PROGNOSTIC VALUE OF DIPYRIDAMOLE THALLIUM SCINTIGRAPHY IN PATIENTS WITH CORONARY ARTERY DISEASE TREATED MEDICALLY

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To evaluate the prognosis of patients with coronary artery disease treated medically using dipyridamole thallium scintigraphy, 277 consecutive patients were followed prospectively. During 2.8 ± 1.8 years of follow-up, 21 patients experienced nonfatal myocardial infarction or died from cardiac causes. Stepwise discriminant analysis using clinical and angiographic variables revealed that the combination of ejection fraction, number of diseased vessels, previous myocardial infarction and left ventricular asynergic score was most statistically significant (chi-square=24, $p=0.0001$) in predicting events. After including scintigraphic findings, the analysis revealed that the combination of negative washout rate, ejection fraction, ST depression during dipyridamole loading, previous myocardial infarction, coronary artery narrowing of $>90\%$, left ventricular asynergic score and number of diseased vessels (chi-square=39, $p<0.0001$) was the best predictor of events. These results indicate that the addition of dipyridamole thallium scintigraphic data to established angiographic markers can help better identify patients with coronary artery disease who are at high risk of cardiac events.
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THE diagnostic usefulness of dipyridamole thallium scintigraphy in patients with coronary artery disease has been previously demonstrated!^{1–5} Its prognostic value has also been recently reported^{6–8} However, dipyridamole thallium scintigraphy has rarely been compared to established angiographic markers for the prediction of prognosis in coronary artery disease.^{6–9} The present study prospectively evaluated the prognosis of patients with coronary artery disease treated medically by clinical, angiographic and scintigraphic findings.

Key words:
Coronary artery disease
Prognosis
Dipyridamole thallium scintigraphy

METHODS

Study patients

Two hundred and seventy-seven consecutive patients with coronary artery disease who were treated medically after initial angiographic and scintigraphic evaluation were studied. The patients ranged from 28 to 84 years of age (mean 61); 219 were men and 58 women. One hundred and ninety patients (69%) had previous myocardial infarction. One-vessel disease was found in 164 patients, 2-vessel disease in 62, 3-vessel disease in 45 and left main stenosis in 6. Patients who had previous coronary artery bypass grafting or percutaneous transluminal coronary angioplasty were excluded.

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Fig.1. Assignment of myocardial segments to coronary arteries. The myocardium was divided into 3 segments in each projection. The segment of the myocardium from 120° to 240° in each projection was considered to represent the outflow tract and was not evaluated. In addition, the apical and inferoapical regions were not assigned to a specific coronary artery because of variable overlap of different coronary arteries. ANT-LAT=anterolateral; ANT-SEPT=anteroseptal; INF=inferior; INF-AP=inferoapical; INF-POST=inferoposterior segment; LAD=left anterior descending coronary artery; LAO=left anterior oblique projection; LC=left circumflex coronary artery; POST-LAT=posterolateral segment; RCA=right coronary artery.

Dipyridamole thallium scintigraphy

Scintigraphic study was performed within 1 week of angiography in all cases. Dipyridamole-loading thallium-201 myocardial scanning was performed at least 15 h after the cessation of cardioactive medication with infusion of 0.568 mg/kg dipyridamole and walking in place for 3 min^{10,11}. Three mCi (111 MBq) of thallium-201 chloride was injected during walking in place, and acquisition of 3 projection-images (anterior, 45° left anterior oblique, 70° left anterior oblique) was begun within 5 min of injection using a gamma camera equipped with a high resolution collimator (Toshiba GCA401-5). Systolic blood pressure, heart rate and electrocardiography were monitored continuously with a lead in the CC5 position. Electrocardiography at rest was compared with that taken immediately after walking to obtain the ST depression magnitude, which was measured at 80 ms after the J point. ST depression of ≥ 0.1 mV was considered to be significant. Scintigraphic images were acquired for 5 min of pre-set time and stored in a computer (Toshiba GMS-55A) for subsequent analysis. Identical delayed images were acquired 3 h later¹².

