8.6%)	5 (7.1%)
Hypertension	21 (30.0%)	26 (37.1%)
Diabetes mellitus	14 (20.0%)	12 (17.1%)
Smoking	21 (30.0%)	29 (41.4%)
Coronary anatomy		
No-vessel disease	24 (34.3%)	28 (40.0%)
One-vessel disease	26 (37.1%)	27 (38.6%)
Two-vessel disease	14 (20.0%)	10 (14.3%)
Three-vessel disease	6 (8.6%)	5 (7.1%)
Cardiac medication		
Dinitrates	36 (51.4%)	31 (44.3%)
Calcium channel blocker	17 (24.3%)	14 (20.0%)
Beta-blocker	10 (14.3%)	7 (10.0%)

ATP-Tl = adenosine triphosphate stress ^{201}Tl scintigraphy; DIP-Tl = dipyridamole stress ^{201}Tl scintigraphy; MI = myocardial infarction; CABG = coronary artery bypass grafting; No parameter = not significantly different between the two groups.

Exercise ^{201}Tl myocardial scintigraphy is the standard diagnostic test for the detection of coronary artery disease (CAD). Gould et al. (*1*) first reported that the pharmacologic stress with dipyridamole (DIP) represented an alternative to exercise stress with ^{201}Tl imaging. Especially, DIP stress ^{201}Tl imaging is useful for the diagnosis of CAD in patients who cannot exercise adequately (*2,3*). Intravenously administered DIP at the conventional dose of 0.56 mg/kg body weight, however, may not produce maximal coronary vasodilation in all patients (*4*).

Recently, we have reported the usefulness of ^{201}Tl imaging with intravenous adenosine triphosphate (ATP) (*5*). To date there have been no studies comparing ^{201}Tl imaging using ATP with that using DIP, with respect to safety and diagnostic accuracy. The purposes of this study were to evaluate the safety and diagnostic accuracy of ATP and DIP stresses and to examine whether ATP stress can be substituted for DIP stress in the detection of CAD. Our third purpose was to assess the effect of intravenous infusion of each agent on the coronary flow reserve (CFR) by the use of a Doppler flow wire (*6–8*).

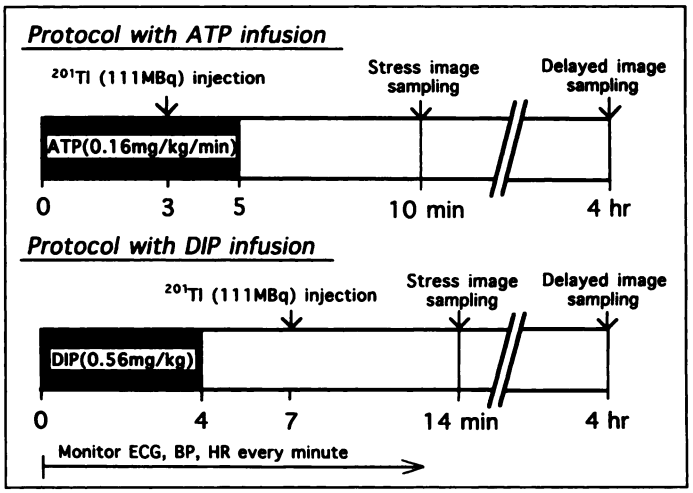

FIGURE 1. Protocol with ATP or DIP infusion in ^{201}Tl imaging.

MATERIALS AND METHODS

Assessment of the Optimal Dose of ATP

Study Population. Nineteen patients with normal epicardial coronary arteries, as depicted by coronary angiography, were selected for the study. They consisted of 13 men and 6 women with a mean age of 59.6 yr (±11.9 yr s.d.; range 38–76 yr).

Study Protocol. The study was performed after completion of diagnostic cardiac catheterization. A 5-F coronary guiding catheter was positioned at the coronary ostium, and a Doppler flow wire, a 175-cm long, 0.014-inch-diameter steerable guidewire with a 15-MHz transducer at its distal tip, was advanced into the left anterior descending coronary artery (LAD). The average peak velocity (APV) and the maximum peak velocity (MPV) were measured by fast Fourier transformation of the velocity signal recorded from the transducer.

