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Scintigraphic assessment of regional cardiac sympathetic nervous system in patients with single-vessel coronary artery disease

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In coronary artery disease, the cardiac sympathetic nervous system is closely associated with myocardial ischemia. I-123 metaiodobenzylguanidine (MIBG) imaging allows us to assess the cardiac sympathetic nervous system regionally. One-hundred and eleven patients with single-vessel disease underwent regional quantitative analysis of MIBG imaging before successful percutaneous transluminal coronary angioplasty (PTCA), and repeat angiography 6 months after PTCA. Based on the results of the follow-up left ventriculogram, patients were divided into 3 groups: 39 angina pectoris (AP), 48 prior myocardial infarction without asynergy (MI without asynergy) and 24 prior myocardial infarction with asynergy (MI with asynergy). AP and MI without asynergy had significant correlations between uptake parameters and regional washout in the territory of diseased vessels, among which the severity score in AP was the most closely correlated with regional washout ($r = 0.79$, $p < 0.0001$). These correlations disappeared in MI with asynergy. To compare regional MIBG parameters in the territory of the diseased vessel as well as in the territories of the other major coronary arteries among the 3 groups, we examined MIBG parameters in 57 patients with left anterior descending artery (LAD) disease selected from among the study patients. Regional washout in the territory of the LAD was significantly higher in the MI without asynergy group than in the other two groups. The left circumflex artery (LCX) region showed significantly reduced MIBG uptake and an increased extent score in the MI with asynergy group compared with the AP group, although only a difference in the extent score existed between the MI with asynergy group and the AP group in the right coronary artery (RCA) region. In addition, the global ejection fraction before PTCA showed a significant negative correlation with each regional washout rate. In this way, regional quantitative analysis of MIBG imaging can detect the regional differences in the cardiac sympathetic nervous system in coronary artery disease, which may be associated with the degree of regional left ventricular dysfunction due to myocardial ischemia.

Key words: myocardial ischemia, I-123 metaiodobenzylguanidine scintigraphy, myocardial viability

INTRODUCTION

I-123 METAIODOBENZYLGUANIDINE (MIBG) has been developed as a tracer which shares the same uptake and storage mechanisms as norepinephrine at presynaptic sites, whose imaging allows us to assess, noninvasively and regionally, the sympathetic nervous function in the human heart. Since myocardial ischemia damages sympathetic nerve fibers and severer or more prolonged myocardial ischemia results in sympathetic denervation, a large number of investigators[1–13] have attempted to assess sympathetic nervous function or to detect myocardial ischemia in coronary artery disease with MIBG imaging. Among them, some[3,4] have reported that sympathetic nervous tissue damage is more extensive than myocardial tissue damage, and others[5] have demonstrated that after myocardial infarction, sympathetic denervation of viable myocardium shows signs of denervation supersensitivity

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which is related to vulnerability to lethal arrhythmias. Cardiac sympathetic nervous function in coronary artery disease has therefore been shown to be closely associated with myocardial ischemia. Nevertheless, it has been difficult to assess the cardiac sympathetic nervous system in coronary artery disease with MIBG imaging since the severity of sympathetic nervous damage depends upon the degree of myocardial ischemia. In addition, patients with coronary artery disease often have complications, some of which affect other aspects of the cardiac sympathetic nervous system, such as hypertension,[14] diabetes mellitus,[15] and heart failure.[16] These diseases lead to a further difficulty when interpreting the MIBG findings, because the enhanced sympathetic nervous system, sympathetic dysfunction and denervation could result in decreased MIBG uptake and/or increased MIBG washout. Furthermore, it is unclear if there are any regional relationships between MIBG parameters and left ventricular dysfunction due to myocardial ischemia, although global MIBG parameters have been shown to be associated with global left ventricular function.[10,11] Therefore, for a better understanding of the cardiac sympathetic nervous system in coronary artery disease by means of MIBG imaging, it is important to investigate the regional relationships between MIBG uptake and MIBG washout in each territory of the coronary arteries.

