

Discordant iodine-123 metaiodobenzylguanidine uptake area reflects recovery time dispersion in acute myocardial infarction

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Iodine-123 metaiodobenzylguanidine (MIBG) uptake was reported to be reduced compared to Tl-201 (Tl) in acute myocardial infarction (AMI). Within such an area, degrees of both sympathetic neural function and ischemic myocardial cell damage are considered to be greatly dispersed. These kinds of damage were reported to effect repolarization time in myocardial cells, and we evaluated our hypothesis that extension of the discordant MIBG uptake area correlates with recovery time (RT) dispersion and relate ventricular arrhythmias in AMI. MIBG and Tl images were obtained in AMI patients. Regional Tl or MIBG uptake was estimated in 9 segments of SPECT by using four-point scoring. The total score was the sum of scores in 9 SPECT segments. Δ Tl-MIBG was calculated by subtracting the total MIBG score from the total Tl score. Corrected RT (RTc) was measured as a signal-averaged ECG. RTc dispersion was defined as the difference between maximal and minimal RTc. The patients were assigned to two groups (group A; \leq Lown 4a, group B; \geq Lown 4b) according to the results of 24-hour Holter monitoring. A positive correlation between RTc dispersion and Δ Tl-MIBG was found. Δ Tl-MIBG and RTc dispersion in group B were greater than those in group A. These results suggested that Δ Tl-MIBG could be used to predict the development of malignant ventricular arrhythmias.

Key words: iodine-123 metaiodobenzylguanidine, acute myocardial infarction, ventricular arrhythmia, recovery time dispersion

INTRODUCTION

MALIGNANT ventricular arrhythmias represent a major complication of acute myocardial infarction. In addition, the development of ventricular tachycardia is an important predictor of prognosis.¹ Although the mechanism responsible for ventricular tachycardia (VT) is not clear, experimental and clinical studies have suggested that VT caused by reentry is a result of the heterogeneity of repolarization.² Furthermore, sympathetic activation³ and myocardial ischemias^{4,5} are important modulators of ventricular repolarization. Heterogeneity of both sympathetic

activation and the degree of ischemia are thought to be risk factors for ventricular tachycardia.⁶⁻⁸ The periinfarct zone contains arrhythmogenic myocardium,⁹ and the presence of reentry circuits in this area has been reported by Kuo et al.¹⁰ Nevertheless, little has been reported concerning the relationship between myocardial ischemia and sympathetic function,¹¹ because no studies have previously evaluated sympathetic function.

The accumulation of iodine-123 metaiodobenzylguanidine (MIBG), which is an analogue of norepinephrine, is believed to quantify sympathetic neuronal innervation.¹² Furthermore, the corrected recovery time (RTc) obtained by surface electrocardiographic mapping, has provided an index of the heterogeneity of repolarization.¹³ If the results of these electrophysiologic and nuclear studies can be applied to patients with malignant arrhythmias after myocardial infarction, the results should represent an important predictor of prognosis.

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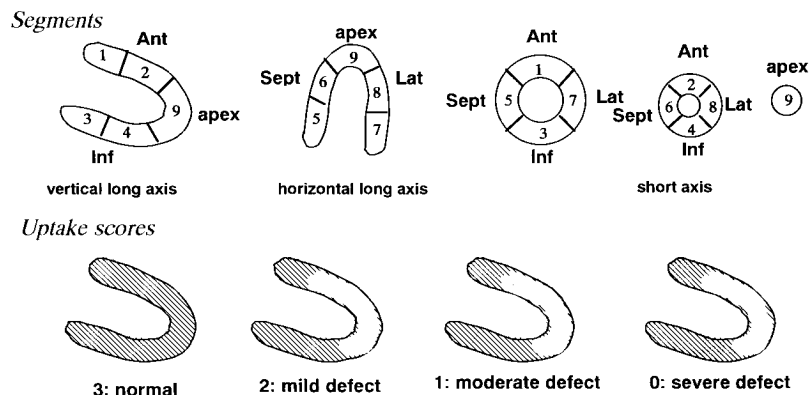


Fig. 1 Schematic representation of 9-segment SPECT vertical long axis view, horizontal long axis view, and short axis view. Ant, anterior wall; Lat, lateral wall; Inf, inferior wall; Sept, septal wall. The severity of perfusion defects was evaluated in each segment: grade 0, severe defect; grade 1, moderate defect; grade 2, mild defect; grade 3, normal.

