THE RELATIONSHIP BETWEEN CHEST PAIN DURING THALLIUM-201 SCINTIGRAPHY WITH DIPYRIDAMOLE AND MYOCARDIAL ISCHEMIA

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Dipyridamole thallium-201 scintigraphy (DP-Tl) and coronary angiography were studied on 74 patients with suspected coronary artery disease. We compared the clinical features, hemodynamic responses, angiographic results and scintigraphic findings of patients who had chest pain during DP-Tl testing ('chest pain' group) with those of patients who did not have chest pain ('no pain' group). Thirty eight (51%) of the 74 patients developed chest pain. Heart rate and rate pressure product during DP infusion of 'chest pain' group were greater than those of the 'no pain' group ($p < 0.05$). Ischemic ST depression was more frequently observed among 'chest pain' patients ($p < 0.01$). There were no differences in angiographic severity of coronary artery disease between 'chest pain' and 'no pain' group. Also, we could find no differences in extent and severity scores of perfusion defects and washout abnormalities between the two groups. However, when patients with myocardial infarction were excluded, the 'chest pain' group had significantly greater extent and severity scores of washout abnormalities than the 'no pain' group (extent score: 38 ± 8 vs 18 ± 5 , $p < 0.05$, severity score: 55 ± 15 vs 18 ± 7 , $p < 0.01$). Our study indicated that in patients without myocardial infarction, patients with 'chest pain' had more severe ischemia than 'no pain' patients. But in patients with myocardial infarction, myocardial ischemia not accompanied by chest pain might be as severe as that with chest pain. The presence or absence of myocardial infarction might have great influence on results regarding the relation of chest pain to myocardial ischemia.

CHEST pain during exercise testing correlates well with the presence and severity of coronary artery disease.^{1,2} However, it has recently become known that asymptomatic myocardial ischemia occurs during exercise testing in some patients with coronary artery disease.³⁻⁷ Although thallium-201 scintigraphy with pharmacolo-

gic coronary vasodilation induced by dipyridamole has been increasingly used for the detection of coronary artery disease,⁸⁻¹⁴ little is known about the relationship between chest pain during dipyridamole load testing and myocardial ischemia.

The aim of this study was to investigate whether or not dipyridamole-induced chest pain indicated the ischemia related to the coronary artery disease or the presence of severe coronary artery disease. We compared the clinical features, hemodynamic re-

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sponses, angiographic results and scintigraphic findings of patients who had chest pain during dipyridamole-thallium testing with those of patients who did not have.

METHODS

Subjects

This study included 74 consecutive patients with suspected coronary artery disease who underwent both dipyridamole-thallium scintigraphy and coronary angiography within one month. Patients consisted of 52 men and 22 women with a mean age of 58 years (range 37 to 73). Patients who had undergone coronary artery bypass graft or coronary angioplasty were excluded. None had a history of diabetes mellitus. The subjects consisted of 21 patients with single-vessel disease, 11 patients with double-vessel disease, 20 patients with triple-vessel disease and 22 patients with normal coronary arteries. Coronary artery disease was defined as a 50 % or more luminal narrowing of one or more coronary artery or its major bran-

ches. Twenty three patients had both clinical history and electrocardiographic evidence (defined as a Q wave of 40 msec or greater) of previous myocardial infarction. All scintigrams were obtained for clinical purposes and angiography was performed for the diagnosis of suspected or known coronary artery disease after obtaining informed consent.

Dipyridamole thallium-201 testing

All cardiovascular medications were discontinued at least 24h prior to dipyridamole tests except for the short-acting sublingual nitrates. Blood pressure was measured every minute using the cuff method, and CM₅-lead ECG monitoring was used during the testing. Dipyridamole was infused intravenously at a rate of 0.14 mg/kg/min for 4 minutes according to the protocol applied by Albrow et al.⁸ Six minutes after dipyridamole infusion, 2 mCi (74 MBq) of thallium-201 was administered intravenously. If chest pain and/or ischemic ST changes occurred during dipyridamole infusion, thallium-201 was given at that time. If the developed symptoms, hemodynamic responses, or ECG changes were severe or prolonged, 125 to 250 mg of aminophylline was given intravenously after finishing radionuclide extraction.

'Chest pain' was determined as anterior chest, arm, or jaw discomfort that occurred after the infusion of dipyridamole and that decreased after the passage of the drug effect or with aminophylline therapy.

