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Assessment of contractile response to dobutamine stress by means of ECG-gated myocardial SPECT: Comparison with myocardial perfusion and fatty acid metabolism

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The present study assessed left ventricular performance during dobutamine stress measured using gated SPECT, and compared the results to myocardial perfusion and fatty acid metabolism. ***Methods:*** Thirty-six patients with myocardial infarction given ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin were examined by gated SPECT at rest and during dobutamine stress (4–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$). After acquiring data at the highest dose, ^{201}TlCl was injected and dual-isotope SPECT was performed to assess myocardial ischemia. Thirty of 36 patients also underwent myocardial SPECT with ^{123}I-BMIPP. Regional wall motion changes during dobutamine infusion were determined from the gated SPECT data and classified as: (1) Improvement, (2) Worsening, (3) No change, and (4) Biphasic response. For myocardial segments of each infarct area, stress ^{201}Tl, rest ^{99m}Tc and ^{123}I-BMIPP uptakes were graded on a five-point scoring system of defects from 0 (normal) to 4 (grossly defective). ***Results:*** Rest ^{99m}Tc defect score index (DSI) in No change area was significantly higher than that in Biphasic area. The ΔDSI (stress ^{201}Tl – rest ^{99m}Tc) in Biphasic area was significantly higher than those in Improvement and No change areas. The ΔDSI (BMIPP – ^{99m}Tc) in Worsening area tended to be higher than that in No Change area. ***Conclusions:*** Regional contractile response to dobutamine stress analyzed by gated SPECT showed that the response in myocardial infarct areas could be classified by rest and stress myocardial perfusion and BMIPP accumulation.

Key words: dobutamine, gated SPECT, myocardial infarction, fatty acid metabolism

INTRODUCTION

MYOCARDIAL HIBERNATION is a condition of chronic left ventricular dysfunction that is associated with severe coronary artery disease. Significant recovery of function, however, can be obtained with revascularization. Dobutamine stress echocardiography[1–3] is a widely available, relatively cheap method for detecting myocardial ischemia, which is thought to be capable of discerning viable myocardium in myocardial infarct areas.

On the other hand, technetium-labeled myocardial perfusion tracers, such as ^{99m}Tc-methoxy-isobutyl isonitrile (^{99m}Tc-sestamibi) and ^{99m}Tc-ethylenebis[bis(2-ethoxyethyl)phosphine] (^{99m}Tc-tetrofosmin), enable the simultaneous assessment of myocardial perfusion and left ventricular function by electrocardiography (ECG) gated myocardial perfusion single-photon emission computed tomography (SPECT).[4,5] In one of our previous studies, serial assessment of regional left ventricular function during low- and high-dose dobutamine stress was performed by means of ECG-gated myocardial perfusion SPECT[6] using short-time data collection.[7]

The aim of this study was to characterize the patterns of dysfunctional myocardium by dobutamine infusion assessed by gated SPECT in relation to rest-stress perfusion, and fatty acid metabolism with ^{123}I-labeled 15-(*p*-iodophenyl)-3*R*,*S*-methyl pentadecanoic acid (BMIPP)[8,9] SPECT.

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MATERIALS AND METHODS

Patient Population

Thirty-six consecutive patients with myocardial infarction (30 men and 6 women; mean age of 60 years) were included in the study once informed written consent was obtained. A diagnosis of infarction was established according to clinical, enzymatic, and ECG criteria. There were a total of 43 myocardial infarct areas, and 11 patients (11 infarct areas) had a history of percutaneous coronary intervention. Of these areas, ECG showed Q-waves in thirty-six and non-Q waves in seven. The period between the onset of infarction and SPECT study was 74.4 ± 74.9 days (range, 5 to 247 days). Patients were excluded from this study if they had symptoms of heart failure, severe angina, non-sinus rhythm, severe ventricular arrhythmias, cardiomyopathy, or severe valvular disease. All patients underwent coronary angiography within 2 months (mean interval, 14.3 ± 12.4 days) of SPECT data acquisition. Coronary angiography was performed according to Judkins' technique.