Data were analyzed using a circumferential profile curve after smoothing and background subtraction of images¹³. The percent-

age of myocardial thallium-201 washout was calculated automatically for every 36 points along the profile curve in each view using the formula: $(I-D)/I \times 100$, where I=initial myocardial activity and D=myocardial activity at the same location at the time of delayed acquisition¹⁴. Therefore, thallium washout was negative if $D > I$ at any point along the profile curve, and was defined as negative washout rate. Diffuse slow washout was defined as washout abnormality in all myocardial segments that were related to the right, left circumflex or left anterior descending coronary artery¹⁵. Defects were classified as fixed if a perfusion defect was observed in both initial and delayed imagings at the same location, or as reversible if complete or partial redistribution was observed in delayed imaging in the area of the initial perfusion defect. The assignment of myocardial segments to coronary arteries is shown in Fig. 1. Extensive fixed and reversible defects were defined as multiple fixed and reversible defects in $2 \geq$ different areas of coronary arteries, respectively¹⁶. The findings were interpreted by 2 observers who were unaware of the angiographic results. Disagreements were resolved by consensus.

Eleven patients, aged 46 to 65 years (mean 56), who had atypical chest pain and angiographically normal coronary arteries served

TABLE I DATA IN 21 PATIENTS WHO HAD MAJOR CARDIAC EVENTS

Patient no.	Age	Gender	Previous MI	Extent of CAD	EF	FD	EFD	RD	ERD	DSW	NWR	Events
1	62	F	0	1	73	+	0	+	0	0	+	MI
2	55	M	+	1	56	0	0	0	0	0	0	MI
3	61	M	0	1	87	0	0	+	0	0	0	MI
4	66	M	0	2	68	0	0	+	+	0	+	MI
5	56	M	0	2	73	0	0	+	+	0	+	MI
6	63	F	+	2	42	+	0	+	0	+	+	MI
7	71	M	+	1	37	+	0	+	0	0	0	NSD
8	75	F	0	2	58	+	0	+	0	0	0	NSD
9	79	M	0	3	51	0	0	+	+	0	+	NSD
10	52	M	+	1	40	+	0	0	0	0	0	SD
11	48	M	+	1	54	+	0	0	0	0	0	SD
12	61	M	+	1	23	+	+	0	0	0	+	SD
13	54	M	+	2	30	+	+	0	0	+	+	SD
14	59	M	+	2	43	+	0	+	+	+	+	SD
15	47	M	+	3	50	+	+	+	0	+	+	SD
16	61	M	+	3	23	+	+	0	0	+	+	SD
17	78	M	+	3	70	+	0	+	+	+	+	SD
18	75	M	+	3	48	+	0	+	+	+	+	SD
19	67	M	+	3	24	+	0	+	0	+	+	SD
20	78	M	0	3	66	0	0	+	0	+	+	SD
21	63	M	+	LM	26	+	0	0	0	0	0	SD

CAD=coronary artery disease; DSW=diffuse slow washout; EF=ejection fraction; EFD=extensive fixed defects; ERD=extensive reversible defects; F=female; FD=fixed defects; LM=left main; M=male; MI=myocardial infarction; no.=number; NSD=non-sudden cardiac death; NWR=negative washout rate; RD=reversible defects; SD=sudden cardiac death.

as normal controls for dipyridamole thallium scintigraphy, and provided a lower limit of normalcy in circumferential profile curves of percent thallium-uptake and washout rate.

Exercise testing

Treadmill exercise testing was performed with the patient off cardioactive medications using a modified Bruce protocol¹⁷. Chest pain, ST depression or submaximal heart rate, which was defined as 85% of the age-predicted maximal heart rate¹⁸, were regarded as indications for stopping exercise. Heart rate, blood pressure, 12-lead electrocardiography and symptoms at rest, during exercise and for the first 5 min after exercise were recorded.

