Quantitative Assessment of Myocardial $^{99m}$Tc-sestamibi Uptake During Exercise — Usefulness of Response Rate for Assessing Severity of Coronary Artery Disease —

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An increase of $^{99m}$Tc-sestamibi uptake in the myocardium during exercise was defined as a response rate, and the feasibility of a response rate for detecting coronary artery disease (CAD) was tested. Eighty-seven patients with suspected CAD had myocardial perfusion imaging with $^{99m}$Tc-sestamibi during exercise and at rest. A dose of 370 MBq of $^{99m}$Tc-sestamibi was injected at the maximal level of exercise, and a myocardial image was obtained 90 min later (exercise image). Then, 740 MBq of $^{99m}$Tc-sestamibi was administered at rest, and myocardial imaging was repeated (rest image). The exercise and rest images were corrected for physical decay and injected doses, and the exercise image was subtracted from the rest image to obtain the corrected rest image. A response rate was calculated as follows: (exercise image – corrected rest image)×100/corrected rest image (%). The global response rates of 20 patients without significant coronary stenosis ($\leq$50%) were higher than those of 67 patients with significant coronary stenosis (81±33% and 50±28%, p<0.01). Global response rates were correlated with the maximal rate pressure products during exercise ($r=0.56$, p<0.01) and delta rate pressure products ($r=0.53$, p<0.01). Regional response rates in myocardial areas perfused by stenotic coronary arteries of $\leq$50%, 75%, 90% and 99–100% were 60±24%, 56±33%, 40±23%,* and 30±23%,* respectively, (*p<0.01 vs without significant coronary stenosis). The response rates decreased as the severity of coronary artery stenosis advanced, and distinguished between coronary stenoses of graded severity. Accordingly, the response rate from myocardial perfusion imaging with $^{99m}$Tc-sestamibi may provide complementary information to the conventional inspection with myocardial tomography regarding the severity of CAD. (Jpn Circ J 1998; 62: 592–598)

Key Words: Coronary artery disease; Coronary perfusion reserve; Myocardial perfusion imaging; $^{99m}$Tc-sestamibi

Myocardial perfusion imaging with thallium-201 ($^{201}$Tl) or technetium-$^{99m}$ ($^{99m}$Tc)-sestamibi has been widely used as a noninvasive tool for the assessment of coronary artery disease (CAD). However, perfusion imaging sometimes underestimates the multi-vessel involvement of CAD. Such underestimates will occur as a result of the ‘spatially relative’ nature of perfusion imaging. In $^{201}$Tl imaging, to supplement such limitations, slow washout of $^{201}$Tl increased $^{201}$Tl uptake in the lung and transient ischemic dilatation of the left ventricle soon after exercise have been reported as additional markers for assessing severe CAD. However, it has been reported that $^{99m}$Tc-sestamibi washout is not different between the normal and ischemic myocardium and thus the evaluation of washout is considered to be less useful than in $^{201}$Tl imaging. The usefulness of assessing lung uptake and left ventricular cavity dilatation is still controversial in $^{99m}$Tc-sestamibi imaging.

The purpose of the present study was to determine a new marker to supplement perfusion imaging with $^{99m}$Tc-sestamibi. An increase of $^{99m}$Tc-sestamibi uptake in the myocardium during exercise was defined as a response rate. The relation of a response rate to the degree of coronary artery stenosis was examined, and the feasibility of a response rate as an index of the presence and severity of CAD was tested in patients with suspected CAD.

Methods

Subjects and Study Protocol

The subjects consisted of consecutive 87 patients with suspected CAD who were admitted to the Yamagata University Hospital (49 men and 38 women; mean age, 62 years). The exclusion criteria consisted of a previous transmural myocardial infarction, known coronary anatomy, previous percutaneous transluminal coronary angioplasty (PTCA) or coronary aorta bypass grafting (CABG), or refused consent. Myocardial perfusion imaging with $^{99m}$Tc-sestamibi was performed during exercise and at rest. Coronary arteriography was performed in all patients within 1 week following the $^{99m}$Tc-sestamibi imaging. We studied 45 patients with single-vessel disease, 12 patients with double-vessel disease, 10 patients with...
imaging was carried out 90 min after the 99mTc-sestamibi injection. Myocardial perfusion was quantitated and defined as a response to coronary perfusion reserve, and calculated as follows:

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\text{response rate} = \frac{\text{exercise image} - \text{corrected rest image}}{\text{corrected rest image}} \times 100\%.
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A response rate was calculated in each territory of the three major coronary arteries (regional response rate) and in the entire left ventricle (global response rate) (Fig 2).

