Availability and limitations of thallium-201 myocardial SPECT quantitative analysis: Assessment as daily routine procedure for ischemic heart disease

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To determine the availability and limitations of the detection of ischemic lesions by stress thallium-201 myocardial SPECT as the daily routine procedure, we compared and evaluated the detectability of the quantitative analysis (%uptake and washout rate (WR)) and visual evaluation in 104 patients with effort angina and 17 normal subjects.

Visual evaluation combined with WR analysis resulted in significantly higher sensitivity (88.0%) but lower specificity (60.2%) than the other methods. The sensitivity by visual evaluation was quite low in multivessel disease (MVD), and in the regions supplied by mild coronary stenosis or by the left circumflex artery. These were markedly improved by combining visual evaluation and WR analysis, but sensitivity in the MVD group was unsatisfactory even with this analytic method in comparison with the single vessel disease group. One of the causes of low sensitivity in the MVD group might be the "true negative": No induction of the ischemia in the regions of milder stenosis, or the regions supplied by the collateral coronary flow.

We therefore conclude that the combination of visual evaluation as a qualitative analysis and WR analysis as a quantitative analysis, is the most useful daily routine procedure as a screening test for detecting ischemia.

Key words: thallium myocardial SPECT, ischemic heart disease, washout rate, Bull's eye display, quantitative analysis

INTRODUCTION

Thallium-201 (^{201}Tl) myocardial scintigraphy is widely used as the specific method for noninvasive imaging of the distribution of regional myocardial perfusion. Especially since the development of single photon emission computed tomography (SPECT), ^{201}Tl myocardial imaging has been established as an indispensable method for the diagnosis of ischemic heart disease (IHD). ^{201}Tl myocardial imaging for IHD plays two main roles in the detection of viability in the myocardial tissue and of stress induced myo-

cardial ischemia with the presence of redistribution.[1] As a result of progress in coronary angiography (CAG) and revascularization, more accurate and objective information is now required to evaluate regional myocardial perfusion. Various new methods for the quantitative analysis of myocardial imaging[2-8] have therefore been developed, and various evaluations of these analyses have been reported.[9-16]

Detection of myocardial ischemia by ^{201}Tl imaging has some limitations, particularly overestimation and underestimation. We have to know the limitations and to try to improve the reliability of this test. However, in routine daily clinical work, it is not desirable to use quantitative methods which are very troublesome or require certain conditions to increase their reliability.

In the present study, to define the availability and limitations involved in the detection of myocardial

ischemia by ^{201}Tl SPECT as the daily routine procedure, visual interpretation and quantitative analysis with Bull's eye display[5] were evaluated and compared in patients with effort angina. Moreover, we investigated the cause of negative results which were obtained in stenotic coronary arteries.

MATERIALS AND METHODS

Study population

The study group consisted of 104 patients with effort angina and 17 normal subjects. All subjects underwent both exercise ^{201}Tl myocardial scan and CAG within a one month period. All patients with effort angina had significant coronary stenosis ($\geq 75\%$ stenosis in diameter according to the AHA report[17]) in one or more main coronary arteries. As shown in Table 1, 44 patients had single vessel disease (SVD), and 60 had multivessel disease (MVD); 40 and 20 patients had double vessel disease (DVD) and triple vessel disease (TVD), respectively. The number in each subgroup with individual coronary arterial lesion is also shown in Table 1. Patients with only stenotic diagonal branch and with left main trunk lesion were excluded from this study. Patients with stenotic high lateral branch were classified as left circumflex artery (LCX) lesion. Sixty nine, 59, and 56 vessels had stenotic lesions in the left anterior descending artery (LAD), LCX, and right coronary artery (RCA), respectively. No patient had a history of myocardial infarction or reception of any revascularizing therapy (percutaneous transluminal coronary angioplasty, percutaneous transluminal coronary recanalization, or coronary artery bypass grafting). None of them had had cardiomyopathy or any valvular disease.