After intracoronary infusion of 2.5 mg of isosorbide dinitrate, the resting APV was measured. After the coronary blood flow was allowed to return to the baseline level after the isosorbide dinitrate administration, ATP (10 mg/ml, 2 ml; Daiichi) was administered by injection into the femoral vein at a dose of 0.10 mg/kg/min through a computerized high-flow infusion pump system. Incremental increase of 0.02 mg/kg/min every 3 min was continued to the final dose by 0.20 mg/kg/min. After the coronary blood flow velocity was allowed to return to the baseline level after ATP administration, DIP was administered at the standard dose of 0.56 mg/kg for 4 min by femoral vein infusion. During the infusions, the coronary blood flow velocity, arterial pressure (mmHg), and heart rate (bpm) were recorded every minute. Near the end of the

TABLE 2
CFR and Hemodynamic Responses with ATP and DIP

	ATP (mg/kg/min)							DIP (mg/kg)	
	Baseline	0.10	0.12	0.14	0.16	0.18	0.20	Baseline	0.56
Sys BP (mmHg)	138.7 ± 21.4	136.3 ± 18.1	134.4 ± 19.7	131.1 ± 18.6	126.7 ± 17.8	125.8 ± 18.0	125.1 ± 18.3	138.2 ± 20.0	126.8† ± 16.2
Dia BP (mmHg)	78.8 ± 14.4	77.5 ± 10.4	74.9 ± 10.2	72.2 ± 8.9	69.9 ± 8.9	69.4 ± 9.4	68.9 ± 9.6	78.5 ± 13.2	69.7† ± 10.2
HR (per min)	65.7 ± 14.2	66.1 ± 12.6	68.0 ± 12.0	70.2 ± 11.8	76.8* ± 11.5	77.7† ± 11.7	78.4† ± 11.4	66.1 ± 14.0	75.7† ± 12.1
APV (cm/sec)	17.7 ± 4.8	22.8 ± 5.4	34.8 ± 13.4	52.9† ± 19.3	72.7† ± 12.4	73.2† ± 13.8	73.5† ± 13.6	17.7 ± 4.9	63.7† ± 13.7‡
MPV (cm/sec)	43.6 ± 8.1	52.7 ± 14.8	68.2 ± 22.3	86.2† ± 23.9	107.3† ± 10.4	108.1† ± 10.8	108.9† ± 11.4	42.3 ± 11.7	101.9† ± 11.7
CFR (ratio)	1.0	1.38 ± 0.37	2.17* ± 1.18	3.29† ± 1.72	4.15† ± 1.05	4.16† ± 1.16	4.16† ± 1.12	1.0	3.58† ± 0.97§
FAE	0/19	0/19	1/19	4/19	7/19†	9/19†	9/19†	0/19	5/19*

*$p < 0.05$ versus baseline; †$p < 0.01$ versus baseline; ‡$p < 0.05$ versus ATP (0.16); §$p < 0.01$ versus ATP (0.16).

Mean ± s.d.; Sys BP = systolic blood pressure; Dia BP = diastolic blood pressure; HR = heart rate; APV = average peak velocity; MPV = maximum peak velocity; CFR = coronary flow reserve; FAE = frequency of adverse effect.

TABLE 3
Diagnostic Analyses in ATP-Tl and DIP-Tl

	ATP-Tl		DIP-Tl	
	All patients	Without prior MI	All patients	Without prior MI
Sensitivity (%)	40 of 46; 87.0%	28 of 33; 84.8%	34 of 41; 82.9%	20 of 25; 80.0%
Specificity (%)	21 of 24; 87.5%	21 of 24; 87.5%	21 of 29; 72.4%	21 of 29; 72.4%
Positive predictive value (%)	40 of 43; 93.0%	28 of 31; 90.3%	34 of 42; 81.0%	20 of 28; 71.4%
Negative predictive value (%)	21 of 27; 77.8%	21 of 26; 80.8%	21 of 28; 75.0%	21 of 26; 80.8%
Predictive accuracy (%)	61 of 70; 87.1%	49 of 57; 86.0%	55 of 70; 78.6%	41 of 54; 75.9%

