Clinical Usefulness of ^{123}I -Metaiodobenzylguanidine Myocardial Scintigraphy in Diabetic Patients With Cardiac Sympathetic Nerve Dysfunction

Hajime Miyanaga, M.D., Satoshi Yoneyama, M.D., Tadaaki Kamitani, M.D.
Shingo Kawasaki, M.D., Toru Takahashi, M.D.
and Hiroshi Kunishige, M.D.

To assess the clinical utility of ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy in evaluating cardiac sympathetic nerve disturbance in diabetic patients, we performed MIBG scintigraphy in 18 diabetic patients and 11 normal controls. Diabetic patients with symptomatic neuropathy (DM2) had a significantly lower heart to mediastinum uptake ratio than did those without neuropathy or normal controls in initial and delayed images (initial image, 1.90 ± 0.27 vs 2.32 ± 0.38 , 2.41 ± 0.40 , $p < 0.01$; delayed image, 1.80 ± 0.31 vs 2.48 ± 0.35 , 2.56 ± 0.28 , $p < 0.01$, respectively). Defect score, assessed visually, were higher in DM2 patients than in patients in the other two groups (initial image, 7 ± 2.6 vs 1.5 ± 1.9 , 0.7 ± 0.9 ; delayed image 10.6 ± 3.3 vs 4.0 ± 2.5 , 1.7 ± 1.6 $p < 0.01$, respectively). The maximum washout rate in DM2 patients was also higher than those in patients in the other two groups. The findings of these indices obtained from MIBG scintigraphy coincided with the % low-frequency power extracted from heart rate fluctuations using a power spectral analysis and the results of the Schellong test, which were used to evaluate sympathetic function. These results suggest that MIBG scintigraphy may be useful for evaluating cardiac sympathetic nerve disturbance in patients with diabetes. (*Jpn Circ J* 1995; **59**: 599–607)

^{123}I -Metaiodobenzylguanidine (MIBG) is a newly developed agent that accumulates in the norepinephrine storage vesicles of adrenergic nerve endings, and thus may permit the evaluation of cardiac sympathetic nerve function^{1,2}. It has been widely used to visualize cardiac sympathetic denervation in patients with ischemic heart disease^{3,4}, dilated cardiomyopathy⁵, or ventricular tachycardia⁶. There have been some reports of abnormally low accumulation of MIBG in hearts of patients with diabetic autonomic neuropathy^{7,8} but its clinical

usefulness in this disease has not been well established. The purpose of the present study was to investigate the relationship between clinical symptoms and the diagnosis of diabetic cardiosympathetic nerve disturbance by autonomic function tests, such as power spectral analysis (PSA) of heart rate fluctuations, and by abnormalities in MIBG imaging, and to assess the value of the latter.

MATERIALS AND METHODS

Subjects were divided into three groups: a) 11 patients without diabetes mellitus (DM), (Control: 9 males and 2 females; mean age $\pm$ SD, 60 ± 11 y); b) 10 diabetic patients without neuropathy, (DM1: 6 males

Key words:

^{123}I -MIBG myocardial scintigraphy
Diabetes mellitus
Power spectral analysis
Autonomic neuropathy

(Received April 25, 1994; accepted October 29, 1994)

Third Department of Internal Medicine, Matsushita Memorial Hospital, Moriguchi City, Osaka, Japan

Mailing address: Hajime Miyanaga M.D., The Third Department of Internal Medicine, Matsushita Memorial Hospital, 5-55 Sotoshimacho, Moriguchi City, Osaka, Japan

Fig.1. (a) Heart to mediastinum ratio: H is the ROI surrounding the heart image in the planar anterior view. M is the ROI in the mediastinum.

(b) Six segments were determined using three tomographic views. abbreviations: A, anterior wall; Sep, septum; Ap, apex; Lat, lateral wall; I, inferior wall; P, posterior wall.