Cardiac imaging was begun 10 minutes after thallium-201 injection and again 3h later. All studies were obtained on a large field-of-view rotating gamma camera (Siemens ZLC-

TABLE I CLINICAL FEATURES OF 74 PATIENTS

	Chest pain N=38	No pain N=36
Male	27 (71%)	24 (67%)
Female	11 (29%)	12 (33%)
Mean age (yr)	57.4	58.3
Previous myocardial infarction	15 (39%)	8 (22%)
Incidence of CAD	27 (71%)	25 (70%)

CAD: coronary artery disease

TABLE II HEMODYNAMIC RESULTS

	Chest pain	No pain	p value
Basal HR (beat/min)	64±13	62±15	NS
DP HR (beat/min)	83±12***	75±15***	p<0.05
Basal SBP (mmHg)	134±22	133±26	NS
DP SBP (mmHg)	128±24*	125±25**	NS
Basal RPP (mmHg×beat/min)	8679±2624	8098±2144	NS
DP RPP (mmHg×beat/min)	10644±2578***	9127±2189**	p<0.05
ST depression≥0.1mV (CM-5 lead)	15/38 (39%)	4/36 (11%)	p<0.01

*p<0.05, **p<0.01, ***p<0.001 vs basal value

HR: heart rate, DP: dipyridamole, SBP: systolic blood pressure, RPP: rate pressure product

TABLE III ANGIOGRAPHIC DISTRIBUTION OF CORONARY ARTERY DISEASE

	Chest pain N=38	No pain N=36
<i>Number of vessels narrowed $\geq 50\%$</i>		
0	11 (29%)	11 (30%)
1	11 (29%)	10 (28%)
2	5 (13%)	6 (17%)
3	11 (29%)	9 (25%)
mean	1.4 ± 1.2	1.4 ± 1.2
<i>Number of vessels narrowed $\geq 90\%$</i>		
0	14 (37%)	20 (56%)
1	13 (34%)	9 (25%)
2	5 (13%)	4 (11%)
3	6 (16%)	3 (8%)
mean	1.1 ± 1.1	0.7 ± 1.0

7500 Digitrac) equipped with a parallel hole, high resolution collimator. Thirty two planar acquisitions were performed during a 180 degree rotation from the 30 degree right anterior oblique to the 60 degree left posterior oblique projection. Each 64×64 matrix was collected for 40 sec during each of 32 steps and contained 15,000 to 20,000 counts. Data processing was performed on a nuclear medicine computer system (Shimadzu Scintipac-700) by means of back projection algorithm with Shepp & Logan and Butterworth filtering and no attenuation correction. Oblique, orthogonal tomographic slices, each 6 mm thick, were reconstructed parallel to the vertical and horizontal long axis and the short axis of the left ventricle.

Quantification of thallium-201 imaging: Circumferential profile analysis was applied to each of the short axis slice from apex to base. These circumferential profiles were plotted in polar coordinates and arranged into a bull's eye map!¹⁵ Male and female normal files had been separately constructed from 18 male and 13 female subjects, respectively. The normal file consisted of one set data of immediate after dipyridamole infusion, 3h delayed image and washout rate profile. For a patient study, each pixel was compared with the corresponding pixel in the gender-matched profile. Pixels that were

TABLE IV PRESENCE OF PERFUSION DEFECTS AND WASHOUT ABNORMALITIES

	Chest pain N=38	No pain N=36
Perfusion defects	25 (66%)	20 (56%)
Washout abnormalities	22 (58%)	15 (42%)
Perfusion defects/ Washout abnormalities	26 (68%)	22 (61%)

more than 2.5 SDs below normal were defined as abnormal!¹⁶ and displayed on a color-coded standard deviation map. These defects and washout abnormalities had to contain at least 3% of the total pixels to be significant!¹⁶ The ratio of the numbers of the pixels below normal limits to those of total pixels defined as an extent score!^{15,17} Furthermore, a severity score was calculated as the sum of the number of standard deviations below the mean normal profiles for all abnormal pixels. These scores were calculated for both dipyridamole image and washout rate image. The extent score was defined as an index which showed the extent of perfusion defects and washout abnormalities, and the severity score was used as an index of the severity of them.

Cardiac catheterization

Coronary arteriography was performed using the standard Judkins' technique. All studies were assessed by two experienced readers who did not know the clinical history or scintigraphic findings of the subjects. Significant coronary stenosis was defined as a luminal diameter narrowing of 50% or greater in either a main epicardial artery or a major branch.

Statistics

Statistical analysis was done using Student's t-test and chi-square test. The values of heart rate, blood pressure and rate pressure product were reported as a mean $\pm$ SD. The values of extent and severity scores were reported as a mean $\pm$ SE. A p value < 0.05 was considered significant.

RESULTS

Clinical features

Fig.1. The comparison of extent scores (1-A) and severity scores (1-B) of perfusion defects and washout abnormalities between 'chest pain' and 'no pain' groups. Among the patients without myocardial infarction, extent and severity scores of washout abnormalities in 'chest pain' group were significantly greater than those in 'no pain' group.