ATP-Tl = adenosine triphosphate stress ^{201}Tl scintigraphy; DIP-Tl = dipyridamole stress ^{201}Tl scintigraphy; MI = myocardial infarction. All parameters showed a tendency of diagnostic rate but there was no significant difference between ATP-Tl and DIP-Tl.

infusions, the electrocardiogram was recorded at 25 mm/sec paper speed to assess changes in the electrocardiographic intervals. The CFR was estimated as follows:

$$\text{CFR} = \frac{\text{maximum APV with injection of vasodilator}}{\text{resting APV}}.$$

Comparison of ATP and DIP for Diagnostic Value and Adverse Effects

Study Population. One hundred and forty patients with suspected CAD were enrolled in this study. These subjects were randomly divided into the ATP infusion group (n = 70) and the DIP infusion group (n = 70). The ATP stress ^{201}Tl imaging group had 43 men and 27 women patients in the mean age of 62.3 yr (±10.3 yr s.d.; range 43–78 yr), and the DIP stress ^{201}Tl imaging group had 47 men and 23 women patients in the mean age of 63.1 yr (±11.2 yr s.d.; range, 38–79 yr). The clinical characteristics of the patient in each group are summarized in Table 1. All 140 patients had cardiac catheterization for diagnosis of CAD within 1 mo of cardiac scintigraphy.

TABLE 4
Adverse Effects of ATP-Tl and DIP-Tl

	ATP-Tl	DIP-Tl
Subjective symptoms		
Chest pain/chest oppression	30 (42.9%)	11 (15.7%)**
severe symptoms	3 (10.0%)	3 (27.3%)
mild symptoms	27 (90.0%)	8 (72.7%)
Dyspnea/SOB	4 (5.7%)	3 (4.3%)
Headache	9 (12.9%)	0
Abdominal fullness	6 (8.6%)	0
Sore throat	8 (11.4%)	2 (2.9%)*
Flushing	5 (7.1%)	0
Duration until symptom disappearance (sec)	61 ± 24	409 ± 138**
ECG changes		
All cases	13 (18.6%)	6 (8.6%)*
ST depression (>1 mm)	7 (10.0%)	5 (7.1%)
AV block (first degree)	2 (2.9%)	0
SVPC	3 (4.3%)	1 (1.4%)
VPC	1 (1.4%)	0
Total number of patients with adverse effects	39 (55.7%)	18 (25.7%)**
Total number of patients without adverse effects	31 (44.3%)	52 (74.3%)**

ATP-Tl = adenosine triphosphate stress ^{201}Tl scintigraphy; DIP-Tl = dipyridamole stress ^{201}Tl scintigraphy; SOB = shortness of breath; AV = atrioventricular; SVPC = supraventricular premature contraction; VPC = ventricular premature contraction; *$p < 0.05$, **$p < 0.01$, significant difference from ATP-Tl.

Cardiac Catheterization. Cardiac catheterization was performed after cardiac medications, drugs and food had been withheld. Significant coronary disease was defined as ≥50% diameter reduction by caliber measurement in one or more epicardial vessels. Stenotic lesion was evaluated in multiple views including, whenever possible, two nearly orthogonal projections. The results were interpreted by two senior angiographers who had no knowledge of the results of the ^{201}Tl imaging.

Thallium-201 SPECT Imaging Analysis. In the ATP infusion group, ATP was infused through a peripheral venous catheter for 5 min at the rate of 0.16 mg/kg/min, this dose was derived from the preliminary dose-finding study. After 3 min of infusion of ATP, 111 MBq (3 mCi) of ^{201}Tl were injected as a bolus into another venous site, and the infusion of ATP was continued for an additional 2 min. In the DIP infusion group, DIP (0.56 mg/kg) was infused for 4 min and the same dose of ^{201}Tl as in ATP study was injected 7 min after beginning of the DIP infusion. Thallium-201 imaging was performed using a large field of view rotating gamma camera equipped with a low-energy, high-resolution collimator interfaced to a computer (Toshiba GMS-550U, Tokyo Japan) (Fig. 1). The details of the imaging with SPECT are described in our previous report (*5*).