Exercise protocol

The exercise test was performed with a supine bicycle ergometer with a graded workload starting at 1.0 Watt/kg body weight and increasing every 3 minutes by 15 Watts. Exercise was stopped at the end point according to the Michigan's Standards. One minute before the end of the exercise, 111 MBq (3.0 mCi) of ^{201}Tl was injected intravenously.

Thallium imaging and image processing

Imagings were started about 5 minutes (early scan) and 4 hours (delayed scan) after thallium injection. Data collection was performed with a rotatable gamma camera with a low energy general purpose collimator interfaced with a dedicated computer (Maxi camera 400 AC/T-Maxi Star system, General Electric). The camera was rotated in 5.6° steps over 180° from the 45° left posterior oblique position to the 45° right anterior oblique position of the patient, and 32 views were obtained. Each image was for 30 seconds in early scan and 50 seconds in delayed scan with time correction.

Images were reconstructed by a filtered back projection method without attenuation correction. Short axis, horizontal long axis, and vertical long axis views of the heart were displayed by each 6 mm thickness of a slice.

Visual evaluation

The three directional tomographic images were visually analyzed by two experienced interpreters. Images were divided into 7 segments and each segment was included in one coronary territory as shown in Fig. 1; anterior or septal wall to LAD

Table 1 Patient population

	n	Age (mean±SD)	Sex male	Sex female
Single vessel disease (SVD)	44	60.3±9.1	40	4
LAD	20			
RCA	13			
LCX	11			
Double vessel disease (DVD)	40	60.3±7.7	34	6
LAD+RCA	12			
LAD+LCX	17			
RCA+LCX	11			
Triple vessel disease (TVD)	20	60.6±9.2	16	4
Normal coronary (control)	17	55.2±11.8	12	5

LAD: left anterior descending artery
RCA: right coronary artery
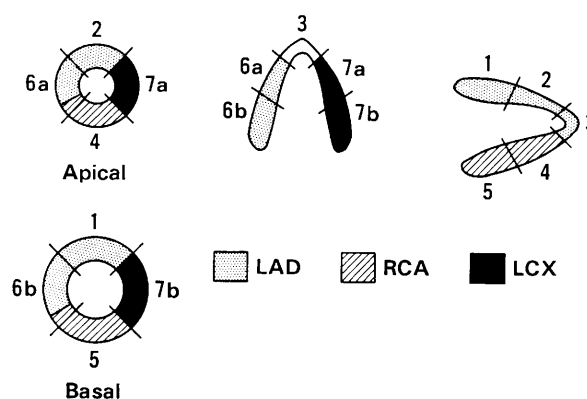LCX: left circumflex artery

Fig. 1 Schematic representation of the myocardial segment and the coronary territories. 1; anterobasal, 2; anteroapical, 3; apical, 4; inferior, 5; posterior, 6a; apical septum, 6b; basal septum, 7a; lateral (apical), 7b; lateral (basal).

territory, lateral wall to LCX territory, and inferior or posterior wall to RCA territory. When a filling defect or decreased uptake of thallium with redistribution was observed in a segment, it was defined as stress induced ischemia.

Quantitative analysis
In the present study, we used two simple quantitative methods which are available for daily routine procedure. In both early and delayed scans, short axial images were divided into 15 slices from apex to base. Apical slices were excluded by using slice No. 5 to slice No. 15. Each slice was divided into 40 radial segments. The degree of thallium uptake (%uptake) was determined by calculating the ratio of the highest count per pixel along each radial segment to the highest count in the left ventricle (%). The washout rate (WR) for each radial segment was also calculated according to the following equation; WR=(counts in early scan—counts in delayed scan)/ (counts in early scan)×100. Then they were shown in a Bull's eye map with a color display,[5] and LAD, LCX, or RCA territory was determined as shown in Fig. 2-a. The normal limit was defined as the one or two standard deviations (SD) below the mean value in each segment derived from the %uptake and WR

of 10 previously studied normal males. The abnormal area which was defined as below the normal limit was blacked out (Fig. 2-b).