Image Interpretation: The myocardial distribution of 99mTc-sestamibi was analyzed in the 3 standard orthogonal tomographic imaging planes as follows: the anterior, septal, inferior and lateral regions in the short axis view; the anterior, apical, and inferior regions in the vertical long axis view; and the septal, apical, and lateral regions in the horizontal long axis view. The left ventricle was divided into 10 segments by splitting the anterior, septal, inferior and lateral walls into basal and middle segments, including 2 extra segments for the apex. Each segment was assigned to the vascular territories of the 3 major coronary arteries as follows: the anterior, septal, and apical segments corresponded to the left anterior descending artery, the inferior to the right coronary artery and the lateral to the left circumflex artery. However, the apical segments were often included in the right coronary artery territory because of the variability in vascular supply. The image was interpreted by 2 independent observers who were unaware of the clinical history and angiographic findings of the patients. A 5-point scoring system was used for evaluating the regional myocardial uptakes of the tracer:

- 4 = normal
- 3 = slightly reduced
- 2 = moderately reduced
- 1 = severely reduced
- 0 = no activity

An increase of 1 or more than 1 of the segmental scores in the rest image was considered an ischemic response.

Response Rate and Hemodynamic Variables

We investigated the relation between the maximal rate pressure products during exercise and global response rates. The delta rate pressure products were defined as the difference of rate pressure products between maximal exercise and rest, and the association between the delta rate pressure products and global response rates was also evaluated.

The patients without significant coronary artery stenosis were divided into two groups according to the maximal rate pressure products achieved during exercise: group 1 with rate pressure products of more than or equal to 30,000 (n=10) and group 2 with rate pressure products of less than 30,000 (n=10). Regional response rates were compared with coronary arteriographic findings in both groups and in patients with significant coronary stenosis.

Quantitative Assessment of 99mTc-Sestamibi Uptake

Data Acquisition and Processing: Myocardial perfusion imaging with 99mTc-sestamibi during exercise and at rest was performed using a 1-day protocol (Fig 1). All cardiovascular medications were discontinued at least 24 h before the exercise testing. A symptom-limited maximal treadmill exercise test was performed using the Bruce protocol. Blood pressure was measured every minute in the left arm by the cuff method, and electrocardiograms were constantly monitored during the test. At the peak level of exercise, a dose of 370 MBq of 99mTc-sestamibi was injected intravenously, and the exercise was continued for 90 sec. The exercise test was performed using the Bruce protocol. A symptom-limited maximal treadmill exercise test was performed using the Bruce protocol. At the peak level of exercise, a dose of 370 MBq of 99mTc-sestamibi was injected intravenously, and the exercise was continued for 90 sec after the 99mTc-sestamibi injection. Myocardial perfusion imaging was carried out 90 min after the 99mTc-sestamibi injection to obtain the exercise image. After the data acquisition of the exercise image, 740 MBq of 99mTc-sestamibi was administered at rest, and myocardial imaging for the rest image was repeated 90 min later. The injected dose of 99mTc-sestamibi was calculated by a radioisotope dose calibrator (Capintec CRC-15R) as the difference between the amount of radioactivity of the syringe before and after injection. All images were obtained on a rotating gamma camera (Multispect 3, Siemens) equipped with a parallel-hole, high-resolution collimator as previously described. Seventy-two images were obtained over a 360° arc. Energy discrimination was provided by a 15% window centered at 140 KeV. Each image was accumulated for 40 sec. The data were stored on a 64x64 matrix. Data processing was performed on a nuclear medicine computer system (Icon, Siemens). A series of contiguous transaxial images of 6 mm thickness were reconstructed by means of a filtered back-projection algorithm without attenuation correction. These transaxial images were then reoriented in the short axis, vertical long axis, and horizontal long axis of the left ventricle.