To investigate the cardiac sympathetic nervous system in coronary artery disease, we performed regional quantitative analysis of MIBG imaging in patients with single-vessel coronary artery disease and examined the relationships between the MIBG parameters before percutaneous transluminal coronary angioplasty (PTCA) and the response of resting left ventricular asynergy to PTCA.

METHODS

Patients

Between April 1995 and September 1997, we selected 147 stable coronary artery disease patients who had coronary artery stenosis (≥ 75%) of the proximal portion of one of the 3 major epicardial coronary arteries on diagnostic coronary angiography and were already scheduled to undergo PTCA. They underwent MIBG imaging within 1 week before PTCA. About 6 months after the first PTCA, they were also scheduled to undergo repeat coronary angiography and left ventriculography. All the patients were given oral antianginal drugs including isosorbit dinitrate, calcium antagonists and antiplatelet drugs, but no patient received beta-blockers or antidepressants during the present study.

Informed consent was obtained from each patient. This study protocol was approved by the hospital's ethics committee.

Coronary angiography and left ventriculography

Diagnostic coronary angiographies before (n =147) and 6 months (n = 119) after the first PTCA were performed by the standard Judkins technique in all patients, as described previously.[17,18] The results of coronary angiography after injection of nitroglycerin were classified according to the reporting system of the American Heart Association. Biplane left ventriculography was also performed in the 30 degree right anterior oblique and 60 degree left anterior oblique projections and recorded at 60 frame/sec. The global left ventricular ejection fraction (EF) was calculated by tracing contours of the 30 degree right anterior oblique ventriculogram with the centerline method.

PTCA

PTCA was performed by the percutaneous femoral approach. After intravenous injection of 10,000 IU heparin at the time of arterial access, sublingual nitroglycerin (0.3 mg) and nifedipine (10 mg) were routinely administered. Control coronary angioplasty was performed in several projections with an 8F catheter (Cordis). Balloon sizes were chosen to approximate the diameter of the adjacent normal arterial segment. Balloon inflations for 60–120 seconds were performed at pressures raging from 4 to 10 atm. After coronary angioplasty, coronary angiography was performed in views nearly identical to those used before angioplasty.

Successful coronary angioplasty was defined as less than 50% residual stenosis at the site of the original stenosis. Restenosis was defined angiographically as ≥ 75% of luminal diameter at the target lesion.

Analysis of regional wall motion on the left ventriculogram

The left ventriculogram was divided into 7 segments (LAD territory; segments 1, 2, 3 and 6, LCX territory; segments 2 and 7, RCA territory; segments 4, 5 and 7) according to the American Heart Association classification. Two independent observers analyzed segmental wall motion. In cases of disagreement, consensus was established with a third observer.

A segment with asynergy was defined as a segment showing akinetic or dyskinetic wall motion including aneurysmal changes. If there was at least one asynergic segment in the territory of the diseased vessel at the repeat left ventriculography 6 months after PTCA, a patient was included in the asynergy group. In this study there was no disagreement between observers concerning asynergic or dyskinetic wall motion.

MIBG scintigraphy

All patients underwent MIBG imaging in the early morning, 24 hours after discontinuing antianginal drugs except sublingual nitroglycerin. A dose of 111 MBq of commercially available MIBG (Daiichi Radioisotopes Labs. Ltd., Tokyo, Japan) was administered intravenously. Cardiac images were acquired 15 minutes (initial image) and 3 hours (delayed image) after the injection of MIBG, using

a three-head gamma camera (Toshiba GCA 9300A/HG, Tokyo, Japan), with 120 degrees rotation per head, 3° increments, 30 seconds per step, and a 128 × 128 matrix. The data were reconstructed by filtered-back projection (Shepp-Logan) on a Toshiba GMS 5500A system. Neither scatter correction nor attenuation correction was performed.