SPECT images were obtained commencing at 7 min and 4 hr after ^{201}Tl injection. The slices were displayed sequentially in all three cardiac planes to assess myocardial perfusion in each vascular territory. The presence or absence of redistribution was visually noted on the 4-hr images. The vascular territories of the three major coronary arteries were assigned as follows: the septal and anterior segments corresponded to the LAD, the inferior and posterior segments to the right coronary and the lateral segments to the left circumflex artery. Pure apical defects were considered abnormal but were not assigned to any individual coronary territory. Thallium-201 images were interpreted visually by two nuclear cardiologists who did not know the results of the coronary angiography. The diagnostic value of the SPECT findings was compared with the results of the coronary artery angiograms.

Statistical Analysis

Results are expressed as the mean ± s.d.. In the ATP infusion group, the results of the CFR, APV, MPV and hemodynamic parameters were analyzed by the Kruskal-Wallis one-way analysis of variance followed by the nonparametric Dunnett's test for multiple comparison. In the DIP infusion group, changes in the CFR, APV, MPV and hemodynamic parameters were compared by the paired Student's t-test with those at baseline. The differences in the CFR, APV, MPV, BP and HR in the ATP infusion group (baseline and 0.16 mg/kg/min) and in the DIP infusion group (baseline and 0.56 mg/kg) were analyzed by the paired Student's t-test. The diagnostic value and frequency of adverse effects of ATP and DIP ^{201}Tl-SPECT imaging were analyzed using the

TABLE 5
Hemodynamic Changes During ATP-Tl and DIP-Tl

	ATP-Tl		DIP-Tl	
	Baseline	Peak effect	Baseline	Peak effect
Heart rate (bpm)	66.2 ± 13.8	77.1 ± 12.1**	65.9 ± 15.2	76.8 ± 13.6†
Systolic BP (mmHg)	140.1 ± 19.6	125.3 ± 19.4**	139.6 ± 20.3	123.9 ± 17.3†
Diastolic BP (mmHg)	79.6 ± 15.2	70.2 ± 10.3*	77.6 ± 14.9	68.2 ± 12.2*
Rate-pressure product (bpm × mmHg × 10^3)	9.2 ± 2.1	9.6 ± 2.5	9.2 ± 2.3	9.5 ± 2.2

*$p < 0.05$, †$p < 0.01$, significant difference from baseline.
ATP-Tl = adenosine triphosphate stress ^{201}Tl scintigraphy; DIP-Tl = dipyridamole stress ^{201}Tl scintigraphy; BP = blood pressure.

chi-square test. A probability value of < 0.05 was considered significant.

RESULTS

CFR and Hemodynamic Responses with ATP and DIP

The CFR was increased significantly by the administration of both ATP and DIP ($p < 0.01$) (Table 2). The maximal change of CFR with ATP was signifiantly ($p < 0.01$) higher than that with DIP. The CFR with ATP and with DIP returned to baseline in 1.4 min (± 0.7 min) and 8.3 min (± 2.3 min), respectively. Both ATP and DIP decreased the systolic and diastolic BP and increased the HR.

Correlation Between Thallium-201 SPECT and Coronary Angiogram

Diagnostic Value and Adverse Effects. Forty-six patients in the ATP infusion group and 42 patients in the DIP infusion group were found to have significant CAD (Tables 3 and 4). The perfusion defects were classified according to the degree of redistribution. For the ATP stress ^{201}Tl SPECT imaging, the sensitivity, specificity and predictive accuracy in all patients were 87.0%, 83.3% and 87.1%, respectively, and that in patients without prior myocardial infarction (MI) was 81.8%, 83.3% and 84.2%, respectively. (Table 3, left). For DIP stress ^{201}Tl SPECT imaging, it was 82.9%, 72.4% and 78.6%, respectively, in all patients and 72.0%, 72.4% and 72.2%, respectively, in those without prior MI (Table 3, right). The difference was not significant.