Figure 3 shows sensitivity, specificity, and accuracy for detection of each lesion by WR and %uptake in our cases. When the normal limits for mean—SD and mean—2SD were compared, the sensitivity and specificity of each condition always had contrary values. In this study, we used conditions which resulted in greater accuracy than others, as the normal limit. Therefore the normal limit was defined as the mean— 2SD in %uptake analysis, and as the mean—SD in WR.

We compared the detectability of each ischemic lesion among visual evaluation, %uptake analysis, WR analysis, and combination of visual evaluation and WR analysis. With a combination of visual evaluation and WR analysis, when an ischemic coronary lesion was detected either by visual evaluation or by WR analysis, it was defined as a positive result. And when the abnormality was not observed by two analytic methods, it was defined as a negative result.

Statistical analysis
The statistical significance of difference was analyzed by Student's unpaired t-test and chi-square test. A p value less than 0.05 was considered statistically significant.

RESULTS

Clinical data and double product during exercise
Double product (DP) and maximum heart rate (HR) during exercise in the MVD group were much lower than those in the SVD group, and those in the normal coronary group were significantly higher than in the IHD group (Table 2).
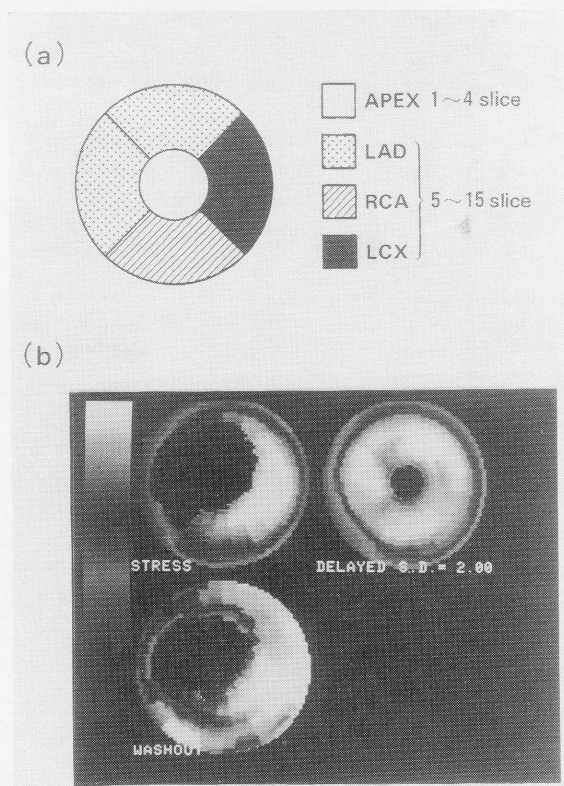
The incidence of electrocardiographic ST-change

Fig. 2 Bull's eye display (%uptake and washout rate). (a) Determination of the coronary territories. (b) An example case; Abnormal area (below the normal limit= mean—2SD) is blacked out at the anteroseptal wall.
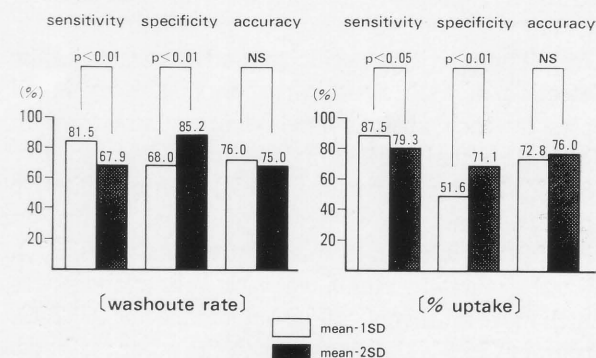

Fig. 3 Sensitivity, specificity, and accuracy for detection of each lesion by WR and %uptake analysis; Comparison of the normal limit defined as mean—1SD and as mean—2SD.