Analysis of MIBG imaging

Regional quantitative analysis of MIBG uptake and washout rate in the left ventricle was performed. In the present study, the severity score and extent score of myocardial denervation were calculated as follows: Severity score = the difference between the normalized maximal counts per point in the abnormal area of the MIBG uptake and the corresponding lower normal limits/the total number of left ventricular points. The extent score (%) = the number of points falling below the corresponding lower normal limits/the total number of left ventricular points × 100. The normal polar map was generated from age-, and gender-matched normal subjects.[17] Regional quantitative analysis of the washout rate of MIBG was also performed. On a bull's-eye representation, the territory in each of the 3 major coronary arteries was defined as described previously.[17,18]

Statistical analysis

Data are expressed as the mean ± SD. A linear regression analysis was carried out between regional MIBG %uptake, extent score, severity score, EF and regional washout rate. Chi-squared test or Fisher's exact test was used to determine the significance of differences in the occurrence rates observed. Comparisons among 3 groups were performed by ANOVA followed by the Bonferroni multiple comparison test. Probability values of less than 0.05 were considered significant.

Table 1 Group characteristics

Group	AP	MI without asynergy	MI with asynergy
Number	39	48	24
male/female	25/14	33/15	18/6
Age (years)	64 ± 6	63 ± 8	61 ± 8
BMI	23 ± 4	22 ± 7	23 ± 6
Smoking	15	22	10
DM	6	8	5
HT	8	10	5
EF (%) before PTCA	63 ± 9	58 ± 7#	53 ± 8*
EF (%) after PTCA#	64 ± 5	59 ± 5	51 ± 7
Location of diseased artery			
LAD	18	27	12
LCX	9	6	3
RCA	12	15	9

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HT, hypertension; EF, ejection fraction; PTCA, percutaneous transluminal coronary angioplasty, LAD; left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. EF after PTCA showed a significant difference ($p < 0.005$) between-groups. *$p < 0.0001$, #$p < 0.005$ compared with the value of the AP group.

RESULTS

Patient population

A total of 147 patients were enrolled, but 36 were excluded for the following reasons: six patients had an unsuccessful PTCA and 24 patients had restenosis detected within 6 months after the first PTCA or at the repeat coronary angiography. In addition, 6 patients refused to undergo repeat coronary angiography. The remaining 111 patients (76 male and 35 female; mean age 63 ± 7 years) completed the study. No patient, in the study, had lethal arrhythmias before or after PTCA. Among the 111 patients, 72 had prior myocardial infarction, which was diagnosed by the clinical history of myocardial infarction and/or the presence of abnormal Q waves on ECG.

Improvement of asynergy after PTCA

On diagnostic angiography before PTCA, 4 angina pectoris patients (5 segments) without prior myocardial infarc-

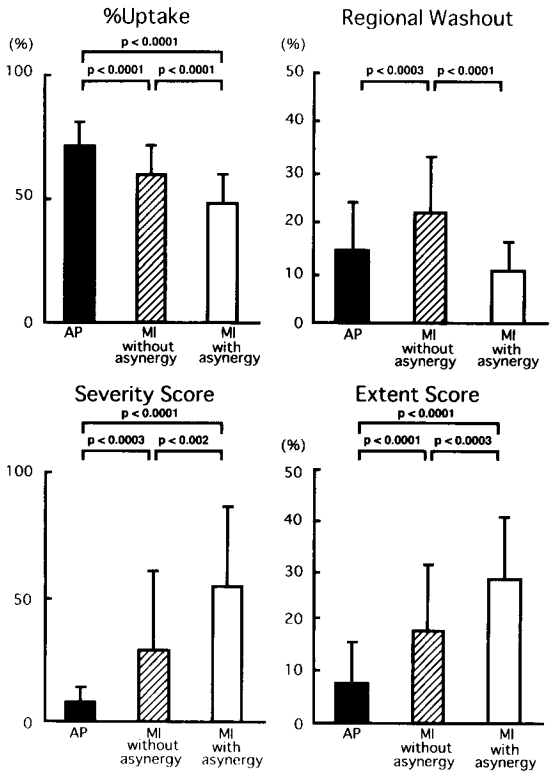

Fig. 1 Comparison of MIBG parameters including MIBG % uptake, severity and extent scores, and regional washout among 39 angina pectoris patients, without prior myocardial infarction group (AP); 48 prior myocardial infarction patients, without asynergy group (MI without asynergy); and 24 prior myocardial infarction patients, with asynergy group (MI with asynergy). Values are expressed as mean ± SD.