Quantification of Myocardial Images: Circumferential profile analysis was applied to each of the short axis slices from the apex to the base as previously described. These circumferential profiles were plotted in polar coordinates and arranged into a bull's eye map. These images were then reoriented in the short axis view; and the septal, apical, and lateral regions in the vertical long axis view; and the septal, apical, and lateral regions in the horizontal long axis view. The left ventricle was divided into 10 segments by splitting the anterior, septal, inferior and lateral walls into basal and middle segments, including 2 extra segments for the apex. Each segment was assigned to the vascular territories of the 3 major coronary arteries as follows: the anterior, septal, and apical segments corresponded to the left anterior descending artery, the inferior to the right coronary artery and the lateral to the left circumflex artery. However, the apical segments were often included in the right coronary artery territory because of the variability in vascular supply. The image was interpreted by 2 independent observers who were unaware of the clinical history and angiographic findings of the patients. A 5-point scoring system was used for evaluating the regional myocardial uptakes of the tracer:

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Fig 1. A 1-day protocol of myocardial perfusion imaging with 99mTc-sestamibi. An increase of myocardial 99mTc-sestamibi uptake during exercise was quantitated and defined as a response rate.
Coronary Arteriography

Selective coronary arteriography was performed in multiple projections using the standard Judkins technique. After visual inspection of the coronary angiograms in all views, the frame of optimal clarity was selected, showing lesion at maximal narrowing and arterial silhouette in sharpest focus. The images were analyzed by an experienced cardiologist blinded to the patients clinical data and scintigraphic results. The severity of coronary stenosis was measured with calipers and expressed as a percentage of lumenal diameter reduction according to the American Heart Association (AHA) criteria. Coronary stenoses were measured in 10 patients by the same observer on a separate day to determine intraobserver variability and were also...
calculated by a second observer to obtain interobserver variability. The measurement of coronary stenoses was highly reproducible in repeated analysis by the same observer ($r=0.95$, $p<0.01$) and between the two independent observers ($r=0.92$, $p<0.01$). Coronary stenoses exceeding 50% of the normal lumen diameter were considered significant.

**Statistics**

Data were reported in mean±1 standard deviation. The unpaired t test and one-way ANOVA followed by the Scheffe’s F test were used for statistical analysis. Linear regression analysis was applied to study the relationship between response rate and rate pressure products. Intra- or interobserver variability was also assessed by linear regression analysis. A p-value < 0.05 was considered significant.

**Results**

**Case Presentation**

Fig 2 shows myocardial perfusion images with $^{99m}$Tc-sestamibi of a patient with normal coronary arteries. Tomographic images during exercise and at rest were normal, and regional response rates were 87%, 88% and 92% in the territories of the left anterior descending artery, right coronary artery and left circumflex artery, respectively.

Myocardial images with $^{99m}$Tc-sestamibi of a patient with angina pectoris are shown in Fig 3. This patient had a coronary stenosis of 99% in the left anterior descending artery. Transient ischemic perfusion abnormalities were observed in the anterior, septal and apical segments on tomographic images. Regional response rates in areas perfused by the left anterior descending artery, right coronary artery and left circumflex artery were 36%, 58% and 66%, respectively.

Fig 4 shows myocardial images with $^{99m}$Tc-sestamibi of a patient with triple-vessel CAD. In this patient, the right coronary artery was occluded, and the left anterior descending artery and the left circumflex artery had stenoses of 75% and 90%, respectively. On the tomographic images, visual inspection revealed the ischemic reversible perfusion abnormality in the myocardium perfused by the right coronary artery. Perfusion abnormality was not detectable in the areas perfused by the left anterior descending artery and left circumflex artery. However, response rate images show diffuse abnormalities in all 3 vascular territories.

**Global Response Rate and Hemodynamic Variables**

Patients without significant coronary stenosis achieved higher rate pressure products during exercise than patients with significant coronary stenosis (29,613±5,212 vs 24,603±5,963 mmHg × beats/min, $p<0.01$).