Transient adverse effects were observed in 55% of the ATP infusion group and 26% of the DIP infusion group. In the former, the adverse effects disappeared rapidly (61 sec ± 24 sec), whereas in the latter, they were prolonged (409 sec ± 138 sec) and eight patients (11.4%) required treatment (three patients required intravenous aminophillin, three required sublingual nitroglycerine and two required both aminophillin and nitroglycerine).

ECG and Hemodynamic Changes. Abnormal ECG findings were more frequent during ATP stress ^{201}Tl SPECT imaging (13/70, 18.6%) than during DIP stress ^{201}Tl SPECT imaging (5/70, 7.1%) ($p = 0.04$) (Tables 4 and 5). One patient had both ST depression and supraventricular premature contraction (SVPC). There were no significant differences between the groups with respect to the incidence of ST depression or SVPC.

The hemodynamic changes in each group are presented in Table 5. The administration of either ATP or DIP significantly increased the heart rate and decreased both systolic and diastolic blood pressure. The rate-pressure product did not change with either ATP or DIP administration. There were no significant differences between the two groups with respect to HR, systolic and diastolic blood pressure or rate-pressure product.

DISCUSSION

Pharmacological stress ^{201}Tl imaging has been mainly used in patients who are unable to perform at an acceptable level of exercise stress. Recently, several reports have suggested that the sensitivity and specificity in the detection of CAD, as well as the safety, of pharmacologic stress are comparable to those obtained with exercise (*9–15*). Coronary blood flow can also be increased to a greater degree by pharmacological substances than by exercise (*16*).

Optimal Dose of ATP with Thallium-201 Imaging

Wilson et al. (*17*) reported a 4.4-fold maximal increase in CBFV at an infusion rate of 0.14 mg/kg/min of intravenous adenosine and 4.0- to 4.8-fold maximal increase with infusion of 10 mg of intracoronary papaverine. Yonezawa et al. (*18*) showed that the CBFV with 0.15 mg/kg/min ATP was almost the same as that with 0.14 mg/kg/min adenosine or 0.56 mg/kg of DIP. We found that the flow increase with the ATP infusion was significantly increased and reached a plateau level of 4.2 (±1.1) at the dose of 0.16 mg/kg/min, which was significantly higher than that with DIP. The mechanism by which DIP induces coronary vasodilation is thought to be through the blockade of cellular adenosine uptake, leading to a subsequent increase in both myocardial and arterial wall adenosine concentrations. According to this hypothesis, DIP has only an indirect vasodilatory effect, whereas endogenous adenosine would directly cause coronary dilation (*19–21*). ATP is rapidly metabolized into adenosine (*22*), and this degradation product, adenosine, demonstrates strong vasodilative action through activation of purine receptor (especially A2 adenosine receptor subtype). ATP also is thought to be a strong coronary vasodilator, much like adenosine or papaverine, and it has a more powerful vasodilating effect than that of DIP.

The frequency of adverse effects with ATP at 0.16 mg/kg/min (7/19; 37%) was lower than that at 0.18 or 0.20 mg/kg/min (9/19; 47%). Thus, we selected the potentially optimal dose of ATP for ^{201}Tl imaging of 0.16 mg/kg/min.

Detection of CAD

The diagnostic accuracy of ^{201}Tl SPECT imaging using ATP is equivalent to that using DIP. In two studies, the overall sensitivity and specificity using ^{201}Tl SPECT imaging with DIP for CAD detection was 80% and 74%, respectively (*23,24*). Using adenosine, the overall sensitivity and specificity was 87% and 89%, respectively (*9–12,25*). Therefore, our present results obtained with ATP are comparable to those obtained with not only DIP but also with adenosine stress ^{201}Tl imaging.