Table 2 Comparison of double product and heart rate

	Double product (DP) (mean±SD)	Heart rate (HR) (mean±SD)
SVD	23,461±5,071	123.2±17.7
DVD	—21,492±5,318 *	—116.0±17.6 **
	**	**
TVD	** 19,720±5,360	** 110.6±16.1
	**	**
Normal	—27,238±3,955	—139.3±21.0

*p<0.05, **p<0.01
SVD: Single vessel disease
DVD: Double vessel disease
TVD: Triple vessel disease

Table 3 Incidence of ST depression or chest symptom at end point

	n	ST depression case (%)	Chest symptom case (%)
SVD	44	32 (72.7)——**——	17 (38.6)
DVD	40	33 (82.5)	28 (70.0) **
TVD	20	17 (85.0)	15 (75.0)
Overall	104	82 (78.8)——**——	60 (57.7)

**p<0.01
Abbreviation as in Table 2.

or chest symptoms during exercise in each group (SVD, DVD, and TVD) is summarized in Table 3. A high incidence of ischemic ST-depressions (0.2 mV or more) was observed in each group, but no statistical difference was noted among the three groups. The incidence of chest symptoms in the SVD group was significantly lower than in the MVD group. Thus, overall sensitivity obtained with electrocardiography and chest symptoms was 78.8% and 57.7%, respectively. But specificity was 35.3% and 94.1%, and accuracy was 72.7% and 62.8%, respectively.

Sensitivity, specificity, and accuracy of each analytic method

Overall sensitivity, specificity, and accuracy in the detection of each stenotic coronary territory in all cases by each analytic method are summarized in Table 4. Visual evaluation was much less sensitive (69.6%) but more specific (84.4%) than quantitative analysis. Thus the accuracy of visual evaluation (75.6%) was similar to quantitative analysis (76%). Visual evaluation combined with WR analysis was much more sensitive (88.0%) but less specific (60.2%), accuracy (76.6%) being similar to the other methods.
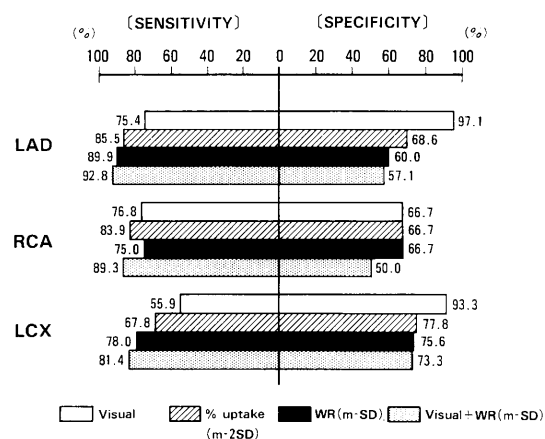
Detection of ischemic lesions of the three major coronary arteries (Fig. 4)
Sensitivity in the detection of ischemic lesion by

Table 4 Comparison of sensitivity, specificity, and accuracy for detection of each stenotic coronary territory by each analytic method

	Visual evaluation	%uptake (mean−2SD)	Washout rate (WR) (mean−SD)	Visual + WR
Sensitivity	69.6%	79.3%	81.5%	88.0%
Specificity	84.4%	71.1%	68.0%	60.2%
Accuracy	75.6%	76.0%	76.0%	76.6%

*p<0.05, **p<0.01

Fig. 4 Sensitivity and specificity in detecting ischemic lesions of the three major coronary arteries.

quantitative analysis was higher than that by visual evaluation. The sensitivity of visual evaluation combined with WR analysis provided the highest value. The sensitivity for LCX lesions by visual evaluation or %uptake analysis was significantly lower than that for LAD or RCA lesions (p<0.05). However, WR analysis improved the sensitivity for LCX lesions, and visual evaluation combined with WR provided sensitivity as high as for LAD and RCA lesions.

The specificity for LAD and LCX lesions by visual evaluation was high (97.1% and 93.3%, respectively), but that for RCA lesions (66.7%) was quite low (p<0.01). The specificity by quantitative analysis for LCX lesions was slightly higher than those for LAD and RCA lesions. Visual evaluation combined with WR analysis gave the lowest specificity for any lesion.