Myocardial Perfusion SPECT during Dobutamine Stress

Thirty min after an intravenous injection of either ^{99m}Tc-sestamibi 600 MBq (n = 28) or ^{99m}Tc-tetrofosmin 740 MBq (n = 8), ECG-gated myocardial perfusion SPECT data collection was performed for 5 min while the patient was at rest. ECG-gated data were acquired using a two-detector gamma camera (VERTEX, ADAC/Philips) equipped with low-energy, general-purpose collimators. The detectors were set up to form a 90° angle (L-shape). Sixteen frames per cardiac cycle were acquired during 180° rotation in a 64 × 64 matrix from the 45° right anterior oblique (RAO) to the 45° left posterior oblique (LPO) projection, with each head performing a 90° rotation. Rapid ECG-gated data acquisition was carried out for 20 sec per step at 6° angular steps in the continuous acquisition mode, so that there was no rotational dead time and the total acquisition time was 5 min.

Intravenous infusion of dobutamine was started with a dose of 4 microgram/kg per min for 8 min by means of an infusion pump system through a peripheral intravenous line. This was followed by doses of 8, 12, 16, and 20 microgram/kg per min, or until limited by symptoms, with increments every 8 min. The criteria for early termination of the dobutamine infusion were a systolic blood pressure ≥210 mmHg, ST segment depression ≥2 mm, supraventricular or ventricular arrhythmias, severe angina, or other intolerable symptoms. ECG-gated rapid SPECT data acquisition was performed again in the last 5 min of each stage during dobutamine infusion. After acquisition of gated SPECT data at the highest dose, 111 MBq of ^{201}TlCl was injected through a second peripheral intravenous line, and dobutamine infusion was continued for an additional one min. Blood pressure, heart rate, and a 12-lead ECG were checked every minute throughout the dobutamine infusion and until the heart rate returned to <100 beats/min and all symptoms disappeared. Approximately 5 to 10 min after the termination, dual-isotope SPECT was also performed to assess myocardial ischemia. Two datasets, stress ^{201}Tl and rest ^{99m}Tc, were obtained in different energy windows (72 keV for ^{201}Tl and 140 keV for ^{99m}Tc), using a symmetrical 20% energy window for both radioisotopes. A dual-isotope SPECT study was performed using the two-detector gamma camera (VERTEX) with the detectors set up to form a 90° angle, a 64 × 64 matrix, a 180° semicircular orbit (RAO 45° to LPO 45°), 36 views, and a 40 seconds per projection data sampling technique. The SPECT data were pre-processed using a Butterworth filter and reconstruction was carried out by the filtered back-projection with a ramp filter.

Myocardial SPECT with I-123-BMIPP

^{123}I-BMIPP (111–148 MBq) was injected into 30 of the 36 patients at rest after a fast of at least 6 hours. Myocardial SPECT data acquisition was started 30 to 40 min after the injection using a three-head gamma camera (PRISM 3000, Philips/Shimadzu), equipped with low-energy, general purpose collimators. The SPECT data were acquired over 360° in 20 (× 3) steps, each of which was 40 seconds in a 64 × 64 matrix and a 15% window centered on the 159 keV photopeak of ^{123}I. The SPECT data were pre-processed with a Butterworth filter and reconstructed by the filtered back-projection. The interval between the dual-isotope SPECT and BMIPP SPECT was 20.3 ± 11.9 days (range from 4 to 45 days), when symptoms and ECG findings remained stable.

Assessment of Myocardial Distribution

On each SPECT image, the left ventricular myocardium was divided into 17 segments[10] as shown in Figure 1. The stress ^{201}Tl, rest ^{99m}Tc-sestamibi (or tetrofosmin), and ^{123}I-BMIPP segmental uptake of each infarct area was graded on a five-point scoring system by two experienced

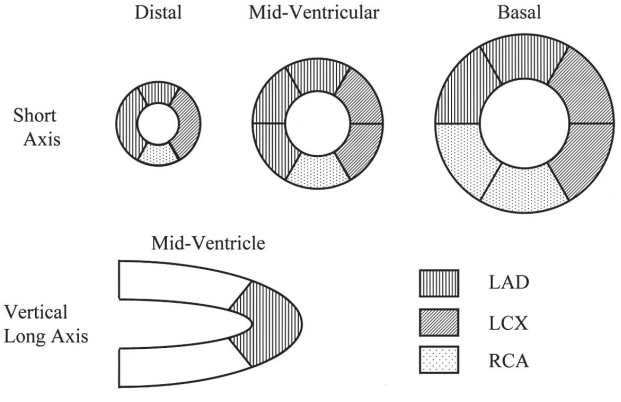

Fig. 1 Assignment of 17 myocardial segments to the three major coronary arteries. LAD, left anterior descending artery; LCX, left circumflex coronary artery; and RCA, right coronary artery.