Adverse Effects and ECG Changes with ATP and DIP

Adverse effects occurred at a high frequency of 56% during ATP stress ^{201}Tl SPECT imaging, but they were mostly transient and mild, disappearing rapidly after drug administration was stopped, and no patients required treatment. With DIP,

adverse effects occurred at a lower rate of 26%, but they were more prolonged after discontinuing drug administration and eight patients required treatment. Cerqueira et al. (*14*) reported that intravenous administration of adenosine induced elevated the incidence of side effects, and 20% of the patients required a dose reduction or early termination. No patient in our study required dose reduction or early termination of ATP infusion. One of the reasons that the adverse effects with ATP differ from those with DIP may be that DIP acts indirectly to inhibit the cellular reuptake of adenosine and metabolism by adenosine deaminase, thus increasing the interstitial adenosine concentration.

Another reason may be the short breakdown time of ATP in plasma (plasma half-time 10–30 sec) (*22*). The frequency of side effects with DIP stress in our study is lower than those in the previous reports (*26,27*). These discrepancies are suggested to be partly due to differences in the durations of observation for side effects and the differences in the dose of intravenous DIP.

ECG changes with ATP stress imaging occurred at significantly higher frequency than with in DIP stress imaging, and first-degree AV block appeared only in ATP stress imaging. All of these ECG changes disappeared rapidly after administration of ATP was stopped.

Study Limitations

One limitation of this study is that both stress agents were used in the same patients. It would have been difficult to examine the same nuclide in the same patient twice within a short time, because this is not sanctioned by the health insurance provision in Japan.

Patient selection bias may have enhanced the sensitivity of the test by including sicker patients (*28*). However, this seems unlikely because we excluded patients with acute myocardial infarction or unstable angina pectoris.

This study was performed without blinding. Because no significant differences were found in the clinical baseline data between the ATP and DIP infusion groups, however, their characteristics seem to have been almost the same.

The plasma ATP level was not measured. Because of the short half-life of ATP, it is difficult to measure local concentrations of ATP at the coronary sinus or peripheral veins.

Finally the number of patients studied was small. The results demonstrating high diagnostic value and low frequency of major adverse effects, however, are almost the same as those given in previous reports (*5,18,29*)

CONCLUSION

Pharmacologic stress myocardial scintigraphy with ATP infusion is accurate and safe. The optimal ATP regimen for this purpose was considered to be a 5-min infusion at 0.16 mg/kg/min. The CFR elicited with ATP infusion was higher than that with DIP infusion, suggesting a potentially enhanced diagnostic value. However, our data on CAD patients suggest that ^{201}Tl SPECT imaging with ATP stress is equivalent to that with DIP stress in the detection of CAD.

