NEGATIVE WASHOUT RATE OF MYOCARDIAL THALLIUM-201
— A Specific Marker for High Grade Coronary
Artery Narrowing —

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A decline is usually observed in the myocardial uptake of thallium-201 in delayed imaging compared with initial imaging. In patients with severe coronary artery disease (CAD), the uptake is sometimes higher in the delayed than in the initial imaging, which is expressed as negative washout rate. To evaluate the diagnostic implications of this negative washout rate the findings of dipyridamole thallium scintigraphy in 582 patients with coronary artery disease were evaluated. The negative washout rate was present in 201 of 582 patients (35%). It had a significant association with high grade coronary artery narrowing of ≥90%. Sensitivity in detecting patients with this high grade narrowing by negative washout rate was 48%, its specificity was 93%, and its positive predictive value was 94%. Sensitivity to detect individual coronary artery narrowing of ≥90% did not decrease according to the extent of CAD, with the highest detection in the left anterior descending coronary artery and the lowest in the left circumflex coronary artery. Since patients with high grade coronary narrowing often require coronary intervention, the results of this study suggest the diagnostic importance of negative washout rate in the identification of the particular subset of patients with CAD. (Jpn Circ J 1992; 56: 975–982)

THALLIUM-201 washout analysis is useful in the identification of patients with coronary artery disease (CAD). The analysis is based upon the rate of decrease of myocardial thallium-uptake in delayed imaging compared with initial imaging; slow rate of decrease is usually regarded as a marker for severe CAD. Myocardial uptake of thallium-201 often increases rather than decreases in the delayed imaging, which is expressed as negative washout rate by definition. The present study evaluates the diagnostic implications of this negative washout rate of myocardial thallium-201 to which not much attention has been given.

METHODS

Study patients
Five hundred and eighty-two patients (423 men and 159 women) with known or suspected CAD were analyzed retrospectively. They were aged 28 to 87 years (mean 60); 311 patients had previous myocardial infarc-
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.

tion that was defined by typical clinical course and electrocardiographic findings with at least twofold elevation of creatine kinase in serum; and left ventricular wall motion abnormality demonstrated on left ventriculogram. One-vessel CAD was found in 217 patients, 2-vessel CAD in 107, 3-vessel CAD in 94, left main CAD in 40 and no significant stenoses in 124. No patient was included after coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

Thallium myocardial scanning
Scintigraphic study was undertaken within 1 week of angiography in all cases. Dipyridamole-loading thallium-201 scanning was performed more than 15 h after the cessation of cardioactive medication, according to Gould's method with infusion of 0.568 mg/kg dipyridamole and walking in place for 3 min. Three mCi (111MBq) of thallium-201 chloride was injected during walking, and acquisition of 3 projection images (anterior, 45° left anterior oblique, 70° left anterior oblique) was begun within 5 min of the injection using a gamma camera equipped with a high resolution collimator (Toshiba GCA401-5). Systolic blood pressure was measured using a mercury sphygmomanometer at rest, at 2 and 4 min after the initialization of dipyridamole injection, and during walking in place. Electrocardiography and heart rate were monitored continuously using a monitoring system (Fukuda Denshi Dynascope 800) with leads in CC5 position; electrocardiography at rest was compared with that taken immediately after walking for the magnitude of ST depression 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 with 5 min of preset time and stored in the computer (Toshiba GMS-55A) for subsequent analysis. Identical delayed images were acquired 3 h later. Data were analyzed using circumferential profile curve after smoothing and background subtraction of images. The percentage of myocardial thallium-201 washout was calculated for each of 36 points along the profile curve in each view with the formula: (I - D)/I × 100, where I = initial myocardial % uptake and D = myocardial % uptake at the time of delayed acquisition at the same location. The washout of thallium, therefore, becomes negative if D > I, which is defined as negative washout rate. The findings were interpreted by 2 observers who were unaware of the angiographic results. Defects were classified as reversible or fixed according to conventional methods. The assignment of
myocardial segment to coronary arteries is shown in Fig. 1. 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 as normal controls, and provided the lower limit of normality in circumferential profile curves of percent uptake.