(c) Defect index (DI): the sum of the number of points in the patient's maximal counts circumferential profile curve where it is lower than the normal lower limit, on each short-axis slice used to construct the bull's-eye image. Severity index (SI): the sum of the area between the patients maximal counts circumferential profile curve and that of the normal lower limit in each short-axis slice used to construct the bull's-eye image.

and 4 females, 65 ± 8 y); and c) 8 patients with manifest diabetic neuropathy (DM2: 3 males and 5 females, 57 ± 10 y) (Table I). None of the patients had clinical evidence of ischemic heart disease, while all had normal electrocardiograms and normal exercise ^{201}Tl scintigrams, except for two DM2 patients with severe diabetic neuropathy (cases 1, 8; Table III) who had normal static ^{201}Tl scintigrams. Informed consent was obtained from each subject.

MIBG Myocardial Scintigraphy

One hundred and eleven MBq of MIBG were injected intravenously to subjects in the fasting state. Imaging was performed 15 min and 4 h after injection, using a rotating gamma camera equipped with a low-energy multipurpose collimator. Images were acquired in 32 projections for 50 sec each, around a 180° arc extending from RAO 30° to LPO 60° . After single photon emission computed tomography (SPECT), anterior planar imaging was also carried out. Three tomographic images were obtained from the SPECT images; vertical long-axis images, short-axis images and horizontal long-axis images. Bull's-eye images were also constructed from short-axis images. After image-processing, five indices were calculated as follows;

1) Heart to mediastinum ratio (H/M): ratio of the mean counts in a region of interest (ROI) surrounding the entire left ventricular (LV) region to the counts in an ROI in the mediastinum (Fig. 1a).

2) Defect score (DS): the left ventricle was divided into 6 regions (anterior, septal, apical, inferior, lateral, and posterior), and each region was scored according to the grade of MIBG concentration (0, normal; 1, slightly decreased; 2, severely decreased; 3, defect) by visual interpretation; a defect score was calculated by summing the scores for all six regions. (Fig. 1b)

3) Defect index (DI): the sum of the points that were lower than the lower limits of normal subjects (95% confidence line) on the maximal counts circumferential profile curve for each short-axis image used to construct the bull's-eye image (Fig. 1c).

4) Severity index (SI): the sum of the area between the patient's maximal counts circumferential profile curve for each short-axis image that was used to construct bull's-eye images and the normal lower limits (95% confidence line), which were calculated from each corresponding short-axis image in normal subjects (Fig. 1c).

5) Washout rate (WR): for each corresponding pixel, (initial pixel count-delayed pixel count)/initial pixel count) was calculated as WR. Maximum and mean WR of the bull's-eye image were obtained in each subject.

All of these indices was calculated twice

Fig.2. Comparison of heart (H) to mediastinum (M) ratios (H/M) in the test and control groups.

Fig.4. Comparison of maximum and mean wash-out rates (WR) in bull's-eye images in the test and control groups.

Fig.3. Comparison of defect scores (DS) in the test and control groups.

by two experienced observers working independently without any knowledge of the other clinical data. The inter-observer variability of H/M, DI, SI and WR ranged from 2 to 5%, 2 to 8%, 1 to 12% and 3 to 10%, respectively, and the results of statistical analyses in this study were the same with the two observers. The two observers agreed in the appraisal of DS in 23/29 cases (79%), and reached a consensus in cases of disagreement.

Power Spectral Analysis (PSA)

Heart rate was recorded with the subject supine, during deep breathing in the supine position, and with the subject standing (100 beats in each position) on a heart recorder

(SRR5, G.M.S Co, Ltd, Tokyo), and power spectral analysis was performed by the maximum entropy method⁹ (MemCalc Soft Suwa Trust Ltd, Tokyo). Values for low-frequency power (LF: 0.04–0.15 Hz), high-frequency power (HF: 0.15–0.4 Hz), and %LF ($100 \times \text{LF} / (\text{LF} + \text{HF})$) were extracted from the power spectrum.