REFERENCES

1. Gould KL, Wescott RJ, Albro PC, Hamilton GW. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic vasodilation: clinical methodology and feasibility. *Am J Cardiol* 1978;41:279–287.
2. Boucher CA, Okada RD. Thallium-201 myocardial perfusion imaging without exercise: rest and dipyridamole studies. *Chest* 1984;86:159–161.
3. Schmoliner R, Dudczak R, Kronik G, et al. Thallium-201 imaging after dipyridamole in patients with coronary multivessel disease. *Cardiology* 1984;70:145–151.
4. Rossen JD, Simonetti I, Marans ML, Winniford MD. Coronary dilation with standard dose dipyridamole and dipyridamole combined with handgrip. *Circulation* 1989;79:566–572.
5. Miyagawa M, Kumano S, Sekiya M, et al. Thallium-201 myocardial tomography with intravenous infusion of adenosine triphosphate disodium in the diagnosis of coronary artery disease. *J Am Coll Cardiol* 1995;26:1196–1201.
6. Wilson RF, Laughlin DE, Ackell PH, et al. Transluminal subselective mesurement of coronary artery blood flow velocity and vasodilator reserve in man. *Circulation* 1985;72:82–92.
7. White CW, Marcus ML, Wilson RF. Methods of measuring coronary flow in humans. *Prog Cardiovasc Dis* 1988;31:79–94.
8. Doucette JW, Corl D, Payne HM, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992;85:1899–1911.
9. Nguyen T, Heo J, Ogilby D, Iskandrian A. Single-photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia: correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. *J Am Coll Cardiol* 1990;16:1375–1383.
10. Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation* 1990;82:80–87.
11. Coyne EP, Belvedere DA, Vande Streek PR, Weiland FL, Evans RB, Spaccavento LJ. Thallium-201 scintigraphy after intravenous infusion of adenosine compared with exercise thallium testing in the diagnosis of coronary artery disease. *J Am Coll Cardiol* 1991;17:1289–1294.
12. Gupta NC, Esterbrooks DJ, Hilleman DE, Mohiuddin PSM. Comparison of adenosine and exercise thallium-201 single-photon emission computed tomography myocardial perfusion imaging. *J Am Coll Cardiol* 1992;19:248–257.
13. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Equivalence between adenosine and exercise thallium-201 myocardial tomography: a multicenter, prospective, crossover trial. *J Am Coll Cardiol* 1992;20:265–275.
14. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the adenosine multicenter trial registry. *J Am Coll Cardiol* 1994;23:384–9.
15. Beller GA. Dipyridamole thallium-201 imaging: how safe is it? *Circulation* 1990;81:1425–1427.
16. Holmberg S, Serzysko W, Varnauskas E. Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. *Acta Med Scand* 1971;190:465–480.
17. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxon DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;82:1595–1606.
18. Yonezawa Y, Yoshikawa J, Shakudo M, et al. Adenosine triphosphate loading thallium-201 myocardial scintigraphy: optimal dose and diagnostic accuracy. *J Cardiol* 1995;25:9–13 (in Japanese with English abstract).
19. Rubio R, Berne RM. Release of adenosine by the normal myocardium in dogs and its relationship to regulation of coronary resistence. *Circ Res* 1969;25:407–415.
20. Berne RM. The role of adenosine in the regulation of coronary blood flow. *Circ Res* 1980;47:807–813.
21. Knabb RM, Gidday JM, Ely SW, Rubio R, Berne RM. Effects of dipyridamole on myocardial adenosine and active hyperemia. *Am J Physiol* 1984;247:H804–H810.
22. Belhassen B, Pelleg A. Electrophysiologic effects of adenosine triphosphate and adenosine on the mammalian heart: clinical and experimental aspects. *J Am Coll Cardiol* 1984;4:414–424.
23. Lam JYT, Chaitman BR, Glaenzer M, et al. Safety and diagnostic accuracy of dipyridamole-thallium imaging in the elderly. *J Am Coll Cardiol* 1988;11:585–589.
24. Popma JJ, Dehmer GJ, Walker BS, Simon TR, Smitherman TC. Analysis of thallium-201 single-photon emission computed tomography after intravenous dipyridamole using different quantitative measures of coronary stenosis severity and receiver operator characteristic curves. *Am Heart J* 1992;124:65–74.
25. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacological vasodilation with adenosine for assessing coronary artery disease. *J Am Coll Cardiol* 1991;18:736–745.
26. Ranhosky A, Kempthorne-Rawson T for the Intravenous Dipyridamole Thallium Imaging Study Group. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990;81:1205–209.
27. Lette J, Tatum JL, Fraser S, et al. Safety of dipyridamole testing in 73,806 patients: the multicenter dipyridamole safety study. *J Nucl Cardiol* 1995;2:3–17.
28. Diamond GA. How accurate is SPECT thallium scintigraphy? *J Am Coll Cardiol* 1990;16:1017–1021.
29. Kinoshita S, Suzuki S, Shindou A, et al. The accuracy and side effects of pharmacologic stress thallium myocardial scintigraphy with adenosine triphosphate disodium infusion in the diagnosis of coronary artery disease. *Jpn J Nucl Med* 1994;31:935–941. (in Japanese with English abstract).