Table 1 Hemodynamic parameters at rest and under peak dobutamine stress

	Rest	Peak stress	p value
Dobtamine dose (μg/kg per min)		22.8 ± 10.4	
Heart rate (bpm)	64.2 ± 10.5	117.9 ± 19.4	<0.0001
Systolic blood pressure (mmHg)	134.5 ± 16.0	147.2 ± 21.1	<0.01
Double product ($\times 10^3$)	8.6 ± 1.8	17.3 ± 3.6	<0.0001
LVEF (%)	48.9 ± 14.9	59.3 ± 18.8	<0.0001
LVEDV (m*l*)	116.8 ± 57.4	91.9 ± 54.3	<0.0001
LVESV (m*l*)	66.0 ± 54.6	45.0 ± 51.2	<0.0001
Stroke volume (m*l*)	50.8 ± 12.9	46.9 ± 15.3	<0.05

Data are expressed as mean value ± SD.
Double product = Heart rate × Systolic blood pressure, LVEF = left ventricular ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume.

Table 2 Clinical characteristics and coronary angiographic findings grouped according to contractile response during dobutamine stress

	Biphasic	Improvement	Worsening	No change
Number of infarct areas	18	12	6	7
Non-Q wave infarction	4 (22.2%)	3 (25.0%)	0	0
Infarct-related artery				
LAD/RCA/LCX	12/4/2	7/4/1	3/2/1	3/4/0
Degree of stenosis (%)	91.9 ± 9.2	65.3 ± 37.3*	81.7 ± 40.2	74.9 ± 32.2
Less than 50% stenosis	0	3 (25.0%)	1 (16.7%)	1 (14.3%)
Maximum dobutamine dose (μg/kg per min)	21.8 ± 10.0	26.0 ± 12.0	18.3 ± 6.3	22.0 ± 9.5

* $p < 0.05$, compared with Biphasic segments.
LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex coronary artery.

observers after consultation to define normal uptake (defect score of 0), mildly reduced uptake (defect score of 1), moderately reduced uptake (defect score of 2), severely reduced uptake (defect score of 3), or absent uptake (defect score of 4). Defect score index (DSI) in each infarct-related artery was calculated as summed defect score in each infarct area divided by the number of infarct-related segments. As shown in Figure 1, there were eight segments in the left anterior descending artery, five in the left circumflex artery, and four in the right coronary artery, respectively.

Assessment of Left Ventricular Performance during Dobutamine Stress

From the gated SPECT data with ^{99m}Tc-sestamibi (or tetrofosmin), the left ventricular end-diastolic volume (LVEDV; m*l*), end-systolic volume (LVESV; m*l*) and left ventricular ejection fraction (LVEF; %) were calculated automatically using the QGS program™ (Cedars-Sinai Medical Center).[11,12] With the QGS program, the left ventricular endocardial surface and volume were determined for all gating intervals in the cardiac cycle. For visual assessment of left ventricular regional wall motion, cine-displays of left anterior oblique and left lateral views of each patient were created. In each infarct area, regional wall motion of each stage was qualitatively assessed according to the three major coronary regions by two experienced observers, as previously reported.[6] Regional wall motion changes during dobutamine stress were classified into four patterns: (1) (Sustained) Improvement; (2) No change; (3) Worsening, or; (4) Biphasic response, which was defined as improvement at a low dose followed by worsening at a high dose.

Statistical Analysis

All data are expressed as means ± one standard deviation. Paired and unpaired Student's t-tests, as well as the Chi-squared analysis determined differences between proportions. Multiple comparisons were performed with a single-factor analysis of variance (ANOVA). For post hoc analysis Tukey's Honestly Significant Difference test was used. A p value <0.05 was considered significant.

RESULTS

Hemodynamic Response to Dobutamine Stress

Table 1 shows the data for various parameters in patients at rest and under peak dobutamine stress. In the 36 patients studied, significant increases occurred in the heart rate and systolic blood pressure, which peaked at 117.9 ± 19.4