²⁰¹Thallium Myocardial SPECT (Tl-SPECT) and Other Examinations

Exercise or static Tl-SPECT was performed within a month before or after MIBG examination in all cases. Blood pressure and pulse rate were measured with the patient supine, and then in every 2 min after the patient had been standing for 10 min (Schellong test). The threshold of vibratory sensation at the head of the ulna was also measured with a vibrometer (SMV-5, Technologue Co, Ltd, Tokyo) during MIBG scintigraphy.

Statistical Analysis

Data are expressed as mean ± SD or ± SE. H/M and DS in both initial and delayed MIBG images and WR were compared among the three groups by one-way ANOVA. LF, HF and %LF in each position for the three groups were compared in the same way. Correlations between %LF and DI or SI were analyzed by standard linear regression analysis. A p value of less than 0.05 was considered statistically significant.

Fig. 5. Comparison of low-frequency power (LF, right) and high-frequency power (HF, left) under three conditions in the test and control groups.

Fig. 6. Comparison of % low-frequency power (%LF) under three conditions in the test and control groups.

RESULTS

H/M in the initial image was 2.4 ± 0.4 (mean $\pm$ SD) in controls, 2.3 ± 0.3 in DM1, and 1.9 ± 0.3 in DM2. H/M in the delayed image was 2.6 ± 0.3 , 2.5 ± 0.4 , and 1.8 ± 0.3 , respectively. H/M was significantly higher in controls and DM1 than in DM2 (initial image, $p < 0.05$; delayed image, $p < 0.01$) (Fig. 2). Conversely, DS in the initial image was higher in DM2 (7.0 ± 2.6 , mean $\pm$ SD) than in DM1 (1.5 ± 1.9) and controls (0.7 ± 0.9) ($p < 0.01$). Similarly, DS in the delayed image in DM2 (10.7 ± 3.6) and DM1 (4.0 ± 2.7) were higher than that in controls (1.4 ± 1.3) ($p < 0.01$) (Fig. 3). The maximum WR was higher in DM2 ($71 \pm 15\%$,

mean $\pm$ SD) than in DM1 ($53 \pm 12\%$) and controls ($43 \pm 8\%$) ($p < 0.01$). The mean WR in DM2 was significantly higher than those in DM1 and controls ($42 \pm 15\%$ vs $30 \pm 8\%$ and $28 \pm 9\%$, $p < 0.05$) (Fig. 4). LF was 533 ± 108 (mean $\pm$ SE) msec² in controls, 367 ± 69 msec² in DM1, and 97 ± 48 msec² in DM2 in the supine position; corresponding values during deep breathing were 1196 ± 290 , 1121 ± 441 , and 164 ± 44 msec², respectively. For standing subjects, the corresponding values were 681 ± 159 , 185 ± 51 and 232 ± 124 msec², respectively. There was a statistically significant difference between controls and DM2 in the supine position, and between controls or DM1 and DM2 during deep breathing ($p < 0.05$) (Fig. 5). HF in the supine position was 224 ± 84 (mean $\pm$ SE) msec² in controls, 80 ± 21 in DM1, and 72 ± 35 in DM2. Corresponding values were 145 ± 24 , 175 ± 68 and 121 ± 74 msec² during deep breathing and 96 ± 25 , 22 ± 7 and 21 ± 7 msec² in the standing position, respectively. A statistically significant difference was present between controls and DM1 or DM2 in the standing position (Fig. 5). %LF values in the controls ($73 \pm 17\%$) and DM1 ($80 \pm 16\%$) were significantly higher than those in DM2 ($52 \pm 22\%$) in the supine position (control and DM2, $p < 0.01$; DM1 and DM2, $p < 0.05$) (Fig. 6). There were no significant differences in %LF among the three groups in the other positions. However, a weak, but significant, correlation was found between %LF in the supine position