Cardiac catheterization

Coronary angiography was performed in multiple oblique projections by the Judkins or Sones technique and recorded on 35 mm cine film at 30 frames/sec. Coronary arteriograms were interpreted by 2 experienced

angiographers who were unaware of the results of scintigraphy. They used calipers and referred to the criteria proposed by the American Heart Association: actual diameter narrowing from 26% to 50%=50%, from 51% to 75%=75%, from 76% to 90%=90%, nearly obliterated lumen, reduced to hair-width (greater than 90% narrowing), with antegrade flow=99%, and complete occlusion=100%.¹⁹ A significant stenosis in the 3 major coronary arteries was defined as $\geq 75\%$ diameter narrowing. Biplane left ventriculography was performed in the 30° right anterior oblique projection and in the 60° left anterior oblique projection with 20° cranial tilt. The ventriculogram was divided into 7 segments: antero-basal, anterolateral, apical, diaphragmatic, posterobasal, septal wall and posterior.¹⁹ The systolic contraction pattern of each of the 7 segments was scored as described previously: 1=normal, 2=moderate hypokinesis, 3=severe hypokinesis, 4=akinesis, 5=dyskinesis and 6=aneurysm present.²⁰

TABLE II COMPARISON OF ANGIOGRAPHIC AND SCINTIGRAPHIC FINDINGS IN PATIENTS WITH AND WITHOUT CARDIAC EVENTS

	Events (n=21)	No events (n=250)	p Value
Age (years)	63±10	61±10	NS
Male/Female	18 (86%)/3 (14%)	196 (78%)/54 (22%)	NS
Previous MI	14 (67)	171 (68)	NS
<i>Angiography</i>			
<i>Extent of CAD</i>			
1-vessel CAD	7 (33)	154 (62)	<0.05
2-vessel CAD	6 (29)	55 (22)	
3-vessel CAD	7 (33)	36 (14)	
Left main CAD	1 (5)	5 (2)	
>90% narrowing in any CA	13 (62)	151 (60)	NS
LV asynergic score	16±7	12±5	=0.05
LV ejection fraction (%)	50±19	61±16	<0.02
<i>Dipyridamole thallium scintigraphy</i>			
Chest pain	9 (43%)	110 (44%)	NS
ST depression (mV)	0.11±0.11	0.05±0.08	=0.05
Fixed defects	15 (71)	178 (71)	NS
Extensive fixed defects	4 (19)	30 (12)	NS
Reversible defects	14 (67)	147 (59)	NS
Extensive reversible defects	6 (29)	31 (12)	<0.05
Diffuse slow washout	9 (43)	60 (24)	<0.06
Negative washout rate	14 (67)	72 (29)	=0.0003

CA=coronary artery; CAD=coronary artery disease; LV=left ventricular; MI=myocardial infarction; NS=not significant.

The left ventricular asynergic score was the sum of the points attributed to each of these 7 segments. Thus, in a patient with normal systolic contraction in all 7 segments of the LV angiogram, the left ventricular asynergic score would be 7. Using the standard area-length method, end-diastolic volume, end-systolic volume and ejection fraction were calculated on an OSCON Angiogram Analyzer System from traced silhouettes of the left ventriculogram in the right anterior oblique projection.

Follow-up

After hospital discharge, questionnaires were sent to all patients annually. If there was no reply, the patient or a family member was contacted by telephone. No attempt was made to standardize therapy. Medications at the time of discharge after initial evaluation were nitrates in 261 patients, calcium blockers in 243, beta-blockers in 6, digitalis in 26, diuretics in 109 and antiarrhythmic drugs in 70. The follow-up period was defined as the

time from cardiac catheterization until cardiac event, death or August 1990. Cardiac event was defined as either myocardial infarction or cardiac death. Coronary intervention, such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, was not considered as an event, because the results of scintigraphy and/or angiography may have influenced the decision to perform such intervention. The follow-up period was terminated in cases of intervention. Cardiac death was considered sudden if deterioration and death occurred within 1 h of the onset of symptoms. Patients who died of noncardiac causes were considered event-free until the day of their death. Follow-up to event, death or August 1990 was completed in 271 (98%) of 277 patients.