Detection of ischemic lesion in relation to severity of coronary stenosis (Fig. 5 and Fig. 6)
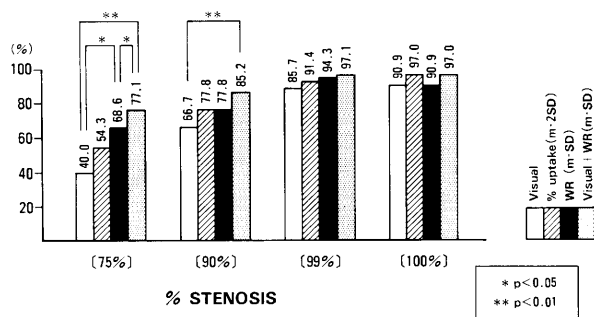The analytical methods were compared for sensitivity

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Fig. 5 Sensitivity in detecting ischemic lesions in relation to the severity of coronary stenosis.
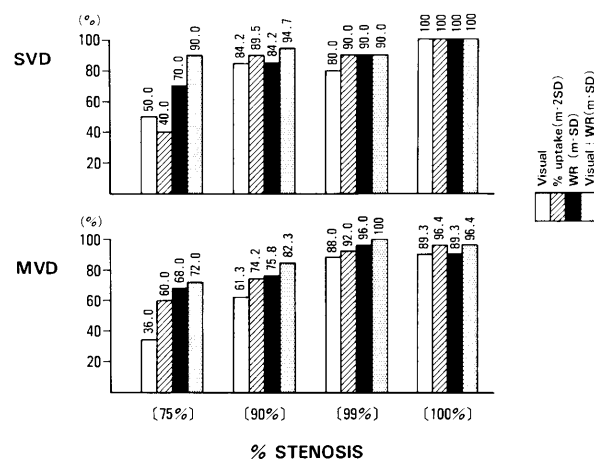
Fig. 6 Comparison of sensitivity in relation to the severity of stenosis in the SVD group and the MVD group.

Fig. 7 Sensitivity in detecting all ischemic lesions in each patient in relation to the number of diseased vessels.

Fig. 8 Sensitivity in detecting each ischemic lesion in relation to the number of diseased vessels.

in the detection of ischemic lesions in relation to the severity of coronary stenosis (Fig. 5). Sensitivity in more than 99% stenosis was very high with any analytic method; in particular 97% sensitivity was obtained with a combination of visual evaluation and WR analysis. Sensitivity in 90% stenosis was 66.7% by visual evaluation and 77.8% by quantitative analysis, whereas visual evaluation combined with WR analysis provided 85.2% sensitivity. On the other hand, sensitivity in 75% stenosis was only 40% by visual evaluation and 77.1% even with a combination of visual evaluation and WR analysis.

Furthermore, sensitivity in SVD and MVD groups was compared (Fig. 6). The results in the MVD group showed a similar tendency in all cases. Sensitivity in 75% and 90% stenosis in the SVD group was higher than in the MVD group for each analytic method. In particular, visual evaluation combined with WR raised sensitivity in the SVD group to 90.0% in 75% stenosis and 94.7% in 90% stenosis.
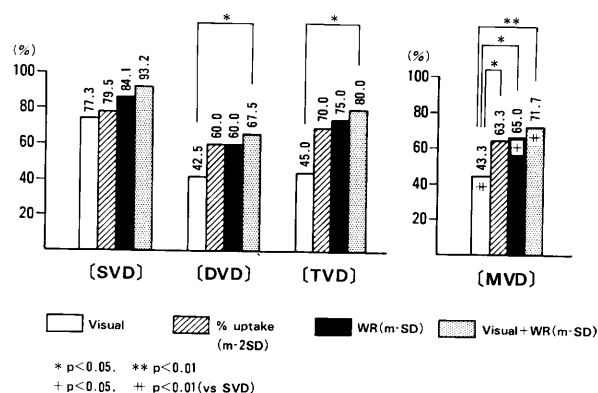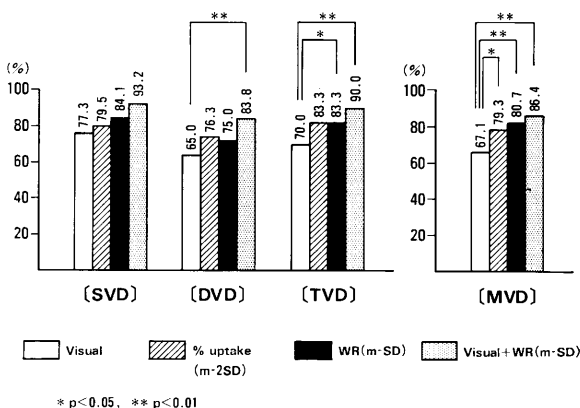
Detection of ischemic lesion in relation to the number of diseased vessels