MI: Myocardial infarction

* $p < 0.05$, ** $p < 0.01$ vs 'no pain' group

Thirty eight (51%) of 74 patients complained of chest pain during the dipyridamole-testing. There were no significant differences in sex, age, or incidence

of previous myocardial infarction between 'chest pain' and 'no pain' groups (Table I). Twenty seven patients (71%) in the 'chest pain' group and 25 patients (70%) in the 'no

pain' group had coronary artery disease.

Hemodynamic responses and ECG changes during dipyridamole thallium-201 imaging

During dipyridamole-testing, a mild reduction in systolic blood pressure was accompanied by an increase in heart rate, so rate pressure product increased slightly (Table II). Heart rate and rate pressure product during dipyridamole infusion of the 'chest pain' group were significantly greater than those of 'no pain' group ($p < 0.05$). Horizontal or downsloping ST segment depression ≥ 1 mm in CM₅-lead ECG was more frequently observed in the 'chest pain' group than in the 'no pain' group (39% vs 11%, $p < 0.01$). All of the 19 patients with dipyridamole-induced ST depression had coronary artery disease.

In patients without myocardial infarction, hemodynamic responses during dipyridamole testing were similar to those of all patients. Ischemic ST depression was more frequently observed in 'chest pain' group than in the 'no pain' group (10 of 12, 83% vs 2 of 17, 12%, $p < 0.01$).

In patients with myocardial infarction, hemodynamic changes were similar in all patients. ST depression in CM₅-lead ECG was observed in 5 of 15 patients (33%) in the 'chest pain' group and 2 of 8 patients (25%) in the 'no pain' group.

Angiographic findings

In the 'chest pain' group, 27 patients (71%) had coronary artery disease involving 54 vessels, and 24 patients (63%) had 90% or greater stenosis (Table III). Twenty five patients (70%) in the 'no pain' group had coronary artery disease involving 49 vessels, and 16 patients (44%) had $\geq 90\%$ stenosis. Two groups showed similar angiographic findings regarding the incidence, extent, or severity of coronary artery disease.

Scintigraphic findings

Twenty six patients (68%) in the 'chest pain' group and 22 patients (61%) in the 'no pain' group showed perfusion defects and/or washout abnormalities (Table IV). There was no difference between the two groups in the frequency of scintigraphic abnormalities.

The 'chest pain' group tended to have greater extent and severity scores of perfusion defects (extent score: 27 ± 8 vs 23 ± 9 ,

severity score: 47 ± 12 vs 41 ± 14) and of washout abnormalities (extent score: 23 ± 6 vs 14 ± 6 , severity score: 34 ± 8 vs 18 ± 9) than the 'no pain' group, but these were not statistically significant (Fig. 1). However, in patients without myocardial infarction, the 'chest pain' group showed significantly greater extent and severity scores of washout abnormalities than the 'no pain' group (extent score: 38 ± 8 vs 18 ± 5 , $p < 0.05$, severity score: 55 ± 15 vs 18 ± 7 , $p < 0.01$). In patients with myocardial infarction, extent and severity scores of perfusion defects and washout abnormalities of the 'no pain' group were greater than those of the 'chest pain' group.

In patients without coronary artery disease, extent and severity scores of perfusion defects and washout abnormalities in both the 'chest pain' and 'no pain' groups were less than those with coronary artery disease (perfusion defect—extent score: 4 ± 3 , severity score: 7 ± 4 , washout abnormalities—extent score: 6 ± 4 , severity score: 10 ± 4).

DISCUSSION

There have been many reports about silent myocardial ischemia during exercise in patients with coronary artery disease, and the concept of silent myocardial ischemia has been now widely accepted³⁻⁷. Although thallium-201 scintigraphy with dipyridamole has been widely used for the detection of coronary artery disease⁸⁻¹⁴ the relationship between chest pain during dipyridamole-testing and myocardial ischemia is unknown.

Technical considerations

Previous studies using body surface ECG mapping have reported that dipyridamole-induced ST depression usually includes CM₅-lead¹⁸. Therefore, we monitored CM₅-lead ECG during dipyridamole-testing. But 12-lead ECG monitoring is desirable, because ST depression was found only in other leads in some cases.

In this study, we included atypical chest pain (arm and jaw discomfort) as anginal pain. Because this pain occurred after the onset of dipyridamole infusion and abated with aminophylline therapy or after the passage of drug effect, we classified them as dipyridamole-effect. Patients with angina pectoris do not always have typical chest

pain, and frequently complain of atypical pain. The typical angina with ST depression is known to be one of the end points of dipyridamole-testing.¹⁸ We examined the relation of chest pain (including atypical pain) to myocardial ischemia.