**Coronary angiography**

Coronary angiography was performed in multiple oblique projections by the Judkins or the Sones technique and was recorded on 35 mm cine film at 30 frames/sec. Coronary arteriograms were interpreted by 2 experienced angiographers unaware of the results of scintigraphy, using the criteria proposed by the American Heart Association! A significant stenosis in the 3 major coronary arteries was defined as ≥75% diameter narrowing and in the left main trunk as >50%; the degree of coronary artery narrowing was divided into 75, 90, and 99% or more!!

**Statistical analysis**

Results are expressed as mean ±1 standard deviation. To compare the means of the continuous variables Student’s t test was used, and contingency tables were analyzed using chi-square test (Results are also presented as sensitivity, specificity and positive predictive value: sensitivity = number of true positive detections/total number of positives in the group tested; specificity = number of true negative detections/total number of negatives in the group tested; positive predictive value = true positives/true positives + false positives). A p value of >0.05 was considered not significant. The statistical computations were performed using SPSS-PC+ computer program.

**RESULTS**

**The association of negative washout rate with clinical markers of ischemia**

During dipyridamole loading, 278 patients (48%) had chest pain, 203 patients (35%) had ST depression of ≥0.1 mV, and 215 patients (37%) required aminophylline to relieve the adverse effects of dipyridamole. Two hundred and one patients (35%) had negative washout rate in at least 1 major coronary arterial area. A typical case is shown in Fig. 2. Patients with negative washout rate had higher incidence of chest
TABLE I  DETECTION OF PATIENTS WITH HIGH GRADE CORONARY ARTERY NARROWING (≥90%) IN ANY ONE OF THE MAJOR CORONARY ARTERIES BY NWR

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48% (188/390)</td>
<td>93% (179/192)</td>
<td>94% (188/201)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI (+) (n=311)</td>
<td>48% (124/257)</td>
<td>91% (49/54)</td>
<td>96% (124/129)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI (-) (n=271)</td>
<td>48% (64/133)</td>
<td>94% (130/138)</td>
<td>89% (64/72)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*p value for negative washout rate versus patients with coronary artery narrowing of ≥90% in any one of the major coronary arteries. NWR=negative washout rate; MI=myocardial infarction; PPV=positive predictive value.

TABLE II  INDIVIDUAL VESSEL DETECTION (≥90% NARROWING) BY NWR

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>49% (122/248)</td>
<td>95% (318/334)</td>
<td>88% (122/138)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LC</td>
<td>23% (34/150)</td>
<td>98% (421/432)</td>
<td>76% (34/45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RCA</td>
<td>35% (64/182)</td>
<td>96% (382/400)</td>
<td>78% (64/82)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*p value for individual coronary artery narrowing of ≥90% versus negative washout rate in each corresponding coronary arterial area. LAD=left anterior descending; LC=left circumflex coronary artery; NWR=negative washout rate; PPV=positive predictive value; RCA=right coronary artery.

TABLE III  INDIVIDUAL VESSEL DETECTION (≥90% NARROWING) BY NWR IN 1-VESSEL, 2-VESSEL, 3-VESSEL AND LMCAD

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD narrowing (≥90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1VD (n=101)</td>
<td>45% (45/101)</td>
<td>96% (111/116)</td>
<td>90% (45/50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2VD (n=58)</td>
<td>47% (27/58)</td>
<td>94% (46/49)</td>
<td>90% (27/30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3VD+LMTD (n=89)</td>
<td>56% (50/89)</td>
<td>84% (38/45)</td>
<td>88% (50/57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LC narrowing (≥90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1VD (n=25)</td>
<td>20% (5/25)</td>
<td>100% (191/192)</td>
<td>83% (5/6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2VD (n=40)</td>
<td>25% (10/40)</td>
<td>96% (64/67)</td>
<td>77% (10/13)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>3VD+LMTD (n=85)</td>
<td>22% (19/85)</td>
<td>86% (42/49)</td>
<td>73% (19/26)</td>
<td>NS</td>
</tr>
<tr>
<td>RCA narrowing (≥90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1VD (n=42)</td>
<td>17% (7/42)</td>
<td>98% (171/175)</td>
<td>64% (7/11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2VD (n=52)</td>
<td>33% (17/52)</td>
<td>93% (51/55)</td>
<td>81% (17/21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3VD+LMTD (n=88)</td>
<td>46% (40/88)</td>
<td>80% (37/46)</td>
<td>82% (40/49)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

*p value for individual coronary artery narrowing of ≥90% versus negative washout rate in each corresponding coronary arterial area. LAD=left anterior descending; LC=left circumflex coronary artery; LMTD=left main trunk disease; NWR=negative washout rate; PPV=positive predictive value; RCA=right coronary artery; VD=vesSEL disease.

pain (62 vs 42%; p<0.0001), ischemic ST depression (54 vs 31%; p<0.001), and use of aminophylline (60% vs 32%; p<0.0001) than those without negative washout rate.

