Modulation of Ventricular Repolarization and R-R Interval Is Altered in Patients with Globally Impaired Cardiac ^{123}I -MIBG Uptake

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Background: Cardiac ^{123}I -metaiodobenzylguanidine (MIBG) imaging is widely used to assess cardiac sympathetic neuronal function. However, physiologic significance of impaired cardiac MIBG uptake is not fully elucidated. The purpose of the present study was to determine influences of abnormal cardiac sympathetic neuronal function on heart rate variability (HRV) and ventricular repolarization process.

Methods: Twenty-nine patients with prior myocardial infarction were divided into two groups by a heart-to-mediastinum ratio (H/M) of MIBG scintigraphy. Ten patients with globally decreased MIBG uptake (group I: $\text{H/M} < 1.5$), 19 patients with partially decreased MIBG uptake (group II: $\text{H/M} \geq 1.5$), and 17 control subjects with normal MIBG uptake (group III) were studied. Holter recording and a standard 12-lead electrocardiography were used for evaluation of HRV, QT-RR relation, and QT dispersion.

Results. Low, high, and total frequency components decreased in groups I and II, as compared to that of group III. The reduction of these frequency domain measures was more severe in group I than in group II, but the differences did not reach statistical significance. Circadian variation of frequency domain measures disappeared in group I. The slope of QT-RR relation was significantly greater in group I than in groups II and III. QT dispersion was also greater in group I (64 ± 25 msec) than in group II (43 ± 19 msec) and group III (28 ± 9 msec).

Conclusion. These results suggest that patients with sympathetic neuronal dysfunction inferred from globally impaired cardiac MIBG uptake have an altered modulation of ventricular repolarization process as well as decreased HRV.

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metaiodobenzylguanidine; heart rate variability; ventricular repolarization; autonomic nervous function; QT dispersion

^{123}I -Metaiodobenzylguanidine (MIBG) accumulates in the norepinephrine storage granules of postganglionic sympathetic neurons. Radiolabeled MIBG scintigraphy has been widely used to assess distribution and function of myocardial sympathetic nerves. Reduced cardiac MIBG uptake is related to sympathetic denervation in the setting of

left ventricular damage or dysfunction associated with failing heart^{1,2} or myocardial infarction.³ However, Morozumi et al.⁴ reported two cases of markedly decreased cardiac MIBG uptake in healthy volunteers. The globally impaired cardiac MIBG uptake in a whole heart was also detected in some patients with syndrome X.⁵ Whether the glo-

bally impaired cardiac MIBG uptake is of any physiologic significance is still unclear.

QT interval, an index of ventricular repolarization, is influenced by autonomic tone and heart rate.⁶ QT dispersion reflects regional variations in ventricular repolarization.⁷ A greater QT dispersion was found in patients with long QT syndrome,⁸ myocardial infarction,⁹ and hypertrophic cardiomyopathy¹⁰ and may be a risk factor for lethal ventricular arrhythmias and sudden death.¹¹ However, it remains unknown whether ventricular repolarization process and QT dispersion could be modified in patients with abnormal cardiac MIBG uptake. Recently, Shimono et al.¹² reported that analysis of relation between QT and R-R intervals is useful to determine modulation of ventricular repolarization process with heart rate and autonomic nervous function.

The purpose of the present study was therefore to determine alteration in modulation of ventricular repolarization process and QT dispersion in patients with cardiac sympathetic neuronal dysfunction inferred from the globally reduced cardiac MIBG uptake.

METHODS

Patient Characteristics

Patients with prior myocardial infarction were divided into two groups by a heart-to-mediastinum ratio (H/M) of MIBG uptake. These included 10 patients (mean age: 71 ± 7 years) with globally and severely decreased cardiac MIBG uptake ($H/M < 1.5$, group I) and 19 patients (65 ± 11 years) with partially decreased MIBG uptake in each infarct region but with normal MIBG uptake in the remote region ($H/M \geq 1.5$, group II). Seventeen subjects (53 ± 17 years) with normal MIBG uptake (group III) served as controls. Patients with chronic atrial fibrillation, left and right bundle branch block, second- and third-degree atrioventricular block, pacemaker implantation, Wolff-Parkinson-White syndrome, or acute myocardial infarction were excluded. Orthostatic tests and treadmill exercise tests were performed in all patients. Orthostatic hypotension was defined as a decline of 20 mmHg or more in systolic blood pressure on assuming the upright position. None of the study subjects had received reserpine, tricyclic antidepressants, antiarrhythmic drugs, or other drugs that could interfere with cardiac MIBG uptake or QT interval.