Table 2 Comparison of MIBG parameters between the territories in the diseased vessel (LAD) and the other coronary arteries

Group	AP	MI without asynergy	MI with asynergy
Number	18	28	11
male/female	12/6	22/6	7/4
Age (years)	64 ± 7	63 ± 8	61 ± 8
BMI	23 ± 6	23 ± 5	23 ± 8
Smoking	8	14	4
DM	4	6	3
HT	5	7	3
EF (%) before PTCA	63 ± 10	56 ± 8*	50 ± 10*
EF (%) after PTCA*	64 ± 5	58 ± 5	47 ± 9
<LAD regions>			
% uptake	74.4 ± 6.4	60.1 ± 16.6	44.7 ± 8.1
Severity score	8.2 ± 10.8	40.1 ± 40.3	76.9 ± 31.1
Extent score	9.7 ± 8.7	23.4 ± 12.5	36.3 ± 8.9
Regional washout	10.9 ± 9.8	22.1 ± 11.5	12.2 ± 6.2
<RCA regions>			
% uptake	69.7 ± 6.9	64.9 ± 9.8	63.0 ± 11.6
Severity score	3.9 ± 6.1	8.6 ± 10.6	10.6 ± 9.4
Extent score	4.5 ± 6.0	7.4 ± 6.2	10.6 ± 7.5#
Regional washout	13.4 ± 9.7	18.8 ± 12.0	13.5 ± 15.4
<LCX region>			
% uptake	76.0 ± 10.9	67.9 ± 14.5	60.0 ± 13.1*
Severity score	9.6 ± 15.1	20.3 ± 23.1	18.0 ± 8.7
Extensive score	8.0 ± 8.9	12.7 ± 8.8	18 ± 8.7*
Regional washout	15.5 ± 11.7	24.9 ± 13.9#	27.0 ± 10.2#

Abbreviations as in Table 1. #$p < 0.05$ and *$p < 0.005$ compared with the values of the AP group. EF after PTCA showed a significant difference ($p < 0.005$) between-groups.

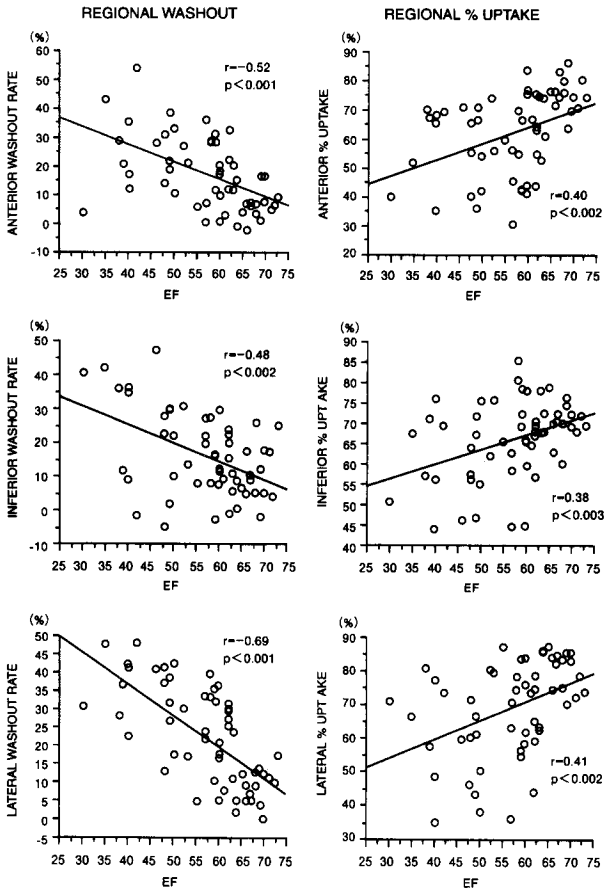

Fig. 2 Correlations between ejection fraction (EF) before percutaneous transluminal coronary angioplasty (PTCA) and regional washout and MIBG % uptake in the LAD single vessel disease.