Response rates were higher in patients without significant coronary stenosis than in those with significant coronary stenosis (81±33% and 50±28%, $p<0.01$). As shown in Fig 5, there was a positive correlation between the maximal rate pressure products during exercise and response rates ($r=0.003x–17.17$, $r=0.56$, $p<0.01$). Response rates also correlated with the delta rate pressure products ($r=0.003x+12.64$, $r=0.53$, $p<0.01$).

**Regional Response Rate and the Severity of Coronary Stenosis**

Regional differences in the response rates in patients without significant coronary stenosis were examined. Response rates in the regions of the left anterior descending artery, right coronary artery and left circumflex artery were 83±33%, 78±33% and 79±31%, respectively. There were no differences in response rates between the vascular territories.

The patients of group 1 achieved higher rate pressure products than those with significant coronary stenosis (33,565±1,879 vs 24,603±5,963 mmHg × beats/min, $p<0.01$). The patients of group 2 exercised to the same rate pressure products as those with significant coronary stenosis (25,660±4371 vs 24,603±5,963 mmHg × beats/min, $p=ns$). As shown in Fig 6, regional response rates in the myocardial regions in groups 1 and 2 and perfused by coronary stenoses of $\leq 50\%$, 75%, 90%, and 99–100% were 96±37%, 65±16%, $* 60±24%,* 56±33%,* 40±23%,”* and 30±23%,”* respectively, (*$p<0.01$ vs group 1 and ”$p<0.01$ vs group 2). As the severity of coronary stenosis advanced, the response rates decreased. Response rates in areas with coronary stenosis of 90% and 99–100% were significantly lower than those in group 2, although there were no differences in maximal rate pressure products between the patients with significant coronary stenosis and group 2.

**Detection of Coronary Artery Disease**

We then determined the normal range of the response rate. The lower limit of response rate was defined as 48% (mean–1 standard deviation in patients without significant...
coronary stenosis).

In patients with significant coronary stenosis, a total of 201 segments were analyzed for regional response rate, whereas a total of 670 myocardial segments were visually inspected on tomographic images. Sensitivity and specificity to detect significant coronary stenosis of more than 50% were 65.7% and 67.6%, respectively, for the response rate, and 56.6% and 93.1%, respectively, for the visual inspection. In patients with multi-vessel disease, sensitivity to detect multi-vessel involvement was 54.5% for the response rate and only 31.8% for the visual inspection (Table 1), whereas specificity was 75.4% for the response rate and 87.7% for the visual inspection. Superiority of the response rate for detecting multi-vessel involvement was mainly due to the correct assessment of perfusion abnormality in the lateral wall. Out of 22 patients with multi-vessel disease, 15 patients had coronary stenosis in the left circumflex artery. However, the visual inspection failed to detect hypoperfused myocardium in the lateral wall in 13 of the 15 patients (87%).

**Discussion**

In the present study, the response rate was determined as the increase of myocardial 99mTc-sestamibi uptake during exercise. Response rates were correlated with the maximal rate pressure products during exercise and delta rate pressure products, and had an inverse correlation with the degree of coronary stenosis.

**Supplementary Markers for Assessing Coronary Artery Disease in Perfusion Imaging**

Perfusion imaging with 201Tl or 99mTc-sestamibi has been accepted widely as a useful tool for the noninvasive diagnosis of CAD.