Radioisotope Imaging

After an overnight fast, patients underwent cardiac MIBG study. Planar and SPECT images were acquired 3 hours after injection of 111 MBq of ^{123}I -MIBG. A scintillation camera (CA-9300 A/DI, Toshiba, Tokyo, Japan) with a parallel-hole general-purpose collimator (low energy, high resolution type) was used. The camera was interfaced to the digital data acquisition system (CA-5500A, Toshiba). The energy window of ^{123}I was centered at 143 to 175 keV. Planar images were acquired at anterior, 45° left anterior oblique, and lateral views using a 512 x 512 matrix format for 90 seconds. Then 60 images for SPECT data were acquired 360° acquisition in 6° increments. The reconstructed tomographic data were displayed in the horizontal long axis, vertical long axis, and short axis. Planar and SPECT images were evaluated independently by two observers unaware of results of the other studies. Global cardiac MIBG uptake was determined by the heart-to-mediastinum activity ratio (H/M) on a planar image. Left ventricular (LV) activity was counted using a manually drawn region of interest and mediastinum activity using a 10 x 10 pixel region of interest placed over the upper mediastinum area. Seventy-four MBq of ^{201}Tl chloride was intravenously administered at rest after an overnight fast. The cardiac planar and SPECT images of Tl were obtained similarly to the cardiac MIBG images. Intervals of MIBG study and Tl study ranged from 1 to 2 weeks.

We defined the globally impaired cardiac MIBG uptake as markedly decreased uptake in the whole heart, and the H/M ratio less than 1.5 (Fig. 1).

Analysis of Heart Rate Variability

Twenty-four-hour Holter electrocardiographic (ECG) recordings (SM 26 and 28, Fukuda Denshi, Tokyo, Japan) were digitized at a sampling rate of 1000 Hz by an analogue-to-digital converter and were analyzed using a Holter analysis system (DMW-9000, Fukuda Denshi). The first 512-second consecutive R-R intervals without premature beats were selected from 0, 5, 11, and 17 o'clock of the data. Fast Fourier transform spectral analysis was performed to determine power of a low frequency component (LF) at 0.04 to 0.15 Hz, a high frequency component (HF) at 0.15 to 0.40 Hz, and a total frequency (TF) at 0 to 0.4 Hz. LF was regarded

Figure 1. Representative examples of cardiac MIBG planar images (A) obtained in the anterior (Ant), left lateral (L-Lat), 45-degree left lateral oblique (LAO) projections and SPECT images of TI (D) in a 71-year-old man with prior inferior myocardial infarction (group I), MIBG planar images (B) and SPECT images of TI (E) in a 64-year-old man with prior inferior myocardial infarction (group II), and MIBG planar images (C) and SPECT images of TI (F) in a 70-year-old woman with paroxysmal supraventricular tachycardia (group III) are shown. Cardiac uptake was markedly decreased in MIBG planar images (A), although TI images showed normal except for the infarct-related area (D) in group I. In contrast, MIBG and TI images were normal except for the infarct-related area (B and E) in group II for the study design. In the group III patient, MIBG and TI images were normal (C and F).

as an index of sympathetic tone with vagal modulation, and HF, as an index of vagal tone. As an index of sympathovagal balance, the ratio of LH to HF (LF/HF) was employed, as in a previous re-

port.¹³ Circadian variation of above frequency domain measures was assessed by their maximal differences among four values selected from 24-hour Holter recordings in each patient.

QT Interval and QT Dispersion

In each patient, the relation between QT interval and heart rate was determined with 24-hour Holter recording. The first 10 consecutive sinus beats from every hour were selected to determine hourly QT interval and R-R interval. When the R-R intervals changed abruptly during the first 10 beats, the following 10 consecutive beats after stabilization were selected. QT interval was determined from the earliest deflection of QRS complex to the end of T wave. The point at which the maximal down-slope of T wave crossed the isoelectric line was used as the end of T wave, as in a previous report.¹⁴

QT dispersion was determined with a standard 12-lead ECG (25-mm/s paper speed), and defined as a difference between maximum and minimum QT intervals. In the following analyses, QT interval was corrected for heart rate (QT_C) using Bazett's formula¹⁵ (QT_C = QT/square root of R-R interval).