tion and 41 patients (73 segments) with prior myocardial infarction showed signs of asynergy. Six months after PTCA, all asynergic segments in the 4 angina pectoris patients without prior myocardial infarction had improved. Of the 73 asynergic segments in 41 patients with prior myocardial infarction, 39 segments had improved. The remaining 34 segments in 24 patients with prior myocardial infarction remained asynergic. Based on the presence of asynergy on the left ventriculogram 6 months after the first PTCA, we divided the 111 study patients into 3 groups: 39 angina pectoris without prior myocardial infarction (AP), 48 prior myocardial infarction patients without asynergy (MI without asynergy) and 24 prior myocardial infarction with asynergy (MI with asynergy). The clinical characteristics of the 3 groups are shown in Table 1. Global EF before and after successful PTCA was significantly improved in the MI without asynergy group ($p < 0.01$), but there was no significant change in global EF in AP and MI with asynergy groups.

MIBG parameters in coronary artery disease

Figure 1 shows MIBG parameters in each group. Percentage uptake in the territory of the diseased vessel was significantly higher in the AP group (71.4 ± 7.5%) than in the other two groups (vs. 59.7 ± 12.5% in the MI without asynergy group, $p < 0.0001$ and vs. 49.0 ± 9.2% in the MI with asynergy group, $p < 0.0001$), whereas the MI without asynergy group had a significantly higher % uptake than the MI with asynergy group ($p < 0.0001$). In contrast, severity and extent scores were significantly lower in the AP group (7.0 ± 9.2 and 8.3 ± 7.8%, respectively) than in the other two groups (vs. 29.1 ± 33.8 in the MI without asynergy group, $p < 0.0003$ and vs. 52.6 ± 33.9 in the MI with asynergy group, $p < 0.0001$ in severity score, and vs. 18.2 ± 12.2% in the MI without asynergy group, $p < 0.0001$ and vs. 28.6 ± 11.9% in the MI with asynergy group $p < 0.0001$ in extent score), whereas these scores were significantly higher in the MI with asynergy group than those in the MI without asynergy group ($p < 0.002$ and $p < 0.003$, respectively). With regard to the regional washout rate in the territory of the diseased vessel, the MI without asynergy group (21.8 ± 11.4%) had a significantly higher regional washout than in the other two groups (vs. 14.1 ± 9.3% in the AP group, $p < 0.0003$ and vs. 12.6 ± 10.3% in the MI with asynergy group, $p < 0.0001$) but there was no significant difference between the AP and the MI with asynergy groups.