Fig.7. Correlation of % low-frequency power (%LF) and defect index (DI) or severity index (SI) in diabetic patients of this study.

vertical long axis short axis horizontal long axis
(a) ^{123}I -MIBG (delayed images)

II/M 2.0 (2.6 ± 0.3)
DS 12 (1.4 ± 1.3)
DI 240 (10 ± 20)
SI 1268 (30 ± 58)
WR(max) 82% (43 ± 8)
LF (SUPINE) 5 msec² (533 ± 108)
HF (SUPINE) 11 msec² (224 ± 84)
%LF(SUPINE) 31% (73 ± 17)
(mean $\pm$ SD, SE of normal subjects)

(c) The results of indices obtained from MIBG and PSA

vertical long axis short axis horizontal long axis
(b) ^{201}Tl (initial images)

Fig.8. ^{123}I -MIBG, ^{201}Tl and the results of indices of a subjects (case 6, Table III) in group DM2.

and DI or SI (%LF vs DI, $r = -0.44$, $p < 0.05$; %LF vs SI, $r = -0.49$, $p < 0.01$). This correlation was stronger when only data from the diabetic subjects (DM1 and DM2) were analyzed (%LF vs DI, $r = -0.57$, $p < 0.05$; %LF vs SI, $r = -0.59$, $p < 0.05$) (Fig. 7). The maximum fall in systolic blood pressure that was brought about by standing abruptly was significantly greater in DM2 (-29 ± 18 mmHg) than in DM1 (5 ± 18 mmHg) or controls (-7 ± 10 mmHg) (DM2 vs DM1, control, $p < 0.01$). The threshold of vibratory sensation was higher in DM2 ($33 \pm 13 \times 10^{-2}$ G) than in DM1 ($10 \pm 3 \times$

10^{-2} G) or controls ($9 \pm 3 \times 10^{-2}$ G) (DM2 vs DM1, control, $p < 0.01$) (Table II). Table III shows the characteristics of DM2 patients and scintigraphic findings scored by visual interpretation. All of the DM2 patients showed abnormally low MIBG concentrations in the infero-posterior, apical, and lateral regions, with little anterior or septal involvement. A typical MIBG image in DM2 (case 6, Table I) is shown in Fig. 8a. There was a definite decrease in MIBG in the apico-infero-posterior and lateral regions in the delayed images, whereas exercise ^{201}Tl images showed normal homogeneous RI

TABLE I AGE AND SEX OF PATIENT GROUPS IN THIS STUDY

	Control (C)	Diabetes without complication (DM1)	Diabetes with neuropathy (DM2)
number of studies	11	10	8
Sex (male/female)	9/2	6/4	3/5
Age (mean $\pm$ SD), y	60 $\pm$ 11	65 $\pm$ 8	57 $\pm$ 10

TABLE II RESULTS OF THE SCHELLONG TEST AND THE THRESHOLD OF VIBRATORY SENSATION IN THE TEST AND CONTROL GROUPS

	Control	DM1	DM2
Number of patients	11	10	8
Systolic BP (supine/standing) (mmHg)	124 $\pm$ 15/117 $\pm$ 9	129 $\pm$ 14/132 $\pm$ 13	141 $\pm$ 19/111 $\pm$ 18
Change of systolic pressure (mmHg)	-7 $\pm$ 10	5 $\pm$ 18	-29 $\pm$ 18*
Pulse rate (supine/standing) (/min)	61 $\pm$ 12/65 $\pm$ 9	81 $\pm$ 10/87 $\pm$ 9	72 $\pm$ 12/80 $\pm$ 13
Change of pulse rate (/min)	4 $\pm$ 5	6 $\pm$ 6	8 $\pm$ 6
Threshold of vibration ($\times 10^{-2}$ G)	9 $\pm$ 3	10 $\pm$ 3	33 $\pm$ 13**
* $p < 0.05$ vs control and DM1, ** $p < 0.01$ vs control and DM1			mena $\pm$ SD