Statistical analysis

Results are expressed as mean±1 standard deviation. Student's t test was used to compare the means of the continuous vari-

TABLE III THE SITE OF PERFUSION/WASHOUT ABNORMALITY OR HIGH DEGREE CORONARY ARTERY NARROWING IN PATIENTS WITH OR WITHOUT CARDIAC EVENTS

	Events (n=21)	No events (n=250)	p Value
<i>Fixed defects</i>			
LAD	12 (57%)	94 (38%)	<0.08
LC	1 (5)	33 (13)	NS
RCA	6 (29)	81 (32)	NS
<i>Reversible defects</i>			
LAD	10 (48)	112 (45)	NS
LC	5 (24)	34 (14)	NS
RCA	6 (29)	32 (13)	<0.05
<i>Negative washout rate</i>			
LAD	5 (24)	44 (18)	NS
LC	5 (24)	14 (6)	<0.002
RCA	7 (33)	24 (10)	=0.001
<i>CA narrowing of >90%</i>			
LAD	7 (33)	71 (28)	NS
LC	4 (19)	39 (16)	NS
RCA	9 (43)	68 (27)	NS

CA=coronary artery; LAD=left anterior descending; LC=left circumflex; NS=not significant; RCA=right coronary artery.

ables, and contingency tables were analyzed using a chi-square test. Linear discriminant analysis, with stepwise variable selection, was used to assess the potential to predict prognosis. Wilk's Lambda which is the ratio of the within-groups sum of squares to the total sum of squares, was used as the selection and optimization criterion. A Bayes rule with equal prior probability was used for predictions, and results are presented by tabulating the correctly classified patients with cardiac event (sensitivity for prediction of cardiac event), the percent correctly classified patients without cardiac event (specificity for prediction of event-free patients), and total correct prediction (accuracy of prediction). The statistical computations were performed using the SPSS-PC+computer program.

RESULTS

Prognosis after follow-up

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During the 2.8 ± 1.8 years of follow-up, 18 patients died: 3 from heart failure after myocardial infarction, 12 suddenly, and 3 of noncardiac causes. Six patients sustained nonfatal myocardial infarction, which was diagnosed on the basis of characteristic chest pain, electrocardiography and serum enzyme changes. The 3 noncardiac deaths were from cerebrovascular accident, malignancy and car accident. Thus, a total of 21 patients (8%) experienced cardiac events. Angiographic and scintigraphic data in the patients with cardiac events are detailed in Table I. Left ventricular asynergic score and ejection fraction were worse in patients who died of cardiac causes than in those who sustained nonfatal myocardial infarction (18 ± 6 vs 9 ± 4 ; $p=0.001$, and 43 ± 16 vs $67 \pm 16\%$; $p<0.02$, respectively). Patients who died had a higher incidence of previous myocardial infarction (80 vs 33%; $p<0.05$), fixed defects (87 vs 33%; $p<0.02$), extensive fixed defects (27 vs 0%; $p=0.15$), diffuse slow washout (53 vs 17%, $p=0.12$), and multi-vessel coronary artery disease (73 vs 50%; $p=0.15$) than those who had nonfatal infarction, while the incidence of reversible defects (60 vs 83%; $p=NS$) and negative washout rate (67 vs 67%; $p=NS$) was similar in both groups.

Univariate analysis of survival

Patients with cardiac events had a higher incidence of multi-vessel coronary artery disease, extensive reversible defects, diffuse slow washout and negative washout rate than those without events (Table II). Left ventricular asynergic score and ejection fraction were worse, and ST depression was greater in patients with events than in those without events. No differences were found between the medications taken by the 2 groups (95 vs 96% in nitrates, 95 vs 89% in calcium blockers, 5 vs 2% in beta-blockers, 19 vs 9% in digitalis, 57 vs 39% in diuretics and 33 vs 25% in antiarrhythmics).