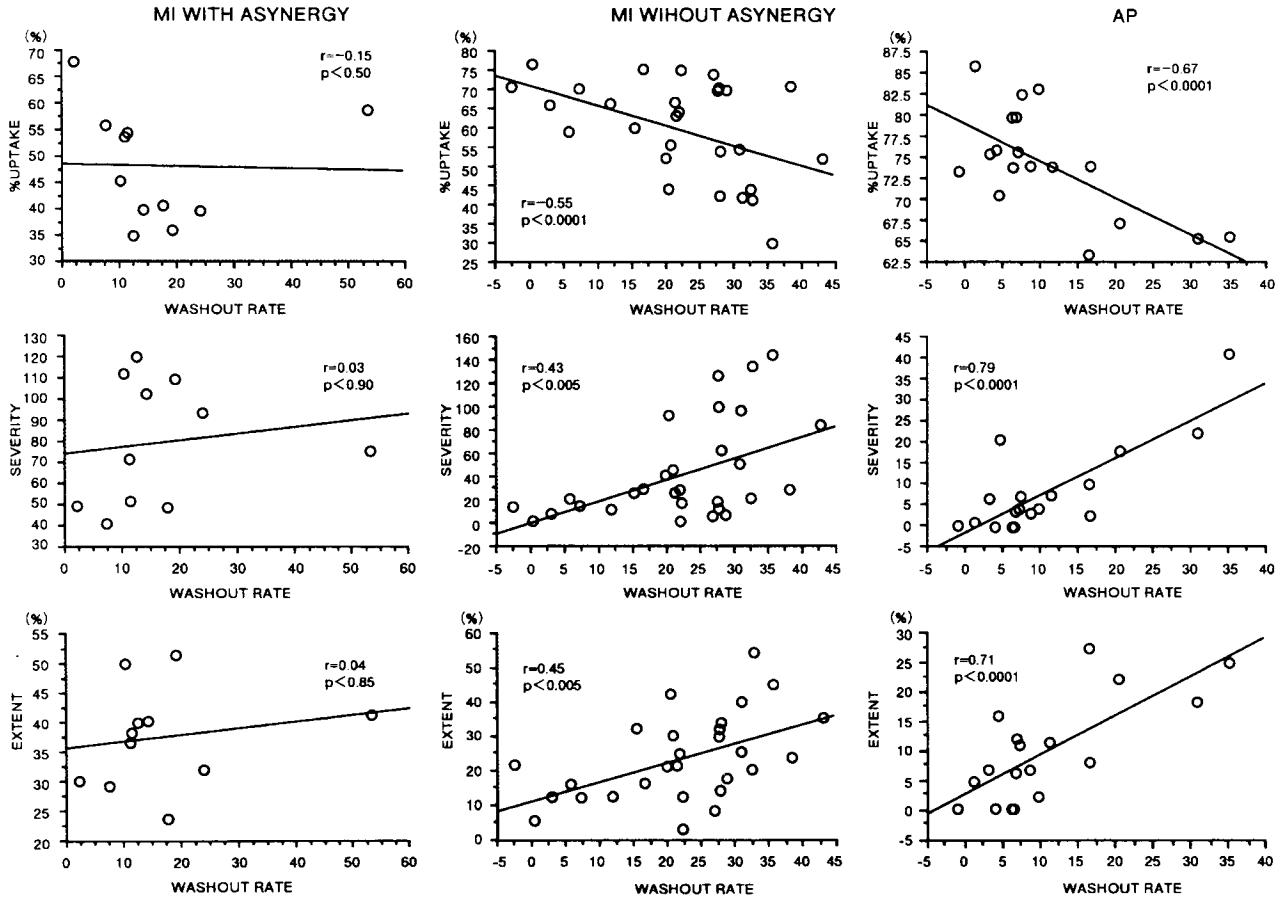

Fig. 3 Correlations between MIBG uptake parameters and regional washout in the territory of the LAD in each group.

Comparison of MIBG parameters for the territories of the diseased vessel and the other vessels

We selected 57 patients with the LAD disease from each group to compare regional MIBG parameters in the territory of the LAD as well as in the territories of the other major coronary arteries among the 3 groups. Group characteristics in the 3 subgroups are shown in Table 2. In the baseline characteristics, only EF was significantly higher in the AP group than in the other two groups. MIBG % uptake was significantly higher in the AP group (74.4 ± 6.4%) than in the other two groups (vs. 60.1 ± 16.6% in the MI without asynergy group, $p < 0.0001$ and vs. 44.7 ± 8.1% in the MI with asynergy group, $p < 0.0001$), whereas it was significantly higher in the MI without asynergy group than in the MI with asynergy group ($p < 0.006$). Severity and extent scores were significantly lower in the AP group (8.2 ± 10.8 and 9.7 ± 8.7%, respectively) than the other two groups (vs. 40.1 ± 40.3 in the MI without asynergy group, $p < 0.002$ and vs. 76.9 ± 31.1 in the MI with asynergy group, $p < 0.0001$ in severity score, and vs. 23.4 ± 12.5% in the MI without asynergy group, $p < 0.0002$ and vs. 36.3 ± 8.9% in the MI with asynergy group, $p < 0.0001$ in extent score), whereas these scores were significantly higher in the MI with asynergy group than in the MI without asynergy group ($p < 0.003$ and $p < 0.002$, respectively). Regional washout in the territory of the LAD was significantly higher in the MI without asynergy group (22.1 ± 11.5%) than in the other two groups (vs. 10.9 ± 9.8% in the AP group, $p < 0.006$ and vs. 12.2 ± 6.2% in the MI with asynergy group, $p < 0.01$). Furthermore, as shown by the severity and extent scores in Table 2, every group had abnormal MIBG uptake parameters in territories other than the LAD territory. The LCX region showed significantly reduced MIBG uptake and an increased extent score in the MI with asynergy group compared with the AP group, although only a difference in the extent score existed between the MI with asynergy group and the AP group in the RCA territory. Regional washout in the territory of the LCX was significantly higher in the MI with and without asynergy groups than that in the AP group, whereas there was no significant difference in the regional washout in the territory of the RCA among the 3 groups. To assess the effect of left ventricular function on regional MIBG washout and % uptake, we also analyzed the correlations between EF before PTCA and regional washout and MIBG % uptake (Fig. 2). EF showed negative correlations with regional washout, but EF showed weaker positive correlations with MIBG % uptake than