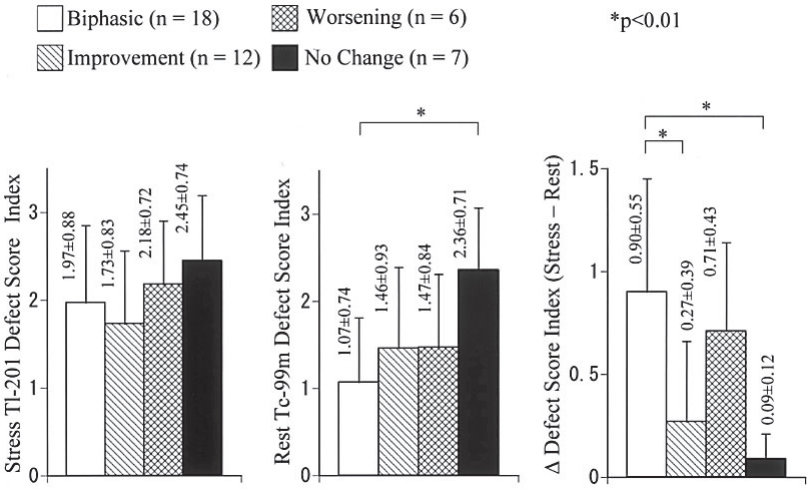

Fig. 2 Comparison of myocardial perfusion grouped according to contractile response during dobutamine stress.

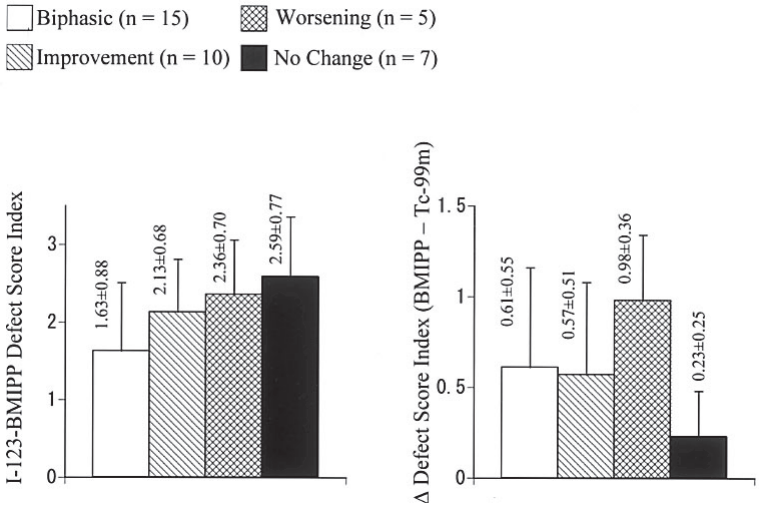

Fig. 3 Comparison of myocardial distribution with I-123-BMIPP grouped according to contractile response during dobutamine stress.

beats/min and 147.2 ± 21.1 mmHg, respectively. The gated SPECT data from rest to maximal stress showed that LVESV decreased ($p < 0.0001$) and LVEF significantly increased ($p < 0.0001$), despite a fall in the stroke volume ($p < 0.05$).

Clinical Characteristics Grouped According to Regional Wall Motion Change

Of the total 43 infarct areas, regional wall motion change was as follows: Biphasic response, 18 (41.9%); Improvement, 12 (27.9%); Worsening, 6 (14.0%); and No change, 7 areas (16.3%). When only 30 patients (37 infarct areas) were examined by BMIPP SPECT, regional wall motion change was Biphasic response in 15, Improvement in 10, Worsening in 5, and No change in 7 areas. Table 2 shows the coronary angiographic findings and clinical characteristics grouped according to the regional wall motion change during dobutamine stress. Non-Q wave infarctions existed in only Biphasic and Improvement areas. On coronary angiography, infarct-related arteries had more severe stenoses in Biphasic segments compared with Improvement area ($p < 0.05$).

Relationship between Myocardial Distribution and Wall Motion Change

The relationship between defect score indices and wall motion change during dobutamine stress is shown in Figures 2 and 3. Rest ^{99m}Tc DSI in No change area was significantly higher than that in Biphasic area ($p < 0.01$). The ΔDSI (stress ^{201}Tl – rest ^{99m}Tc), indicating myocardial ischemia, in Biphasic area was significantly higher than those in Improvement and No change areas (both $p < 0.01$). The ΔDSI (BMIPP – ^{99m}Tc) in Worsening area tended to be higher than that in No Change area, although