Statistical Analysis

Data are expressed as mean $\pm$ SD. Statistical significance was estimated with analysis of variance, followed by a Duncan test to identify differences among groups. Relation of QT interval to R-R interval was determined using a linear regression analysis. A P value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics are shown in Table 1. Mean age of group I was not different from that of group II, but was higher than that of group III. LV ejection fraction assessed by radionuclide angiography was decreased to a similar extent in groups I and II. The proportion of patients with diabetes mellitus was not different between groups I and II, although it tended to be low in group III. No patients had orthostatic hypotension or abnormal heart rate response to exercise. The H/M ratio of MIBG uptake was 1.19 ± 0.09 in group I, 1.90 ± 0.31 in group II, and 2.30 ± 0.39 in group III for the study design.

Figure 1 shows representative examples of MIBG planar images and TI images of the three

Table 1. Patient Characteristics

	Group I	Group II	Group III
No	10	19	17
Gender (M/F)	10/0	15/4	10/7
Age (year)	71.1 ± 7.4*	64.8 ± 11.4*	53.4 ± 16.7
H/M	1.19 ± 0.09*†	1.90 ± 0.31*	2.30 ± 0.39
LVEF (%)	51.3 ± 11.6*	47.2 ± 12.4*	63.6 ± 6.2
Diabetes mellitus (%)	3 (30)	7 (37)	2 (12)
Underlying disease	anterior MI:4 inferior MI:6	anterior MI:12 inferior MI:4 lateral MI:3	AP:2 arrhythmias:15

Mean ± SD, Group I = patients with globally impaired cardiac MIBG uptake; Group II = patients with partially decreased MIBG uptake; Group III = patients with normal MIBG uptake; MI = myocardial infarction; H/M = the ratio of heart to mediastinum; LVEF = left ventricular ejection fraction; AP = angina pectoris; arrhythmias = paroxysmal supraventricular tachycardia (13 patients) and paroxysmal atrial fibrillation (2 patients).

* P < 0.05 vs Group III.

† P < 0.05 vs Group II.

groups. Tl images of group I was normal except the infarct-related area, but cardiac MIBG uptake decreased markedly in the whole heart. In contrast, both Tl and MIBG images were normal except for the infarct-related area in group II. Control patients did not show apparent abnormalities of Tl and MIBG images.

Heart Rate Variability

An average heart rate in each patient obtained by Holter recordings was not different among the three groups (group I: 62.3 ± 7.4 , group II: 62.8 ± 11.2 , and group III: 58.3 ± 4.3 beats/min). Figure 2 shows frequency domain measures of three groups in a day, and Table 2 summarizes their average values. LF, HF, and TF were significantly lower in groups I and II than in group III. There was a trend toward lower values of above frequency domain measures in group I, as compared with group II, but the differences did not reach statistical significance. LF/HF ratio was not different among the three groups. Circadian variations of LF, HF, and TF were significantly greater in group III than in group I, and were the intermediate values in group II. A similar trend of circadian variation of LF/HF ratio was observed but the difference did not reach statistical significance.

QT-RR Relation and QT Dispersion

QT intervals were linearly correlated with R-R intervals in all patients. The range of R-R intervals

Figure 2. Average data of indices of heart rate variability in patients with globally impaired cardiac MIBG uptake (group I, diamonds), partially decreased MIBG uptake (group II, squares), and normal MIBG uptake (group III, triangles) at 0, 5, 11, and 17 o'clock. Abbreviations of these indices are the same as in Table 2. *P < 0.05 vs group III. †P < 0.05 vs group II.

Table 2. Frequency Domain Indices of Heart Rate Variability

	Group I	Group II	Group III
LF (msec ²)	45 ± 28**	109 ± 38**	390 ± 260
HF (msec ²)	54 ± 40**	118 ± 44*	243 ± 204
TF (msec ²)	291 ± 139**	792 ± 235**	1678 ± 952
LF/HF	1.15 ± 0.67	1.27 ± 0.83	1.79 ± 1.23

Mean ± SD, Group I, II and III are defined as in Table 1; LF = low frequency component; HF = high frequency component; TF = total frequency component.

* P < 0.05.

** P < 0.01 vs Group III.

to determine QT-RR relation was not different among the three groups (0.44 ± 0.10 , 0.46 ± 0.17 , and 0.49 ± 0.09 sec in groups I, II, and III, respectively). The slope of the QT-RR linear regression line in group I was steeper than in group III (Fig. 3). The average data of correlation between QT and R-R was shown in Table 3. The slope of the regression line was significantly steeper in group I than in group III, and that of group II was intermediate, although the difference between groups I and II was statistically significant. QTc dispersion was greater in group I (66 ± 26 msec) than in groups II (43 ± 19 msec) and III (28 ± 9 msec) (Fig. 4).