The negative washout rate was the best single marker for predicting cardiac events, with a sensitivity of 67% and a specificity of 71%. Multi-vessel coronary artery disease and extensive reversible defects had sensitivities of 67 and 29%, respectively, and specificities of 62 and 88%, respectively, in predicting events. An analysis of the relation-

TABLE IV COMPARISON OF FINDINGS OF EXERCISE TESTING IN PATIENTS WITH AND WITHOUT CARDIAC EVENTS

	Events (n=19)	No events (n=239)	p Value
Chest pain	9 (47%)	92 (38%)	NS
ST depression (mV)	0.18±0.13	0.12±0.12	<0.09
Duration of exercise (min)	3.9±1.6	5.0±1.9	=0.01
Diagnosis of the test			
Negative	1 (5%)	70 (29%)	<0.08
Undiagnostic	3 (16)	30 (13)	
Positive	15 (79)	139 (58)	

Thirteen patients who were unable to perform exercise testing and 6 patients who were lost to follow-up were excluded from the analysis.

ship between negative washout rate and the severity of individual coronary artery narrowing revealed that 21 of 46 patients with 100% narrowing, and 15 of 33 patients with 99% in the left anterior descending coronary artery, had a negative washout rate in the corresponding area, whereas only 8 of 49 patients with 90%, 5 of 62 patients with 75% and 1 of 87 patients with insignificant narrowing had this scintigraphic marker ($p < 0.0001$). A similar relation was also observed in the left circumflex artery (12/45 in 99 or 100% vs 7/232 in $\leq 90\%$ narrowing; $p < 0.0001$) and the right coronary artery (22/79 in 99 or 100% vs 10/198 in $\leq 90\%$ narrowing; $p < 0.0001$).

Patients with events had a higher incidence of fixed defects in the left anterior descending area, reversible defects in the right coronary arterial area, and negative washout rate in the left circumflex and right coronary arterial areas, as compared with those without events (Table III). No significant association was observed between high grade narrowing in individual coronary arteries and cardiac events (Table III). Seven patients had fixed defects in the left anterior descending area without partial redistribution while they had negative washout rate in the left circumflex and/or right coronary arterial areas. Four of these patients (57%) died suddenly. Thus, this combination of scintigraphic markers had a sensitivity of 19% and a specificity of 99% in the prediction of cardiac events ($p < 0.0001$).

Thirteen patients (5%) were unable to perform exercise testing due to severe car-

diac or extracardiac limitations: unstable angina in 3, congestive heart failure in 2, osteoarthropathy of the lower extremities in 4, neurological deficit in 3, and arteriosclerosis obliterans in 1. In addition, 33 patients (12%) failed to achieve submaximal heart rate despite absence of chest pain or ST depression. The results in these patients were regarded as undiagnostic. The duration of exercise was shorter and ST depression was greater in patients with cardiac events than in those without (Table IV).

Multivariate analysis of survival

Fourteen variables in Table II were considered potential predictors for the occurrence of cardiac events during follow-up, and were included in a stepwise discriminant analysis. After excluding 6 patients who were lost to follow-up, multivariate analysis in 271 patients revealed that the combination of negative washout rate, ejection fraction, ST depression during dipyridamole loading, previous myocardial infarction, coronary artery narrowing of $>90\%$, left ventricular asynergic score and number of diseased vessels was most statistically significant (chi-square = 39, $p < 0.0001$) in the prediction of cardiac events (sensitivity 86%, specificity 77%, accuracy 77%) (Table V). The analysis was repeated after excluding variables related to dipyridamole thallium scintigraphy. The variables that were the most statistically significant (chi-square = 24, $p = 0.0001$) predictors of cardiac events were ejection fraction, the number of diseased vessels, previous myocardial infarction and left ventricu-

TABLE V MULTIVARIATE ANALYSIS IN THE PREDICTION OF CARDIAC EVENTS

Variables	Order	F value	Wilks' Lambda
Negative washout rate	1	13	0.95
LV ejection fraction	2	10	0.97
Number of diseased vessels	7	8	0.97
ST depression during DL	3	8	0.97
LV asynergic score	6	7	0.98
Extensive reversible defects		4	0.98
Diffuse slow washout		4	0.99
Age		1	0.99
Extensive fixed defects		<1	1.00
Gender		<1	1.00
Reversible defects		<1	1.00
Previous MI	4	<1	1.00
CA narrowing of >90%	5	<1	1.00
Chest pain during DL		<1	1.00
Fixed defects		<1	1.00