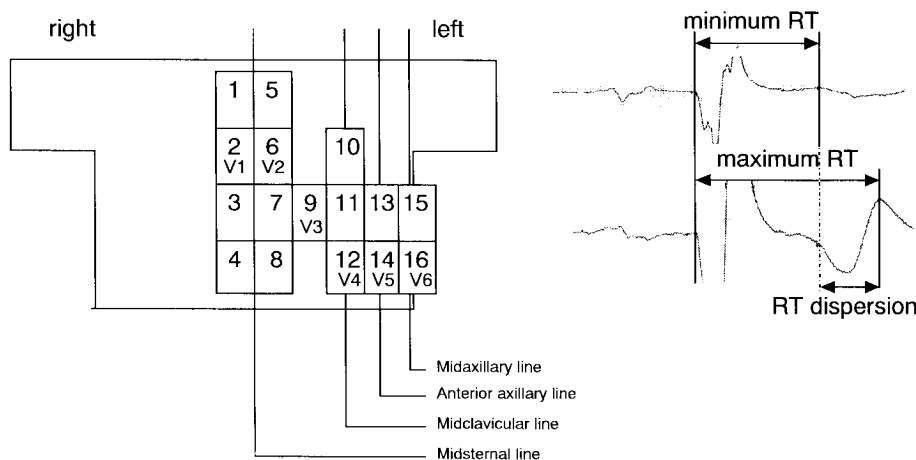


Fig. 2 Body surface electrocardiogram. The location of the 16 precordial leads for surface electrocardiography is shown (left). Corrected recovery time (RTc) dispersion was calculated as the difference between the maximal corrected recovery time and the minimal corrected recovery time (right).

The aims of the present study were, 1) to evaluate the relationship between Tl-201 (Tl) uptake, MIBG uptake, and RTc dispersion, and 2) to determine the relationship between these indices and the development of malignant ventricular arrhythmias in the patients with acute myocardial infarction.

METHODS

Subjects

Twenty patients presenting with their first acute myocardial infarction (AMI) were enrolled in the present study. The study group consisted of 19 men and 1 woman (mean age \pm standard deviation, 60 ± 10 years). Patients who met all of the following criteria were included in the study: chest pain lasting at least 30 minutes, abnormal q waves in 12-lead electrocardiogram, and serum CPK value > 500 IU/l. The infarct affected the anterior wall in 11 patients

and the inferior wall in 9 patients. All patients had undergone successful coronary reperfusion therapy during the acute phase. Twenty-four-hour ambulatory Holter monitoring, Tl and MIBG scintigraphy, and RT measurement were performed during the subacute phase (1 to 3 weeks). Patients were divided into two groups: group A ($n = 11$) developed no life-threatening ventricular arrhythmias, (Lown grade arrhythmias 1 to 4a), whereas group B ($n = 9$) experienced severe ventricular arrhythmias (Lown grade arrhythmias 4b to 5), including 2 patients who had ventricular tachycardia. The clinical profiles of groups A and B are summarized in Table 1.

Nuclear studies

Doses of MIBG and Tl (111 MBq each) were administered intravenously with the patients in a resting state. A StarCam 3000XCT (General Electric, Milwaukee, WI) was used for data acquisition and analysis. Thirty-two

planar acquisitions were performed for 30 seconds each over a 180-degree arc extending from the 45-degree right anterior oblique projection to the 45-degree left posterior oblique projection. By means of filtered back projection, transaxial slices were reconstructed parallel to the vertical and horizontal long axis and the short axis of the left ventricle. SPECT images were evaluated visually in each of 9 segments, and the severity of the perfusion defect was quantified on a 4-grade scale: grade 0, severe defect; grade 1, moderate defect; grade 2, mild defect; grade 3, normal. The sum of the scores in the 9 segments was defined as the total TI or total MIBG score. Δ TI-MIBG was calculated as the total TI score minus the MIBG score (Fig. 1).