DISCUSSION

The present study is the first to demonstrate alteration in modulation of QT interval with heart rate and increased QT dispersion in patients with globally impaired cardiac MIBG uptake in association with prior myocardial infarction (group I), as compared with patients with infarct-related, localized abnormality of MIBG uptake (group II). We also found that frequency domain indices of heart rate variability were attenuated and circadian rhythmicity of the indices disappeared in group I. The present results therefore suggest that patients

Figure 3. Representative examples of relation between QT interval and R-R interval in a patient with globally impaired cardiac MIBG uptake (group I, left panel), partially decreased MIBG uptake (group II, middle panel) and normal MIBG uptake (group III, right panel). These patients are the same as those shown in Figure 1.

Table 3. Correlation Between QT Interval and RR Interval

	Group I	Group II	Group III
r	0.86 ± 0.05	0.80 ± 0.07	0.85 ± 0.08
Slope	0.28 ± 0.03**††	0.22 ± 0.03**	0.18 ± 0.03
Intercept	0.15 ± 0.04**†	0.20 ± 0.03	0.23 ± 0.04

Mean ± SD, Group I, II and III are defined as in Table 1; r = correlation coefficient of QT-RR regression line.

* P < 0.05.

** P < 0.01 vs Group III.

† P < 0.05.

†† P < 0.01 vs Group II.

with globally impaired cardiac MIBG uptake have an altered influence of autonomic nervous system on the sinus node as well as on the ventricular repolarization process. A magnitude of these alterations in group II was less than in group I, but greater than in patients with normal MIBG uptake (group III).

MIBG Uptake

MIBG scintigram reflects a cardiac sympathetic neuronal function. Abnormalities in cardiac MIBG uptake have been reported in patients with various diseases including cardiac transplants,¹⁶ congestive heart failure,^{1,2} ischemic heart disease,^{3,17,18} long QT syndrome,¹⁹ diabetes mellitus,²⁰ and cardiac amyloidosis.²¹ However, patients with these diseases do not always have an abnormal MIBG uptake. In the group I patients of the present study,

MIBG accumulation was markedly decreased not only in the infarct-related area but also in the remote area of infarction, thereby suggesting that myocardial infarction per se might not directly contribute to the globally impaired cardiac MIBG uptake.

Some mechanisms could be proposed for the poor myocardial uptake of MIBG. First, cardiac sympathetic denervation due to loss of cardiac nerve terminals could be involved.¹⁶ All patients of group I had normal orthostatic tests and normal increases in heart rate by exercise. However, we could not thoroughly exclude a possibility of decreased cardiac innervation. Secondly, dysfunction of norepinephrine reuptake at the nerve terminals could contribute to decreased MIBG uptake. Previous studies^{22,23} have reported that a function of uptake-1 is deteriorated in failing hearts. In the present study, however, LV ejection fraction in group I was not different from that of group II. Finally, activation of sympathetic drive would rather decrease cardiac MIBG uptake.¹ However, an average heart rate in each patient measured with 24-hour Holter recording was not different between groups I and II, and LF/HF in the analysis of heart rate variability, as an index of sympatho-vagal balance,¹³ was not different between these two groups. Thus, we could not identify the underlying mechanism for globally impaired cardiac MIBG uptake in our group I patients.

Heart Rate Variability

In sinus rhythm, heart rate variability reflects the influence of the autonomic nervous system on the sinus node, responsiveness of the sinus node to autonomic nervous tone, or both. HF is mainly modulated by vagal activity,²⁴ while LF is modulated by both parasympathetic and sympathetic

Figure 4. Average data of QTc dispersion in group I (globally impaired cardiac MIBG uptake), group II (partially decreased MIBG uptake), and group III (normal MIBG uptake).

nervous system activity.²⁵ These indices were markedly reduced in group I, a consistent finding with Psychari's study²⁶ in which time and frequency domain measures of heart rate variability were decreased in association with reduced MIBG uptake after radiofrequency ablation. Reduced LF or HF in group I may be explained by the impaired vagal function only. However, the LF/HF, which is an index of sympathovagal balance, was not significantly different among the three groups but was rather low in group I. Circadian rhythmicity of LF, HF, and TF disappeared in group I. Taken together, the reduced frequency domain measures would be due to the altered influence of both vagal and sympathetic nerve on the sinus node. The precise location of alteration, i.e., from the nerve activity itself to the intracellular signal transduction, could not be determined in the present study.