Washout rate of thallium-201 after dipyridamole

Although thallium-201 perfusion scintigraphy has become standard as a noninvasive method for detecting and evaluating patients with coronary artery disease, perfusion defects analysis sometimes fails to detect all myocardial regions of diseased coronary arteries. Therefore, defects analysis underestimates the extent of disease in some patients with multi-vessel coronary involvement.¹⁹ This limitation will occur as a result of the "spatially relative" nature of perfusion defects of thallium-201. We reported that in patients without myocardial infarction, the 'chest pain' group had significantly greater extent and severity scores of washout abnormalities than the 'no pain' group. However, there were no significant differences in extent and severity scores of perfusion defects between the two groups. Thirty one of 52 patients with coronary artery disease had multi-vessel coronary stenosis and therefore, myocardial regions of ischemia failed to be detected as perfusion defects in some patients.

Slow washout of thallium-201 was observed in hypoperfused myocardial regions, and was demonstrated to provide information additive to conventional perfusion defects analysis. In the normal zone, there is a fourfold increase in coronary blood flow by administration of dipyridamole, while in the regions supplied by the stenosed vessel, the total flow does not change.^{20,21} The relative decrease in the thallium uptake in the distribution of the stenosed vessel correlates well with the decrease in the coronary blood flow relative to the peak flow in the normal zone. Therefore, slow washout does not always represent myocardial ischemia. However, in addition to initial differences in thallium activity, the washout is much slower in the stenosed area than in the normal area.^{11,22,23}

Dipyridamole and ischemia

Dipyridamole-induced ischemia occurs as

a result of decreased regional supply in coronary blood flow due to "coronary steal".²⁰ Recently, however, some investigators^{24,25} have indicated that both myocardial oxygen demand and supply play a role on dipyridamole-induced ischemia. Dipyridamole causes a small decrease in blood pressure and an associated increase in heart rate. The net effect is only a very small increase in rate pressure product and myocardial oxygen demand will not ordinarily be expected to produce ischemia. In our study, rate pressure product during dipyridamole infusion in the 'chest pain' group was significantly greater than that of the 'no pain' group. Ischemic ST changes occurred more frequently in the 'chest pain' group than in the 'no pain' group. Dipyridamole-induced ischemia appears to be related to both the decrease in oxygen supply by "coronary steal" and the increase in rate pressure product which reflects increased myocardial oxygen demand.^{24,25}

Although there were no differences between the 'chest pain' and 'no pain' groups in the frequency, extent and severity of scintigraphic abnormalities, ischemic ST depression was more frequently observed in the 'chest pain' group than in the 'no pain' group. However, ST depression was insensitive for the diagnosis of coronary disease (19 of 52, 37%). Many patients with reversible scintigraphic abnormalities showed no ECG evidence of ischemia. Thallium-201 defects induced by dipyridamole are caused by a flow-maldistribution between normally perfused and abnormally perfused myocardium. Therefore, reversible abnormalities will occur without ischemia in patients with coronary artery disease.

Significance of dipyridamole-induced chest pain

There are no previous studies reporting the significance of dipyridamole-induced chest pain using quantitative analysis of thallium-201 imaging. Pearlman²⁶ and Zhu²⁷ reported that there were no differences in patient characteristics with and without chest pain during dipyridamole-testing. However, these studies included patients with previous myocardial infarction. Our study showed that there were no differences between the 'chest pain' and 'no pain' groups in both

angiographic severity of coronary artery disease and extent, and severity of scintigraphic abnormalities. However, when patients with myocardial infarction were excluded, the 'chest pain' group showed significantly greater extent and severity scores of washout abnormalities. Thus, in patients without myocardial infarction, chest pain is considered to indicate the occurrence of more severe ischemia than in cases without pain. Previous investigators have reported that patients with myocardial infarction frequently lack chest pain during activities of daily living or exercise-testing²⁸⁻³⁰ and there are various theories to account for the absence of chest pain. The anginal warning system may be defective, the terminal endings of the nerve are destroyed or the sensibility to pain decreases³¹ as a result of myocardial infarction. The occurrence of chest pain has different clinical implications between patients with and without myocardial infarction. The differences in patient population such as the prevalence of myocardial infarction may be contributed to the results regarding the relation of chest pain to myocardial ischemia.

In patients with myocardial infarction, the 'no pain' group had greater extent and severity scores of perfusion defects and washout abnormalities than the 'chest pain' group. Perfusion defects on dipyridamole images contain myocardial scar as well as ischemia. Patients with large myocardial infarctions will show greater extent and severity scores of perfusion defects without ischemia. If ischemia occurs in such cases, it is thought that chest pain is absent as a result of myocardial infarction.

Conclusion

In patients without myocardial infarction, patients with 'chest pain' have more severe ischemia than those with 'no pain'. It is generally said that chest pain during dipyridamole-testing correlates with the occurrence of more severe ischemia. However, in patients with myocardial infarction, the absence of chest pain does not always suggest that myocardial ischemia is less severe than in cases with chest pain. The presence or absence of myocardial infarction has great influences on the results of such investigations regarding the relation of chest pain to myocardial ischemia.

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