TABLE III CHARACTERISTICS OF PATIENTS IN GROUP DM2

	Age	Sex	Symptoms	Duration of diabetes (y)	HbA1c	Abnormal regions	DS (delayed image)	Maximum WR
1.	60	F	TRIOPATHY	15	11.6	AP, LAT, INF, POST	7	59
2.	56	M	NEUROPATHY	22	7.9	SEP, AP, LAT, INF, POST	10	66
3.	46	F	NEUROPATHY	13	10.3	SEP, AP, LAT, INF, POST	10	78
4.	52	M	TRIOPATHY GANGRENE	9	5.9	AP, LAT, INF, POST	9	54
5.	55	F	NEUROPATHY GANGRENE	20	12.9	AP, LAT, INF, POST	10	74
6.	46	F	NEUROPATHY GANGRENE	15	7.4	AP, LAT, INF, POST	12	82
7.	74	M	NEUROPATHY	7	6.9	ANT, SEP, AP, LAT, INF, POST	18	100
8.	67	F	NEUROPATHY	10	7.0	AP, LAT, INF, POST	10	57

Triopathy indicates retinopathy, nephropathy, and neuropathy

abbreviations: ANT, anterior; SEP, septum; AP, apical; LAT, lateral; INF, inferior; POST, posterior

distribution (Fig. 8b).

DISCUSSION

Diabetic neuropathy is a major complication of diabetes, and diabetic autonomic neuropathy has been shown to increase mortality.¹⁰ Several simple and objective

tests based on cardiovascular reflexes have been developed for evaluating autonomic dysfunction, especially in patients with diabetes. These tests, such as the Valsalva test, the deep breathing test, the orthostatic test, and the hand grip test, are clinically useful but are not sensitive enough to evaluate the function of cardiac sympathetic

nerve!¹ Over the past decade, PSA of heart rate fluctuations has proven to be a useful method for evaluating cardiovascular autonomic activity!^{12,13} Two major components, HF and LF, are extracted by PSA from variations in heart rate. HF is known to reflect respiratory sinus arrhythmia and is correlated with parasympathetic activity, whereas LF is thought to reflect mainly sympathetic activity!¹² In one study, PSA was used to evaluate diabetic cardiac autonomic neuropathy, and revealed decreases in both HF power and LF power!¹⁴ In the present study, patients with diabetic neuropathy (DM2) showed low LF when supine or during deep breathing, low HF when standing, and low % LF when supine. These data, which are somewhat compatible with other reports, suggest that diabetic patients, especially those with neuropathy, exhibit disturbances of both parasympathetic and sympathetic nerve activity that can be evaluated by PSA.

MIBG, which was developed by Wieland et al in 1980!¹ is distributed in the vesicles of sympathetic nerve endings, and MIBG scintigraphy has recently been used to visualize cardiac sympathetic nerve innervation, mainly in patients with ischemic heart disease,^{3,4} congestive heart disease!⁵ or dilated cardiomyopathy!^{5,15} It has also been used in patients with diabetes mellitus. Sisson et al¹⁷ reported a decrease in the myocardial uptake of MIBG in diabetic patients with autonomic neuropathy. Mantysaari et al⁸ also demonstrated that myocardial uptake and the net influx of MIBG were significantly decreased in diabetic patients with autonomic neuropathy in both delayed images and initial images, and these findings were observed to a lesser degree in diabetic patients without autonomic neuropathy. Neubauer and Christensen¹⁶ reported decreased norepinephrine concentration in the hearts of long-term diabetic patients with autonomic neuropathy at postmortem examination. These findings coincide with our finding of decreased H/M and high DS in initial and delayed images in DM2 patients and in delayed images in DM1 patients. Although the H/M ratio was not linearly correlated with the true MIBG myocardial uptake ratio, and was decreased in patients with low LV function,⁵ this index can still be used to