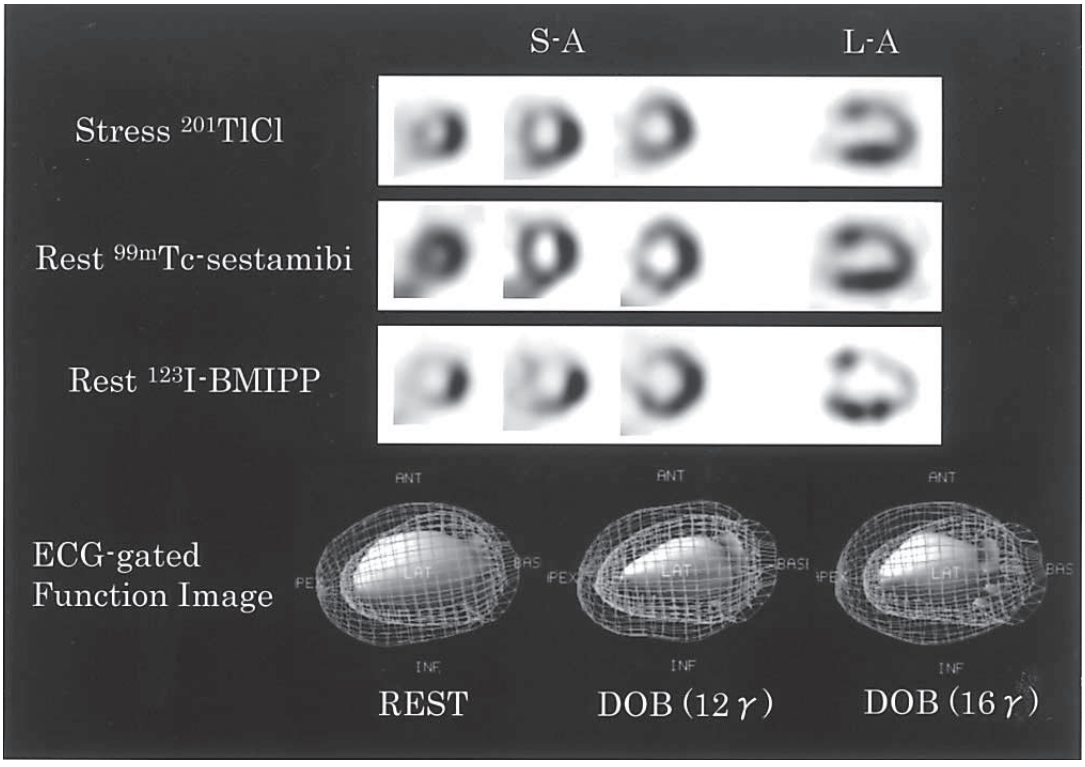

Fig. 4 Short axis (S-A) and vertical long axis (L-A) myocardial SPECT images (*upper*) and left ventricular function images obtained from ECG-gated SPECT at rest and during dobutamine stress (*lower*) of a patient with anterior myocardial infarction. There is a large area of perfusion abnormality involving the anterior and anteroseptal wall on the stress ^{201}TlCl images, which is partially reversible on rest ^{99m}Tc-sestamibi images. The intensity and size of accumulation abnormality are greater on ^{123}I-BMIPP SPECT compared with the perfusion images. The function image (left lateral view) at rest shows severe hypokinesis in the anterior wall. Regional wall motion abnormality in the infarct area fits a biphasic response, which disappears at 12 μg/kg per min of stress, and reappears at 16 μg/kg per min of stress. In the function images, the inner wire cage and the solid surface represent the endocardial surfaces at end-diastole and end-systole, respectively.
DOB, dobutamine; γ, microgram/kg per min

the difference was not statistically significant.

Figure 4 illustrates a patient with myocardial infarction which revealed a biphasic response during dobutamine stress.

DISCUSSION

Assessment of Wall Motion Change during Dobutamine Stress

Dobutamine is a beta-adrenergic agonist with positive inotropic and chronotropic effects. These properties make it suitable for inducing myocardial oxygen demand and provoking myocardial ischemia in cases of coronary stenosis. Recently, administration of dobutamine at low and high doses to patients with myocardial hibernation has unmasked differences in contractile reserve. These differences seem to have significant implications for the prediction of recovery of function after revascularization.[13–18] Four types of responses (i.e. Biphasic response, Sustained improvement, Worsening, and No change) of the dysfunctional myocardium to dobutamine could be differentiated, of which a Biphasic response was the most predictive,[13–15] and a No change pattern was the least predictive of functional recovery. Qureshi et al.[15] evaluated dobutamine stress echocardiography in 34 patients with stable coronary disease, and reported that the positive predictive values of functional recovery were 72% in Biphasic response, 18% in Improvement, 13% in Worsening, and 7% in No change segments. In the present study, regional wall motion changes during low- and high-dose dobutamine stress were analyzed by means of ECG-gated myocardial SPECT as previously reported.[6] The method of dobutamine stress gated SPECT[6,19,20] is highly objective and reproducible, though the protocol is somewhat difficult as compared with dobutamine stress echocardiography.