(1) Detectability of all ischemic lesions in each patient

Only when all ischemic coronary lesions in a patient were detected completely, it was defined as a positive result in that patient. As shown in Fig. 7, sensitivity in the SVD group was high with any analytic method. In the MVD group, however, sensitivity obtained by visual evaluation was lower (43.3%) than by other methods. By visual evaluation combined with WR analysis, sensitivity in the MVD group was increased to 71.7%, but this value was significantly lower than that in the SVD group.

Overall sensitivity in the detection of all ischemic lesions in each patient was 57.7% by visual evaluation, 70.2% by %uptake analysis, 73.1% by WR analysis, and 80.8% by a combination of visual evaluation and WR analysis.

(2) Detectability of each ischemic lesion

When an ischemic coronary lesion was detected, it was defined as a positive result for that lesion. The

analytical methods were compared for sensitivity in detecting each ischemic lesion in relation to the number of diseased vessels, as shown in Fig. 8. In the MVD group, the sensitivity was only 67.1% by visual evaluation, but that was significantly increased by quantitative analysis or by a combination of visual evaluation and WR analysis. The MVD group had slightly lower sensitivity for each method than the SVD group, but there was no statistical difference between them.

DISCUSSION

[201]Tl myocardial scintigraphy is important for the detection of IHD, because this is a specific method which can represent the distribution of the regional myocardial perfusion as a visual image. Recently, quantitative analysis has been introduced to obtain more accurate and detailed information on myocardial perfusion. To use the quantitative analysis adequately, we have to clarify the availability and limitations of the method.

In the present study, we evaluated the two popular quantitative analytical methods, %uptake and WR analysis. Of these two methods, we selected WR analysis to combine with visual evaluation, because WR analysis was more quantitative in detecting regional myocardial ischemia than %uptake analysis which evaluates the relative distribution of myocardial perfusion as well as visual evaluation. The reason for using the Bull's eye display in this study was that it was more suitable for the daily routine procedure. Bull's eye display can represent the whole left ventricular wall in one picture, black out the abnormal regions by selecting normal values, and be managed easily.

Detectability of the lesion vs the number of diseased vessels
In detecting all ischemic lesions in each patient, sensitivity of visual evaluation in the SVD group was as great as in quantitative analysis. Sensitivity in the MVD group was definitely low, but was improved by quantitative analysis or by visual evaluation combined with WR analysis. These results are compatible with several previous reports[9-12] about the availability of quantitative analysis for the MVD group. Visual evaluation may not detect the ischemic lesions if ^{201}Tl uptake is decreased generally in all areas of the myocardium, because it is based on the relative distribution of myocardial perfusion. Therefore, quantitative analysis is a better method in such conditions. However, sensitivity in the MVD group in the present study was only 71.7% even with a combination of visual evaluation and WR analysis, and was definitely low in comparison with the results

in the SVD group. Thirty-seven patients (61.7%) among a total of 60 in the MVD group had undetected lesions in any diseased coronary territory in either visual evaluation or WR analysis. But 30 (81.1%) of these patients had at least one detected lesion. Twenty-six (86.7%) out of these 30 had milder coronary stenosis in undetected lesions than in detected lesions, and 2 patients had similar stenosis in both undetected and detected lesions. During exercise, chest symptoms and ST-depression appeared earlier and DP values were lower in the MVD group. Considering these results, ischemia seemed not to be induced in the regions of milder stenosis (="true negative"), because exercise was stopped when ischemia was induced only in the regions of severer stenosis. However, the results of the present study did not prove CAG to be a perfect standard. It is necessary for FDG as a tracer of glucose metabolism[18] to be more easily utilized as a more suitable standard for ischemia. In addition, the collateral vessels to major diseased coronary arteries developed more in the MVD group than in the SVD group (SVD; 13/44 patients vs MVD; 35/60, p<0.01). Rigo et al[19] reported that non-jeopardized collateral coronary vessels might account for a normal-appearing ^{201}Tl scintigram in segments which were supplied by severely narrowed coronary arteries. We must note as a limitation that these collateral flows lead to negative results in ^{201}Tl scintigraphy.