roughly, but easily, indicate the degree of MIBG uptake by the heart. In the present study, DM2 patients showed the highest WR of the three groups, even though we merely measured the change in counts over 4 h without considering the decay of ¹²³I. Nakajo et al¹⁷ showed that the ratio of intravesicular accumulation of MIBG to total tissue concentration in rat heart was relatively low immediately after injection, but increased up to 50% at 4 h later due to rapid washout of MIBG in the extravascular tissue of the rat heart. However, in the human heart, a non-neuronal uptake mechanism was not thought to be significant in an investigation of transplanted human hearts!¹⁸ Therefore, our data might suggest an acceleration of intravesicular MIBG turnover in diabetic patients. The MIBG scintigram showed a decreased concentration in the infero-posterior region, even in normal subjects!^{19,20} and Kobayashi et al²¹ reported a significant artifactual defect adjacent to the liver with a liver/heart uptake ratio of more than 2:1. Infero-posterior, infero-septal and apical involvement has also been reported in other heart diseases, such as hypertrophic;²² dilated!^{14,22} or drug-induced cardiomyopathy!¹⁴ and idiopathic long QT syndrome!²³ DM2 subjects in this study also showed a decreased concentration of MIBG in the infero-posterior, apical, and lateral regions of the LV wall, which later might spread to the anterior or septal regions when images are interpreted visually or even semiquantitatively by comparison with circumferential profile curves of normal subjects. These findings may suggest that sympathetic denervation in DM patients, not specific in this disease, shows localization of involvement, or segmental heterogeneity. DM2 patients showed a definite disturbance of peripheral nerves, indicated by a rise in the threshold of vibratory sensation, and sympathetic nerve dysfunction, indicated by an abnormal fall in systolic blood pressure (Schellong test). These findings coincide with those of the MIBG study. PSA also showed abnormal LF, HF and %LF in DM2, and when %LF was compared with DI or SI, each calculated from bull's-eye images, a weak but significant inverse correlation was found. MIBG scintigraphy showed similar abnormalities in these indices, more prominent in DM2 pa-

tients than in DM1 patients who had not yet developed autonomic neuropathy, even though they were not detected by other examinations. This finding suggests that MIBG may be able to detect cardioautonomic neuropathy in DM patients at an early stage, when patients are not yet aware of the disturbance.

Limitations of This Study and Method

First, diabetic patients often suffer asymptomatic myocardial ischemia and microangiopathy. Not all of the subjects in this study were examined by coronary angiography. However, all of the subjects did have normal electrocardiograms and normal exercise ^{201}Tl myocardial SPECT, except two DM2 subjects with normal images at rest. ^{201}Tl myocardial SPECT is a reliable diagnostic tool for myocardial ischemia and has high a sensitivity, but can not be used to completely rule out coronary artery disease, such as triple-vessel disease or stunned myocardium. As a result, the possible influence of myocardial ischemia on MIBG findings in some subjects can not be denied. Second, Morozumi et al¹⁵ reported that H/M and WR of MIBG were correlated with left ventricular function. In this study, all of the subjects were classified as functional class I (NYHA), although only a few patients had been examined by pool scintigraphy or contrast levography. Therefore, it is possible that the results in this study regarding H/M and WR were affected by LV function. Third, as mentioned above, we calculated WR (maximum and mean) from the change in the rate of radioactivity in the corresponding pixels in the bull's-eye image, and did not evaluate the actual myocardial washout of MIBG. Although accurately evaluating WR in the inferior region is difficult when the activity of MIBG in the liver is high, in practice, WR calculated in this way serves to differentiate patients quite well. Finally, another important limitation is that denervation of sympathetic nerves accompanies severe myocardial ischemia, such as occurs in myocardial infarction. Therefore, MIBG scintigraphy would not be able to provide a precise evaluation of diabetic cardiosympathetic dysfunction in the event of myocardial infarction.