In patients with severe heart failure, both LF and HF were reduced and consequently TF was reduced, as seen in group I patients. Many studies^{1,2} have reported that cardiac MIBG uptake was reduced in patients with heart failure. Despite similar LV ejection fraction between groups I and II in the present study, the reduction of frequency domain indices of heart rate variability was more severe in group I than in group II, although these differences did not reach statistical significance. Therefore, alteration in heart rate variability in the patients with globally impaired cardiac MIBG uptake could not be attributed to a reduced cardiac function per se.

Modulation of QT Interval with Heart Rate

QT interval is influenced by heart rate and autonomic tone. R-R interval was linearly correlated with QT interval in the present study, a consistent finding with the previous studies.^{6,12} The slope of the regression line of QT-RR was greater in group I than in group II. Greater QT-RR slope was reported in a variety of diseases including idiopathic long QT syndrome,²⁷ hypertrophic cardiomyopathy,²⁸ and diabetic patients with neuropathy.²⁹ The mechanism of this greater QT-RR slope is still obscure, but could be attributed, at least in part, to sympathetic denervation and to a greater response of the ventricular repolarization process to increases in plasma or local norepinephrine levels as compared with the response of sinus node, that is, shortening of QT interval was greater when R-R

interval was shortened due to increased adrenergic activity in group I. In patients with localized reduction of sympathetic innervation assessed by ¹¹C-hydroxyephedrine (HED), these areas with defective HED uptake showed longer ventricular refractoriness, a phenomenon compatible with sympathetic denervation.³⁰ However, these areas did not show supersensitive shortening of refractoriness to infused isoproterenol.³⁰ Inoue et al.³¹ reported that a supersensitive response of ventricular refractoriness to adrenergic stimulation with norepinephrine infusion was demonstrated in denervated myocardium of dog.

A decrease in HF in group I may reflect a withdrawal of vagal activity. Therefore, the patients with globally impaired cardiac MIBG uptake in the present study may have decreased cardiac innervation of both autonomic limbs.

QT Dispersion

The present result of greater QT dispersion in group I suggests that these patients have more heterogeneous processes of ventricular repolarization. A greater QT dispersion has been reported in patients with a variety of diseases. These include myocardial infarction,⁹ long QT syndrome,¹³ hypertrophic cardiomyopathy,¹¹ and chronic heart failure.³² Greater QT dispersion in group I was not primarily attributed to underlying disease or LV dysfunction because none of group I patients had long QT syndrome or hypertrophic cardiomyopathy and LV ejection fraction did not differ between groups I and II. Heterogeneous ventricular repolarization process in the patients with globally impaired cardiac MIBG uptake might be rather associated with heterogeneously decreased innervation or dysfunction of sympathetic nerve. Heterogeneous vagal denervation or dysfunction could also contribute to increase in QT dispersion, since vagal nerve modifies ventricular repolarization process.³⁷

Limitations

The present study was limited for several reasons. First, the average age of groups I and II patients was higher than that of group III. Inferior MIBG uptake decreases along with ages in subjects without apparent cardiac disease, although there is no significant difference in the H/M ratio based on ages.³³ Aging is also known to affect autonomic function. Both LF and HF decrease with age, but

the decrease is small in subjects above 40 years of age.³⁴ The differences of cardiac MIBG uptake, heart rate variability, or ventricular repolarization process were revealed between groups I and II, although the average age was not different between these groups. Secondly, measurement of QT interval is sometimes difficult and is not free from intraobserver errors. To eliminate this inherent limitation and because of technical feasibility, some investigators used the top of the T wave to determine repolarization duration instead of measuring the QT interval itself by some investigators.³⁵ However, we utilized the conventional method of QT determination as in previous studies.^{36,37} Finally, the analysis of QT-RR slope is not an established method to determine effects of autonomic balance on the ventricular repolarization process. However, patients with a variety of cardiac diseases in which the sympathetic nervous system could be affected show a steeper slope of QT-RR relation.²⁷⁻²⁹ Therefore, we used the QT-RR relation to assess autonomic influence on the ventricular repolarization process.

Clinical Implications

A combination with analyses of heart rate variability, QT-RR relation, and QT dispersion will provide useful information to understand the influence of the autonomic nervous system on the cardiovascular system in patients with abnormal cardiac MIBG uptake. The globally impaired cardiac MIBG uptake, which might be associated with alteration in vagal activity, adrenergic supersensitivity, and heterogeneous ventricular repolarization, could be a harbinger of catastrophic cardiac events, such as ventricular arrhythmias³⁸ and cardiac sudden death,³⁹ in these patients. Further studies are required in this context.

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