RTc measurement

The dV/dt of the T wave was obtained by the filtering

technique and recorded as a signal-averaged ECG with a Multicardiner VCM-3000 (Fukuda Denshi Co., Tokyo, Japan). The ECGs from each of 16 leads were amplified, digitized and passed through a low pass filter (300 Hz; slope, 18 dB/octave) and a high pass filter (20 Hz; slope, 6 dB/octave). Signals from 20 beats were averaged. The recovery time (RT) was defined as the interval between the QRS onset and the time of the maximum dV/dt for the T-wave. The RT was calculated manually for each lead. Each RT value was corrected (RTc) for heart rate by Bazett's formula: $RTc = RT \times RR^{1/2}$. The RTc dispersion was defined as the difference between the maximum RTc and the minimum RTc values (Fig. 2).

24-hour ambulatory Holter monitoring

All patients underwent 24-hour Holter monitoring 7 days after the onset of infarction to detect premature ventricular contractions (VPC). Holter recordings consisted of continuous 2-channel recordings analyzed with a Holter analyzer DMW-9000H (Fukuda Denshi).

Statistics

Correlations between RTc dispersion and total TI, total MIBG and Δ TI-MIBG were assessed by linear regression analysis. Comparisons between the two groups were made by Student's unpaired t test or Fisher's exact probability test. Data are expressed as the mean \pm standard deviation. A value of $p < 0.05$ was considered statistically significant.

Table 1 Patient profiles for groups A and B

	Group A	Group B	
Age (years old)	60.5 \pm 10.1	60.0 \pm 11.5	n.s.
Gender (Male : Female)	10 : 1	9 : 0	n.s.
Infarct area (anterior : inferior)	6 : 5	5 : 4	n.s.
Heart rate (bpm)	65.8 \pm 6.7	68.3 \pm 13.4	n.s.
LVEF (%)	44.0 \pm 12.9	42.4 \pm 8.3	n.s.
peak CPK (IU)	1928 \pm 1383	2946 \pm 2456	n.s.
Total TI score	18.7 \pm 4.1	19.9 \pm 3.2	n.s.
Total MIBG score	12.5 \pm 4.7	10.2 \pm 4.7	n.s.

LVEF, left ventricular ejection fraction. Values are mean \pm standard deviation.

Table 2 Summary of patient data

Patient no.	Age yr	Infarct area	Treatment	Total-TI	Total-MIBG	Δ TI-MIBG	RTc dispersion (msec)	VPC grade
1	57	ANT	N, C, A	22	14	8	103.4	0
2	60	INF	N, C	21	15	6	95.1	0
3	72	INF	N, C	20	19	1	66.8	0
4	66	ANT	N, C	22	15	7	104.3	1
5	41	ANT	N, C	17	9	8	113.8	1
6	52	ANT	N, C	19	10	9	114.9	1
7	61	INF	N, C	16	7	9	81.5	1
8	69	ANT	N, C	10	3	7	106.5	1
9	65	INF	N, C	23	17	6	75.1	1
10	70	ANT	N, C	15	10	5	61.2	4a
11	61	INF	N, C	23	14	9	114.1	4a
12	72	ANT	N, C	25	15	10	115.2	4b
13	44	ANT	N, C	17	14	3	106.0	4b
14	47	ANT	N, C	24	13	11	147.2	4b
15	54	ANT	N, C	17	10	7	86.8	4b
16	71	INF	N, C	19	3	16	149.6	4b
17	73	INF	N, C	21	16	5	102.8	4b
18	68	INF	N, C	15	4	11	104.1	4b
19	60	INF	N, C	21	14	7	110.0	4b
20	43	ANT	N, C	18	7	11	122.1	5

Yr, years old; INF, inferior; ANT, anterior; N, Nitrate; C, Ca antagonist; A, anti-arrhythmia drug.