Detection of patients with high grade coronary artery narrowing of ≥90% in any one of the major coronary arteries by negative washout rate

Of 773 stenoses in the 3 major coronary arteries

Japanese Circulation Journal Vol.56, October 1992
Negative Washout Rate

TABLE IV  INDIVIDUAL VESSEL DETECTION (≥90% NARROWING) BY NWR IN PATIENTS WITH MYOCARDIAL INFARCTION

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD narrowing (≥90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD in LAD area</td>
<td>68% (61/90)</td>
<td>91% (29/32)</td>
<td>95%</td>
<td>(61/64)</td>
</tr>
<tr>
<td>FD in LAD area</td>
<td>33% (17/51)</td>
<td>97% (32/33)</td>
<td>94%</td>
<td>(17/18)</td>
</tr>
<tr>
<td>LC narrowing (≥90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD in LC area</td>
<td>21% (7/33)</td>
<td>90% (9/10)</td>
<td>88%</td>
<td>(7/8)</td>
</tr>
<tr>
<td>FD in LC area</td>
<td>28% (7/25)</td>
<td>79% (11/14)</td>
<td>70%</td>
<td>(7/10)</td>
</tr>
<tr>
<td>RCA narrowing (≥90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD in RCA area</td>
<td>49% (19/39)</td>
<td>78% (7/9)</td>
<td>90%</td>
<td>(19/21)</td>
</tr>
<tr>
<td>FD in RCA area</td>
<td>28% (18/64)</td>
<td>76% (19/25)</td>
<td>75%</td>
<td>(18/24)</td>
</tr>
</tbody>
</table>

*p value for individual coronary artery narrowing of ≥90% versus negative washout rate in each corresponding coronary artery area. FD=fixed defect; LAD=left anterior descending; LC=left circumflex coronary artery; NWR=negative washout rate; PPV=positive predictive value; RCA=right coronary artery; RD=reversible defect.

arteries, 580 (75%) were of ≥90%, 193 (25%) were of 75%. Three-hundred ninety patients (67%) had high grade coronary artery narrowing of ≥90% in at least one of the major coronary arteries; 257 of 311 patients (83%) with myocardial infarction and 133 of 271 patients (49%) without myocardial infarction had this high grade narrowing. The association of negative washout rate with the presence of coronary artery narrowing of ≥90% in any one of the major coronary arteries is shown in Table I. Negative washout rate had high positive predictive value and specificity, and modest sensitivity in the detection of patients with this high grade coronary artery narrowing.

Individual vessel detection (≥90% diameter narrowing) by negative washout rate

In the detection of high grade narrowing in individual vessels, the left anterior descending coronary artery was identified with the highest sensitivity and positive predictive value while the left circumflex coronary artery had the lowest (Table II). Sensitivity in the detection of left anterior descending and right coronary arteries was higher in 3-vessel and left main CAD than in 1-vessel CAD while specificity to detect each 3 coronary artery was lower in 3-vessel and left main CAD than in 1-vessel CAD (Table III). The detection of high grade narrowing in an individual vessel in patients with previous myocardial infarction is shown in Table IV. Severely narrowed coronary arteries with reversible defects in their territories were better identified than those with fixed defects. No significant association was observed between negative washout rate and high grade narrowing in left circumflex and right coronary artery when each coronary arterial area had fixed or reversible defects (Table IV).