Order indicates the order of selection in the analysis. Blank spaces indicate variables not selected by the analysis. CA=coronary artery; DL=dipyridamole loading; LV=left ventricular; MI=myocardial infarction.

lar asynergic score (sensitivity 67%, specificity 74%, accuracy 74%). After excluding 13 patients who were unable to perform exercise testing, the analysis was repeated in 258 patients and included the exercise testing variables listed in Table IV. This analysis revealed that the combination of negative washout rate, duration of exercise, ejection fraction, ST depression during dipyridamole loading, coronary artery narrowing of >90% and the number of diseased vessels was most statistically significant (chi-square=35, $p < 0.001$) in the prediction of cardiac events (sensitivity 68%, specificity 80%, accuracy 79%). The analysis was also repeated in 258 patients using variables related to noninvasive tests only. The resulting sensitivity of 68%, specificity of 80% and accuracy of 79% were similar to those in the previous analysis.

DISCUSSION

Thallium-201 myocardial imaging has been established as a noninvasive examination with high predictability in the diagnosis of coronary artery disease^{21,22} Its prognostic value in identifying high-risk patients has also been demonstrated.²³⁻³¹ Using exercise stress testing, several studies have reported thallium-201 imaging is superior to cardiac catheterization in predicting future cardiac

events.^{28,30} The usefulness of dipyridamole thallium scintigraphy was recently demonstrated in the diagnosis of patients with coronary artery disease, as well as in stratifying these patients into high-and low-risk groups. However, the prognostic value of this pharmacologic stress imaging technique over established angiographic markers is not well documented.⁶⁻⁹

In this prospective follow-up study of 277 consecutive patients with coronary artery disease, 21 patients experienced myocardial infarction and/or cardiac death. The extent of coronary artery disease and poor left ventricular performance were associated with major cardiac events, which is consistent with previous studies.³²⁻³⁵ However, negative washout rate, which is one of the scintigraphic markers, was the best single predictor in univariate analysis, with a sensitivity of 67% and a specificity of 71%, in the prediction of cardiac events, and was the most important variable, even superior to angiographic variables, in multivariate analysis. Poor left ventricular systolic function was an important marker for cardiac death, but not for nonfatal myocardial infarction. Thus, the ability of this marker to predict cardiac events was reduced. In contrast, negative washout rate was an important predictor for both cardiac death and nonfatal infarction. In addition, poor left ventricular perform-

ance was a predictor for death and good left ventricular function was a predictor for myocardial infarction. In particular, patients who had anterior infarction with no redistribution and negative washout rate in other areas were at risk of sudden death. In addition to negative washout rate, inclusion of ST depression during dipyridamole loading improved the predictability which was obtained solely by clinical and angiographic variables. The present study indicates that the addition of dipyridamole thallium scintigraphic data to established angiographic markers can help better identify patients with coronary artery disease who are at high risk of cardiac events.

Several scintigraphic markers have been reported to be important in multivariate analysis for predicting cardiac events in patients with suspected or known coronary artery disease: i.e., the number of segments with reversible defects, the number of perfusion defects, maximal severity in perfusion defects, and pulmonary uptake of thallium²³⁻³⁰. Above all, pulmonary uptake of thallium is well recognized and has been reported to be the best predictor of a cardiac event^{27,28}. This scintigraphic marker has been reported to have a sensitivity of 51% and a specificity of 92% when used as a single predictor²⁷. Negative washout rate had a higher sensitivity and a lower specificity than pulmonary uptake. However, several other studies by the same author^{25,28} or from the same institute^{23,27} did not always show a significant association between pulmonary uptake and cardiac events in uni- and multivariate analysis. This discrepancy may be due to the different methods of analyzing pulmonary uptake of thallium: i.e., quantitative versus visual methods²⁹. On the other hand, negative washout rate is calculated automatically using the simple formula mentioned earlier.