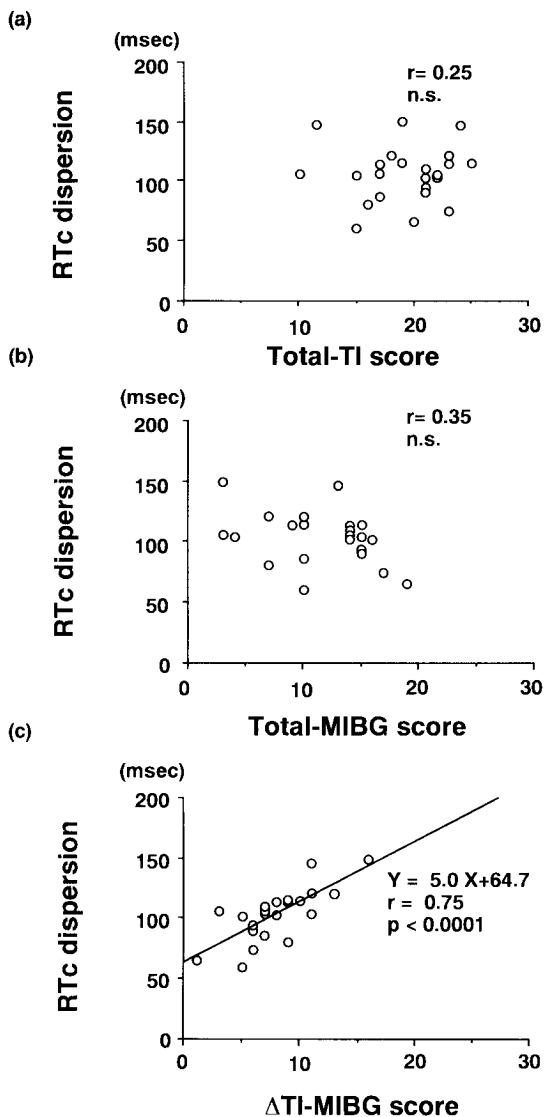


Fig. 3 (a) Correlation between RTc dispersion and the total TI scores. No significant correlation was found between RTc dispersion and the total TI score. (b) Correlation between RTc dispersion and the total MIBG score. No significant correlation was found between RTc dispersion and the total MIBG score. (c) Correlation between RTc dispersion and the Δ TI-MIBG score. A significant correlation was found between RTc dispersion and the Δ TI-MIBG score.

RESULTS

Clinical characteristics of groups A and B

There were no significant differences in age, gender, heart rate, left ventricular ejection fraction, peak CPK value or left ventricular ejection fraction between groups A and B (Table 1). All patients received nitrate and calcium-channel antagonist. No patient received β -blocking agents or major tranquilizing agents. One patient was treated with a loop diuretic drug, and one patient was treated with a group Ib anti-arrhythmia drug. Three patients in group

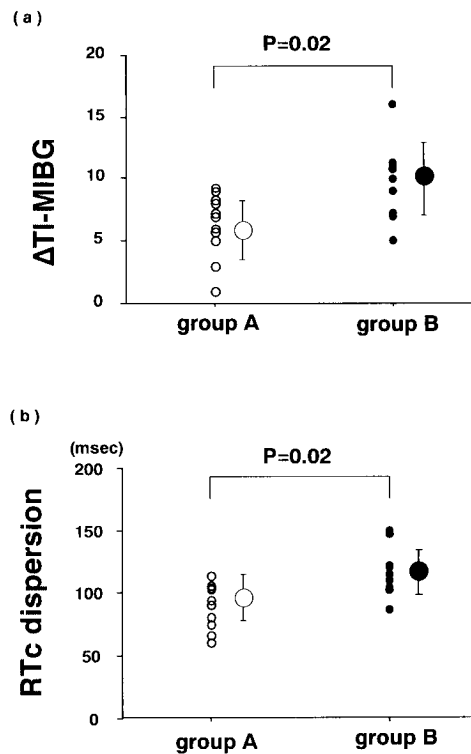


Fig. 4 (a) Δ TI-MIBG scores in groups A and B. Δ TI-MIBG was lower in group A than in group B ($p = 0.02$). (b) RTc dispersion in groups A and B. RTc dispersion was less in group A than in group B ($p = 0.02$).