In patients with multi-vessel CAD, homogeneous reduction of tracer uptake sometimes fails to detect all hypoperfused myocardial regions and results in an underestimation of multi-vessel coronary involvement. Such underestimates will occur as a result of the ‘spatially relative’ nature of perfusion scintigraphy. It is important to identify patients with multi-vessel coronary disease because they carry a high risk for future cardiac events. In 201Tl scintigraphy, to overcome such limitations, the additional analysis of 201Tl washout, lung 201Tl uptake, and transient cavity dilatation of the left ventricle have been utilized for the detection of advanced CAD. A pattern of diffuse slow washout of 201Tl has been demonstrated in patients with left main or triple-vessel CAD. However, the washout of 99mTc-sestamibi is not used in routine 99mTc-sestamibi imaging because a second injection of 99mTc-sestamibi is necessary for imaging at rest. In addition, it has been reported that 99mTc-sestamibi washout is not different between the normal and ischemic myocardium. The presence of increased lung 201Tl activity immediately postexercise is noted in patients with extensive CAD. Increased lung 201Tl uptake after exercise has been correlated with an increase in pulmonary capillary wedge pressure and suggests the development of left ventricular dysfunction due to exercise-induced myocardial ischemia. Although Giubbini et al have shown that 99mTc-sestamibi lung uptake after exercise is significantly higher in patients with left ventricular dysfunction than in normal subjects, Hurwitz et al have demonstrated that increased pulmonary uptake may be more difficult to apply with 99mTc-sestamibi than with 201Tl imaging. Whether lung uptake of 99mTc-sestamibi is useful or not for assessing extensive CAD is still controversial. Transient ischemic cavity dilatation of the left ventricle in 201Tl imaging has been reported in patients with severe CAD. This left ventricular cavity dilatation is considered to reflect a diffuse subendocardial hypoperfusion induced by dipyridamole or exercise. Mazzanti et al have documented that the assessment of transient ischemic dilatation of the left ventricle on poststress images obtained 15 min after 99mTc-sestamibi administration is essentially as useful as on 201Tl images. However, in that report the 99mTc-sestamibi imaging...
carried out 15 min after the injection was not standard, because data acquisition should be delayed after the injection of $^{99m}$Tc-sestamibi to decrease subdiaphragmatic activity.

Response Rate and the Severity of Coronary Artery Disease

$^{99m}$Tc-sestamibi distributes in the myocardium in proportion to coronary blood flow, and its washout after exercise in both normal and ischemic myocardium is constant. Thus, myocardial perfusion at the time of injection can be estimated by $^{99m}$Tc-sestamibi. In the present study, an increase of $^{99m}$Tc-sestamibi uptake during exercise was quantitated, and the response rate was proposed as a marker of coronary perfusion reserve. Quantitative assessment of myocardial $^{99m}$Tc-sestamibi uptake during exercise has been previously documented by Buell et al. However, they did not report on the clinical feasibility and diagnostic accuracy of their method. In the present study, we examined the clinical feasibility of the response rate in the prospective patient population with suspected CAD and found the clinical usefulness of this method for the noninvasive diagnosis of CAD.

The mean response rate of patients without significant coronary stenosis was 81±33%, and this indicates that myocardial uptake of $^{99m}$Tc-sestamibi was increased during exercise. Because myocardial uptake of $^{99m}$Tc-sestamibi is proportional to the ratio of coronary blood flow to cardiac output, the increase in the myocardial uptake of $^{99m}$Tc-sestamibi during exercise indicates that coronary blood flow increases to a larger extent than cardiac output. Response rate showed a positive correlation with the maximal rate pressure products and delta rate pressure products. Regional response rate was low in myocardial areas perfused by a stenotic coronary artery. Response rates in myocardial areas perfused by a stenotic coronary artery of 90% and 99–100% stenosis were significantly lower than those in group 2 ($p<0.01$), although there were no differences in rate pressure products between the patients with significant coronary stenosis and group 2. Because coronary perfusion reserve decreases as the post-stenotic pressure falls, myocardial uptake of $^{99m}$Tc-sestamibi may decrease in regions with coronary artery stenosis. As shown in Fig 6, response rates had an inverse correlation with the degree of coronary stenosis.

Study Limitations

Although various supplementary markers in $^{201}$Tl imaging have been proposed for assessing CAD, we did not perform $^{201}$Tl perfusion imaging in the present study; thus we could not compare the findings of $^{99m}$Tc-sestamibi with those of $^{201}$Tl.

Regional response rates showed a substantial overlap between normal and abnormal because of the wide standard deviations. This may be explained by the fact that response rates are influenced not only by coronary stenosis, but also by biological tracer washout, extraction fraction of the tracer, the cardiac output and the rate pressure products achieved during exercise.

Conclusion

The response rate is decreased as the severity of coronary artery stenosis advances, and it can distinguish between coronary stenoses of graded severity. Thus, the additional analysis of the response rate may provide complementary information concerning the presence and severity of CAD to conventional myocardial perfusion imaging with $^{99m}$Tc-sestamibi.

References