Detectability of the lesion vs the site of the three major coronary arteries
Sensitivity in detecting LCX lesions by visual evaluation was definitely low, similar to a previous report,[10] because of many anatomical variations and the small area supplied by the LCX arteries. But sensitivity was improved by quantitative analysis or by visual evaluation combined with WR analysis. In the present study, 2 patients with LCX lesions (75% and 90% stenosis) in the SVD group had negative results in the lateral walls in spite of having depressed electrocardiographic ST segments. Both of these patients showed signs of abnormality in the inferior walls. Two patients with LAD and LCX lesions (DVD group) also had positive results not in the lateral walls but in the inferior walls. These 4 patients had non-dominant RCA. These results suggest that although ischemia was actually induced in the inferior wall by LCX lesions in these patients, this ischemia was judged to be an RCA lesion. This might be one cause of the lower specificity for RCA lesions in comparison with LAD or LCX lesions.

Detectability of the lesion vs the severity of coronary stenosis
Sensitivity in detecting the ischemic lesions in milder

coronary stenosis was very low. "True negative" might be observed in regions of milder stenosis in the MVD group, due to ischemia induced in regions of severer stenosis. But even in the SVD group, the sensitivity in 75% stenosis was low in visual evaluation and %uptake analysis. Five of 10 patients in the SVD group in whom no abnormality was detected by visual evaluation had 75% stenosis in one major coronary artery. Although all of them except one LCX patient had neither chest symptoms nor electrocardiographic ST-depression during exercise, the quantity of their stress load was enough (DP was at least 24,638, and HR more than 124/min). These results might be "true negative" due to angiographical overestimation or deficiency of stress. However, the fact that abnormalities in all of them but one were detected by WR analysis suggests that "false negatives" were shown in regions of milder stenosis.

Other limitations and availability

Four patients (75% stenosis in two and 90% stenosis in the other two) in the SVD group showed negative results in WR analysis, although visual evaluation gave positive results. This suggested that diffusely high WR throughout the entire LV wall due to adequate exercise capacity resulted in a "false negative" in these patients. Previous reports[13-15] had indicated that the WR was affected by the quantity of the stress load. This weak point in WR analysis may be eliminated by relative representation of the WR.[15,16] In above 4 patients, all abnormalities could be detected by using relative WR analysis. Considering these results, a combination of the WR as a quantitative analysis and visual evaluation as a qualitative analysis should be a useful method to improve detectability.

In quantitative analysis, as shown in Fig. 3, sensitivity and specificity depend considerably on the normal value range. This is an unavoidable limitation in quantitative methods. Therefore, detection by quantitative analysis only may be biased; so a combination of visual evaluation and WR analysis is suggested to compensate for the weakness involved in using only one of these methods.

In a combination of visual evaluation and WR analysis in the present study, we defined the positive results as the presence of an abnormality by at least one analytical method in order to obtain higher sensitivity. This method is surely the most useful combination to use in a noninvasive screening test. But, because a "negative result" must mean the absence of an abnormality detected by both methods, lower specificity by this method is inevitable (Table 4 and Fig. 4). This lower specificity must be improved by final judgement with other noninvasive studies (echocardiography, electrocardiography, etc.) or with

invasive CAG findings.

There were limitations to the detection of MVD or mildly stenotic SVD lesion even with a combination of visual evaluation and WR analysis. The limitations were not overcome in the present study in which the CAG finding was used as the most acceptable standard. Therefore, in the evaluation of myocardial viability or ischemia, ^{201}Tl scintigraphy should be judged in the light of information provided by other studies.