regional washout.

Relationships between regional MIBG uptake and regional washout

Figure 3 shows the relationships between regional MIBG uptake and regional washout in the territory of the diseased vessel (LAD). The AP and MI without asynergy groups had a significant negative correlation between MIBG % uptake and regional washout, and significantly positive correlations between severity and extent scores and regional washout. Among these correlations, the severity score in the AP group was the most closely correlated with regional washout. In addition, these correlations were closer in the AP group than in the MI without asynergy group. In contrast, the MI with asynergy group had no correlations between regional MIBG uptake parameters and washout.

DISCUSSION

In coronary artery disease, we quantitatively analyzed MIBG uptake parameters and washout regionally. Abnormal MIBG uptake parameters and washout were detected in the territory of the diseased vessel as well as in the other coronary artery territories. In the territory of the diseased vessel, there were close correlations between MIBG uptake and MIBG washout in the synergic myocardial region but no correlations in the asynergic myocardial region.

Cardiac sympathetic nervous system in coronary artery disease

The effect of myocardial ischemia on the cardiac sympathetic nervous system has been reported both experimentally and clinically.[1–13,19–22] According to the findings of these studies, progression of impairment of the cardiac sympathetic nervous system by myocardial ischemia is considered to be as follows; At first, ischemic attacks impair reuptake function of norepinephrine[20,22] and subsequently cause disruption of the sympathetic nerve membrane,[21] which finally results in sympathetic denervation. During the process, systemic sympathetic activity,[19] and norepinephrine release from damaged sympathetic nerve terminals,[23] increase so that the severity of cardiac sympathetic nerve damage depends upon the degree of myocardial damage due to myocardial ischemia.

Regarding the data from MIBG studies on coronary artery disease, there is a consensus that myocardial infarction patients have MIBG defects due to myocardial denervation. It is likely that extremely severe ischemia, even in stable angina pectoris, causes cardiac sympathetic denervation,[7,8,24] but it is difficult to believe that anginal attacks in stable angina pectoris could usually result in MIBG defect,[17] especially due to sympathetic denervation. In the present study, stable angina pectoris patients often had MIBG defects (severity and extent scores) but 16 (41%) of them had no obvious defect in the ischemic region (extent score $\leq 4\%$). To determine whether or not these MIBG defects in stable angina pectoris result from sympathetic denervation, we compared MIBG kinetics in the diseased vessel territory of stable angina pectoris patients who were unlikely to have sympathetic denervation and myocardial infarction patients who obviously had sympathetic denervation. As a correlation between MIBG uptake and washout has already been shown in coronary artery disease,[10] the present study demonstrated the strongest positive correlation between the severity score and regional washout in the territory of diseased vessels in angina pectoris patients, in contrast to the correlation in the territory of diseased vessels which became weaker in patients with prior myocardial infarction and ultimately disappeared in patients with asynergic myocardium due to myocardial infarction. Therefore, as this close positive correlation was present in the less damaged myocardial region, the closer correlation appears to represent local sympathetic dysfunction or sympathetic overactivity due to ischemia[9] and might be specific for sympathetic nerve viability. In contrast, to become weaker the correlation might implicate progression of sympathetic denervation due to severe myocardial ischemia or infarction.