A and 4 patients in group B had diabetes. No patient had any electrolytic abnormalities.

Table 2 summarized subject characteristics and the results in this study.

Nuclear studies and RTc dispersion

RTc dispersion did not correlate with either the total TI score ($r = 0.25$, Fig. 3a) or the total MIBG score ($r = 0.35$, Fig. 3b), but a significant correlation was found with Δ TI-MIBG ($r = 0.75$, $p < 0.0001$, Fig. 3c).

Ventricular arrhythmias and nuclear studies

There were no significant differences between groups A and B in the total TI score and the total MIBG score (Table 1). The mean Δ TI-MIBG was 9.7 ± 3.2 in group B and 6.3 ± 2.5 in group A. The Δ TI-MIBG in group B was greater than that in group A ($p = 0.02$, Fig. 4a).

Ventricular arrhythmias and RTc dispersion

RTc dispersion was 117.0 ± 20.4 msec in group B and 93.4 ± 19.0 msec in group A. RTc dispersion in group B was longer than that in group A ($p = 0.02$, Fig. 4b).

Case presentation (Fig. 5)

Figure 5 shows representative scintigraphic images and the RTc dispersion in a patient with acute anterior wall myocardial infarction. The TI images demonstrate mild

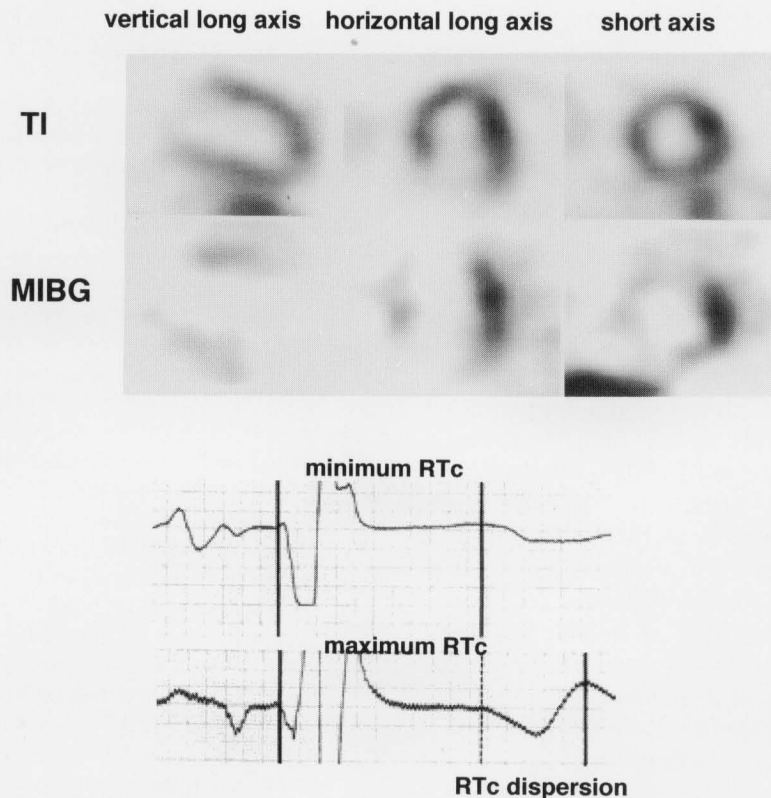


Fig. 5 Representative example of TI-MIBG mismatch in a 49-year-old man with acute myocardial infarction.

hypoperfusion in the anterior wall (total TI score = 25), whereas the MIBG images show severe hypoperfusion in the anterior and septal walls (total MIBG score = 9). This is a typical case of TI-MIBG mismatch ($\Delta\text{TI-MIBG} = 16$). The RTc dispersion was increased to 149.2 msec in this patient and the ventricular tachycardia occurred 7 days after infarction.