REFERENCES

1. Pohost GM, Zir LM, Moore RH, et al: Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 55: 294–301, 1977
2. Maddahi J, Garcia EV, Berman DS, et al: Improved noninvasive assessment of coronary artery disease by quantitative analysis of regional stress myocardial distribution and washout of thallium-201. *Circulation* 64: 924–935, 1981
3. Gewirtz H, Palodino W, Sulliran M, et al: Value and limitation of myocardial thallium washout rate in the noninvasive diagnosis of patients with triple-vessel coronary artery disease. *Am Heart J* 106: 681–686, 1983
4. Burow RD, Pond M, Schafter AW, et al: "Circumferential profiles"; A new method for computer analysis of thallium-201 myocardial perfusion imaging. *J Nucl Med* 20: 771–777, 1979
5. Garcia EV, Van Train K, Maddahi J, et al: Quantification of rotational thallium-201 myocardial tomography. *J Nucl Med* 26: 17–26, 1985
6. Matsuda H, Murata H, Toyama H, et al: Development of a new quantitative analysis for thallium myocardial SPECT images; Quantitative STEREO-VIEW method and evaluation of its clinical usefulness. *Jpn J Nucl Med* 26: 845–854, 1989
7. Maeda H, Lee JD, Misawa T, et al: Bull's-eye analyses in polar coordinate. *Jpn J Nucl Med* 25: 759–765, 1988
8. Klein JL, Garcia EV, DePuey EG, et al: Reversibility Bull's-eye map to quantify reversibility of stress-induced SPECT thallium-201 myocardial perfusion defects. *J Nucl Med* 31: 1240–1246, 1990
9. Rigo P, Bailey IK, Griffith LSC, et al: Stress thallium-201 myocardial scintigraphy for the detection of individual coronary arterial lesions in patients with and without previous myocardial infarction. *Am J Cardiol* 48: 209–216, 1981
10. Tamaki N, Yonekura Y, Murai T, et al: Stress thallium-201 transaxial emission computed tomography; Quantitative versus qualitative analysis for evaluation of coronary artery disease. *J Am Coll Cardiol* 4: 1213–1221, 1984
11. Narita M, Kurihara T, Murano K, et al: Quantitative analysis of exercise stress thallium-201 myocardial tomography; The evaluation of Bull's eye map representation for the detection of coronary artery disease.

Jpn J Nucl Med 24: 55–64, 1987

12. Kojima Y, Murata H, Nishimura S: Comparative evaluation of some analysis of stress-redistribution thallium-201 myocardial SPECT for myocardial ischemia. *Jpn J Nucl Med* 24: 1511–1520, 1987

13. Kaul S, Chesler DA, Pohost GM, et al: Influence of peak exercise heart rate on normal thallium-201 myocardial clearance. *J Nucl Med* 27: 26–30, 1986

14. Narita M, Kurihara T, Murano K, et al: Factors affecting myocardial thallium-201 washout rate after exercise stress and their significance for the detection of coronary artery disease. *Jpn J Nucl Med* 25: 141–150, 1988

15. Nakajima K, Muramori A, Taki J, et al: Evaluation of ischemic heart disease by thallium-201 washout-rate map using SPECT. *Jpn J Nucl Med* 26: 617–623, 1989

16. Okuzumi I: Assessment of relative washout rate(rWR) in stress Tl-201 myocardial SPECT. *Jpn J Nucl Med* 26: 329–338, 1989

17. AHA Committee Report: A reporting system on patients evaluated for coronary artery disease. *Circulation* 51: News from the American Heart Association, 1975

18. Camici P, Araujo LI, Spinks T, et al: Increased uptake of ^{18}F-fluorodeoxyglucose in postischemic myocardium of patients with exercise-induced angina. *Circulation* 74: 81–88, 1986

19. Rigo P, Becker LC, Griffith LSC, et al: Influence of coronary collateral vessels on the results of thallium-201 myocardial stress imaging. *Am J Cardiol* 44: 452–458, 1979