Comparison of MIBG parameters among the territories of the diseased vessel and the intact coronary arteries

To assess MIBG parameters in territories other than that of the diseased vessel, we selected patients with the LAD disease. In the territory of the LAD, MIBG washout was significantly higher in the MI without asynergy group than in the other two groups. This showed that locally enhanced sympathetic activity of the remaining viable sympathetic nerve fibers was prominent in the MI without asynergy group. This may indicate that enhanced sympathetic activity could make the reduced or asynergic wall motion in the infarct area work as much as possible to maintain cardiac function. Sympathetic denervation of viable myocardium (denervated but viable myocardium), which is usually present in the periinfarction area has implicated susceptibility to lethal ventricular arrhythmias in patients with myocardial infarction.[4,13] Nevertheless, we had no patients with prior myocardial infarction who were confirmed to have lethal arrhythmias or who died suddenly during the 6 month follow-up. This may indicate that regional sympathetic denervation might mainly become arrhythmogenic during the early acute phase of the ischemic event.[2] Although these studies have focused on the area adjacent to the infarct region, the present study demonstrated that a large number of regions such as the territories of the RCA and the LCX remote to the ischemic or infarct regions showed abnormal MIBG uptake in all 3 groups. In particular, the LCX region showed significantly enhanced MIBG washout in the MI without asynergy, and both reduced MIBG uptake and enhanced

washout in the MI with asynergy group compared with the AP group, although the RCA region showed only a difference between the MI with asynergy and AP groups in the extent score. These results indicated that changes in local cardiac sympathetic nervous function, probably due to enhanced sympathetic activity, occurred more prominently in regions remote to the infarct region than in regions remote to the ischemic region. Kobayashi et al.[11] have demonstrated a negative correlation between MIBG myocardial washout and EF in patients with left ventricular dysfunction. Since both MI groups had a significantly reduced EF compared with the AP group and there were significant negative correlations between EF and regional washout in the LCX and RCA regions, enhanced sympathetic activity might result from left ventricular dysfunction, which may contribute to the enhancement of contractility of the normal myocardium to maintain cardiac function. The regional differences between sympathetic activity in the LCX and RCA regions are probably because sympathetic innervation is rich in the territory of the LCX but poor in the territory of the RCA.[25] In addition, MIBG uptake of the liver might more or less influence that of the RCA region.

Study limitation

We assessed regional left ventricular wall motion with left ventriculograms, but because left ventriculograms provide only two-dimensional information, a comparison with three-dimensional images, such as two-dimensional polar maps obtained with SPECT, is not ideal. In addition, at present this method can not analyze smaller regions, because severity and extent score maps can not display each score in the numerous regions associated with washout and % uptake maps.[17] Therefore, to minimize the misalignment between the left ventriculogram and the MIBG polar map and the observed discrepancy in regional wall motion, we selected single vessel disease patients with a proximal lesion of one of the 3 major coronary arteries and only analyzed MIBG parameters and the recovery from asynergy in each territory of the 3 major coronary arteries. It is well known that MIBG kinetics are affected by various factors including diabetes mellitus and hypertension, so that it is necessary to assess every factor affecting MIBG kinetics, especially in coronary artery disease patients, since they often have diabetes mellitus, hypertension, and other factors which affect MIBG kinetics. But it is very difficult to evaluate these factors in each patient because they are cross-linked and complicatedly entwined. Although we did not assess these factors in the present study, selected patients are common in coronary artery disease and most of the factors affecting MIBG kinetics were well controlled.

CONCLUSION

The present study demonstrated that various degrees of change in MIBG parameters in all territories of the 3 major coronary arteries occurred in patients with single-vessel disease. Among these MIBG parameters, a close correlation between the MIBG severity score and regional washout was observed in the noninfarcted region of the diseased vessel, but its relation disappeared in the infarcted region with asynergy. In this way regional quantitative analysis of MIBG imaging can detect differences in regional impairment of the cardiac sympathetic nervous system in patients with coronary artery disease, which may be associated with the degree of regional left ventricular dysfunction due to myocardial ischemia.

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