DISCUSSION

The present study demonstrated that negative washout rate was common in CAD, and had a high specificity and a positive predictive value in the detection of high grade coronary artery narrowing of ≥90%. If thallium myocardial scintigraphy of a given patient shows negative washout rate, the likelihood that the patient has high grade narrowing of ≥90% is ≥90%. Previous studies reported that patients with severe coronary artery narrowing had a propensity to have angina often poorly responsive to medical treatment. Therefore, these patients are likely to become candidates for percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. Successful revascularization for these patients results in relief of angina, increased exercise capacity and improvement in quality of life. Thus, negative washout rate can be considered as a noninvasive marker for patients who may require coronary revascularization. Thallium...
myocardial scanning based upon conventional analysis yielded moderate to high sensitivity in detecting coronary artery narrowing of ≥70% 19,20, sensitivity to detect mild narrowing (50 to 70% or 50 to 75%) has been improved with the use of single photon emission computed tomography 21–23. Extensive CAD such as 3-vessel and left main CAD is identified with additional complex analysis of scintigraphic findings: i.e., lung uptake or diffuse slow washout of thallium-201 24. As far as we know, however, there has been no scintigraphic marker identified to be useful in detecting the particular subset of patients with high grade coronary artery narrowing of ≥90%. The results of our study demonstrate that a simple washout analysis can separate a severe degree of coronary narrowing from a moderate narrowing.

The sensitivity of negative washout rate for detection of individual vessel narrowing of ≥90% was highest in the left anterior descending coronary artery and lowest in the left circumflex coronary artery. The low sensitivity for the left circumflex is similar to that found in previous studies in which individual vessel narrowing (>50%) was detected using conventional analysis based upon perfusion defects 19,20. Since the left circumflex coronary artery usually has a small vascular bed and is located posterolaterally far from the camera, this may be one of the reasons for the low sensitivity, whether perfusion defect or washout rate is utilized 19. The sensitivity in detecting individual vessels was reported to depend upon the extent of CAD; the highest sensitivity in 1-vessel CAD and the lower one in multi-vessel CAD 19,21. In contrast, the present study of negative washout rate demonstrates the highest sensitivity detecting 3-vessel and left main CAD. This discrepancy may be caused by the difference in conventional analysis being spatially relative and in washout analysis being non-relative 25 but may also be related to dipyridamole loading, which has maximal pharmacological effect to all coronary beds and has a high ability to uncover multiple washout and/or perfusion abnormalities.

The incidence of chest pain was higher than that of ST depression during dipyridamole loading in this study. Chest pain not associated with significant ST depression was often atypical and may be due to the stimulation of adenosine P1-receptors which were reported to be partially responsible for the anginal pain 26. The negative washout rate was observed in approximately 30% of fixed defects, and this may be due to the low sensitivity of the conventional analysis based upon perfusion defects in detecting viable myocardium, since myocardial viability was demonstrated in 30–50% of fixed defects using reinjection and/or positron emission tomography 26,27.

The thallium washout analysis is important in the diagnosis of CAD but needs to be applied cautiously. It is heavily influenced by technical and physiologic factors 28,29. When subtle change of washout rate is analyzed, the thallium decay constant and other aspects of technical accuracy are must be necessary 28,29. Although the strict definition of washout abnormality which we applied in this study may be the reason for low sensitivity in detecting high grade coronary narrowing, this strictness of the definition allows the negative washout rate to be relatively free from the influence of the technical problems. Becker et al reported that exercise performance was the most important determinant of regional thallium washout and that the number of diseased vessels or the presence or absence of disease in a given vessel had little effect on washout 29. However, the results of our previous study with dipyridamole loading in 466 patients with CAD showed a significant association between the washout abnormality and the extent of CAD in spite of similar exercise level and maximal heart rate in 1-, 2-, 3-, and left-main CAD 30. Washout analysis with the use of dipyridamole may be different from that of exercise, since myocardial washout of thallium-201 during dipyridamole thallium scintigraphy is reported to be slower than that of exercise stress testing 31. The small number of patients, around 10 than in each group, might also have limited the statistical analysis of their study 29. Although aminophylline was reported to increase the myocardial washout of thallium-201 32. A higher incidence of the use of this drug in patients with negative washout rate indicates that a confounding effect of aminophylline was negligible in this study. With a large number of patients, the present study underscores the clinical useful-

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ness of thallium washout analysis since the analysis, being independent of perfusion defects, contributed significantly in the identification of patients who have high grade narrowing of the coronary arteries.

Acknowledgments

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