Relationship between Wall Motion Change and Myocardial Distribution

The rest Tc-99m DSI in Biphasic area was significantly lower than that in No change area. In other words, infarct areas with increased wall motion at low-dose dobutamine infusion had higher myocardial perfusion compared with No change area, consistent with previous observations.[15,16,18] Sawada et al.[21] evaluated myocardial response by low- and high-dose dobutamine stress echocardiography in relation to positron emission tomography using nitrogen-13 ammonia and fluorine-18 fluorodeoxyglucose for imaging of perfusion and metabolism. They showed that a biphasic response to dobutamine was indicative of segments with normal perfusion, suggesting transmural viability, and the presence of severe coronary artery disease, which supports our results.

The ΔDSI (stress ^{201}Tl – rest ^{99m}Tc) in Biphasic area was significantly higher than that in No change area. In other words, infarct areas with decreased wall motion at high-dose dobutamine infusion revealed more severe myocardial ischemia compared with No change areas.[14,17] In Biphasic areas, initial improvement in wall motion probably represents the recruitment of contractile reserve at low-dose dobutamine stress. It follows that with increased dobutamine dose, ischemia ensues, resulting in a renewed worsening of wall motion. However, clear-cut differentiation of the Biphasic area and Improvement area is difficult. It becomes Biphasic area if ischemia occurs at higher dobutamine stress in Improvement area. In the assessment of myocardial viability, some investigators described the usefulness of gated SPECT during low-dose dobutamine stress,[22] except high-dose administration. However, other investigators have demonstrated the incremental value of additional low-dose stages and intermediate doses (15 and 20 microgram/kg per min) for detection of viability.[13,23]

^{123}I-BMIPP is an analogue of 15-(*p*-iodophenyl) pentadecanoic acid (IPPA),[24] with a methyl-branch that has been introduced into the β position of the carbon chain. The initial uptake of BMIPP is largely determined by regional myocardial blood flow. After transport into myocytes through a membrane fatty acid-binding protein, most BMIPP undergoes adenosine triphosphate (ATP)-dependent activation of the native long-chain fatty acids to acyl-coenzyme A.[25] BMIPP retention is affected by regional blood flow, a decreased triglyceride pool, and increased back diffusion due to reduced ATP content under ischemic conditions. Thus, BMIPP distribution may provide comprehensive information about metabolic function in patients with ischemic heart disease.[26–29]

In the present study, the BMIPP DSI in No change and Worsening areas tended to be higher than that in Biphasic area. The ΔDSI (BMIPP – ^{99m}Tc) in Worsening area tended to be higher than that in No change area. Everaert et al.[30] studied regional wall thickening changes in 16 patients with myocardial infarction by means of ECG-gated SPECT during low-dose (10 microgram/kg per min) dobutamine stress and compared with BMIPP SPECT. They showed that an increase or decrease in wall thickening during dobutamine infusion was associated with the presence of a considerable amount of BMIPP mismatched myocardium (discordant between myocardial perfusion and BMIPP distribution), whereas no change in wall thickening was preferentially associated with a BMIPP matched pattern, which supports our results.

In summary, the present results were as follows: Biphasic areas showed mildly reduced rest myocardial perfusion, severe ischemia, and mildly reduced BMIPP uptake; Improvement areas showed moderately reduced rest myocardial perfusion, mild ischemia, and moderately reduced BMIPP uptake; Worsening areas showed moderately reduced rest myocardial perfusion, severe ischemia, and severely reduced BMIPP uptake; and No change areas showed severely reduced rest myocardial perfusion, almost no trace of ischemia, and severely reduced BMIPP uptake.

Study Limitations

Both regional wall motion and myocardial perfusion were assessed visually. In addition, the regional wall motion of each stage was evaluated according to the three major coronary regions, without using segmental analysis. Quantitative segmental analysis was not used because declines in the regional wall motion of a small infarct area are likely to be underestimated due to neighboring normal myocardium. In the usual segmental quantification, therefore, the detectability of wall motion change may be lower than semiquantitative readings of wall motion images in the routinely applied method. Thus, it is critical to establish an optimal method for quantitative analysis.

CONCLUSION

Regional contractile response to low- and high-dose dobutamine stress analyzed by ECG-gated SPECT showed that the response in myocardial infarct areas could be classified by rest and stress myocardial perfusion and ^{123}I-BMIPP myocardial accumulation.

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