Delayed imaging usually shows lower myocardial activity of thallium-201 than the initial imaging. However, in patients with severe coronary artery disease, the activity is sometimes higher in the delayed imaging than in the initial imaging, and is expressed as negative washout rate. In our previous study in patients with suspected coronary artery disease, a significant association was observed between negative washout rate and

high grade coronary artery narrowing of $\geq 90\%$. The ability of negative washout rate to detect patients with high grade narrowing showed a sensitivity of 48%, a specificity of 93%, and a positive predictive value of 94%³⁶. Despite this significant association, and the present finding that negative washout rate was the best predictor, no association was found between the severity of coronary artery narrowing and cardiac events. These observations suggest that negative washout rate is a physiologic marker related to severe impairment of myocardial perfusion, and is more important than anatomical findings assessed by coronary arteriograms in identifying high-risk patients. Negative washout rate may also be superior to reversible defects in detecting severe coronary artery narrowing and myocardial viability³⁶ which would help to identify high-risk patients. Ladenheim et al reported that both the extent and severity of stress-induced perfusion defects may contribute to the prognostic stratification²⁴. Our results suggest that the extent, and particularly, the severity of washout abnormality are also important for this purpose, although the correlation between thallium-201 washout and quantitative analysis of perfusion defects remains to be determined.

The finding in our study that ST depression induced by dipyridamole was the third most important predictor in multivariate analysis, following negative washout rate and ejection fraction, highlights the prognostic value of electrocardiographic changes during dipyridamole loading. The primary purpose of electrocardiographic monitoring during dipyridamole thallium scintigraphy is to enhance the safety of the examination. Adverse effects of dipyridamole, such as myocardial ischemia and bradyarrhythmias, require appropriate treatment immediately. The value of electrocardiographic changes during dipyridamole thallium scintigraphy for purposes of diagnosis has not been well evaluated³⁷. Our previous study in 437 patients with suspected coronary artery disease revealed that ST depression in single lead electrocardiography had a sensitivity of 51% and a specificity of 89% in the overall detection of coronary artery disease³⁸. Recently, we and others demonstrated that the electrocardiographic marker of ischemia was useful

in identifying multi-vessel coronary artery disease or multi-vessel perfusion patterns.³⁹ Together with these studies, the present study indicated that although ST depression in electrocardiography did not improve the sensitivity of thallium-201 imaging in the overall detection of coronary artery disease, it did help to identify a particular subset of patients who either had severe coronary artery disease or who might be at high risk of cardiac events. Therefore, electrocardiographic changes, as well as thallium-201 myocardial imaging should be focused on in the analysis of dipyridamole thallium scintigraphy.

Exercise testing has been reported to have prognostic value in patients with coronary artery disease.⁴⁰⁻⁴² In the present study, treadmill exercise testing was not indicated in 5% of the patients due to severe cardiac or extracardiac diseases. Testing was undiagnostic in an additional 12% of the patients. Not all patients with coronary artery disease can undergo adequate exercise for the interpretation of electrocardiographic responses, which may be one of the limitations of exercise testing. In contrast, dipyridamole thallium scintigraphy can be safely performed in patients with heart failure and/or unstable angina.^{43,44} The duration of exercise, rather than ischemic changes in electrocardiography, had a significant association with cardiac events in this study. Multivariate analysis again demonstrated the superiority of the prognostic value of scintigraphic examination to that of exercise testing. Thus, dipyridamole thallium scintigraphy has a broader application than exercise testing as a noninvasive examination in coronary artery disease, and has better prognostic value.

Controversies still remain over the clinical usefulness of washout analysis.^{45,46} Technical problems in the measurement of washout rates are one of the limitations. Furthermore, no study has associated abnormal washout with the prognosis of patients with coronary artery disease. Nevertheless, the prognostic value of negative washout rate, which was the best single predictor for cardiac events in the present study, highlights the clinical usefulness of thallium washout analysis.

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