DISCUSSION

Previous studies have shown that prolongation of the QT interval is a risk factor for ventricular arrhythmia in the patients with myocardial infarction.¹⁴⁻¹⁸ The relationship between QT dispersion and susceptibility to arrhythmias has also been reported in patients with acute myocardial infarction.¹⁹

Zabel et al. have reported that QT dispersion correlates both with the dispersion of the monophasic action potential recorded from the left ventricular endocardium (APD 90) and RT.²⁰ Sasaki et al. have reported that the APD 90 correlates with RT obtained by surface electrocardiography.²¹ We therefore used RTc dispersion in the present study.

Lekakis et al. and Dae et al. have reported that the defect in MIBG uptake is larger than the defect in TI uptake in the patients with acute myocardial infarction.²² This type of

mismatch is believed to represent denervated but viable myocardium.²³ Our results demonstrate that RTc dispersion does not correlate with either the total TI score or the total MIBG score, but a significant correlation was found between RTc dispersion and $\Delta\text{TI-MIBG}$. This suggests that denervated but viable myocardium could be responsible for the heterogeneity of repolarization, and such myocardium is believed to be the reentrant focus. Increased catecholamine release after myocardial infarction is thought to change the conduction pathway and to induce a unidirectional block.²⁴ Microscopic examination has demonstrated a discontinuous structure (border zone) during recovery from infarction in animal studies.^{25,26} Furthermore, unidirectional block has been shown to induce reentrant arrhythmias in this area.²⁷ Denervated but viable myocardium in the present study represents a border zone. Our results therefore suggest that the reentrant circuit is located in an area with reduced MIBG uptake compared with TI uptake.

Fu et al. reported that QT dispersion prolongation has been associated with poor cardiac function and ventricular arrhythmias.²⁸ In our study, since there were no significant differences between groups A and B in the ejection fraction, we did not investigate the relationship between the degree of cardiac function and RT dispersion.

Our data demonstrated that both RTc dispersion and

Δ TI-MIBG were greater in group B than in group A. The presence of denervated but viable myocardium is dependent on whether the myocardium had been salvaged by acute coronary reperfusion. Dae et al. has reported that arrhythmias other than reperfusion arrhythmias occur less frequently in patients who have undergone successful reperfusion therapy.²⁹

Previous studies have reported that there is less QT dispersion in patients with successful reperfusion therapy.^{30,31} Theoretically, Δ TI-MIBG should be greater in patients who receive reperfusion therapy, because of the presence of greater amounts of viable tissue, but the present study demonstrated a higher frequency of arrhythmias in such patients. The reason for this finding is unknown, but the increase in Δ TI-MIBG may be dependent not on the amount of viable tissue (TI) but rather on the amount of denervated tissue (MIBG). Therefore, both Δ TI-MIBG and RTc dispersion are useful predictors of the development of malignant arrhythmias.

Study limitation. In this study, arrhythmia was evaluated for only 24 hours by Holter monitoring 7 days after the onset of acute myocardial infarction, but arrhythmia after acute myocardial infarction changes by the day, and it is difficult to evaluate these changes based on data for only 24 hours. If the occurrence of arrhythmia had been evaluated for several days, we speculate that more accurate results may have been obtained.

CONCLUSIONS

1. RTc dispersion did not correlate with either the total TI score or the total MIBG score, but there was a good correlation between RTc dispersion and Δ TI-MIBG.
2. Both RTc dispersion and Δ TI-MIBG were greater in patients with severe ventricular arrhythmias than in patients without life threatening arrhythmias.
3. Δ TI-MIBG could be used to predict the development of malignant ventricular arrhythmias.

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