Conclusion

MIBG scintigrams showed definite abnormal findings, such as decreased H/M, high DS, and rapid WR in patients with diabetes, especially those with autonomic neuropathy. Even in patients without autonomic neuropathy, DS in delayed images was different from that in the control, but to a lesser degree. An inverse correlation was found between %LF, extracted by PSA, and DI or SI. The Schellong test revealed an abnormality in DM2 patients. Our results suggest that abnormal findings in a MIBG scintigram reflect cardiac sympathetic nerve disturbance in diabetic patients. We conclude that MIBG scintigraphy is useful for easily and clearly evaluating cardiac sympathetic nerve dysfunction and may be able to detect this condition at an early stage, when the patient is not yet aware of symptoms.

REFERENCES

1. Wieland DM, Wu JI, Brown LE, Mangner TJ, Swanson DP: Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with [^{131}I] iodobenzylguanidine. *J Nucl Med* 1980; **21**: 349–353
2. Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, Beierwaltes WH: Myocardial imaging in man with I- 123 metaiodobenzyl-guanidine. *J Nucl Med* 1981; **22**: 129–132
3. Nisimura T, Uehara T, Oka H, Kumita S, Mitani I, Yokota I, Hayashida K, Haze K, Ohe T: Serial assessment of denervated but viable myocardium following acute myocardial infarction by using ^{123}I -MIBG and ^{201}Tl myocardial SPECT. *Jpn J Nucl Med* 1990; **27**: 709–718
4. Satoh K, Katoh K, Murata H, Nishimura S, Yamaguchi H: Assessment of ischemic damage of the cardiac sympathetic nerve function by semiquantitative analysis of ^{123}I -MIBG (metaiodobenzylguanidine) SPECT-comparison with ^{201}Tl -Cl-SPECT. *Jpn J Nucl Med* 1990; **27**: 821–831
5. Schofer J, Spielmann R, Schuchert A, Weber K, Schluter M: Iodine-123 metaiodobenzylguanidine scintigraphy: A noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1988; **12**: 1252–1258
6. Nisimura T, Kurita T, Ohe T, Hayashida K, Uehara T, Mitani I, Oka H, Hayashi M: Case of myocardial infarction with ventricular tachycardia which had discrepancy of defect size between ^{123}I -MIBG and ^{201}Tl Cl myocardial imaging. *Jpn J Nucl Med* 1989; **26**: 419–423
7. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, Glovriak JV, Sherman P, Beierwaltes BS, Beierwaltes WH: Metaiodobenzylguanidine to map scintigraphically the adrener-

- gic nervous system in man. *J Nucl Med* 1987; **28**: 1625–1636
8. Mantysaari M, Kuikka J, Mustonen J, Tahvanainen K, Vanninen E, Lansimies E, Uusitupa M: Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetes patients using [¹²³I]metaiodobenzylguanidine. *Diabetes* 1992; **41**: 1069–1075
 9. Ohtomo N, Terachi S, Tanaka Y: Nonlinear time series analysis - 1. A new method of analysis and the theoretical background. *Bull Fac Eng Hokkaido Univ* 1991; **158**: 43–55
 10. Ewing DJ, Campbell IW, Clarke BF: The natural history of diabetic autonomic neuropathy. *Q J Med* 1980; **49**: 95–108
 11. Ewing DJ, Martyn CN, Young RJ, Clarke BF: The value of cardiovascular autonomic function test: 10 years experience in diabetes. *Diabetes Care* 1985; **8**: 491–498
 12. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gorden D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H: Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; **248**: H151–H153
 13. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Dell'Orto S, Piccaluga E, Turiel M, Basseli G, Cerutti S, Malliani A: Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; **59**: 178–193
 14. Ueda N: Detection of diabetic autonomic neuropathy -utilization of power spectral analysis of heart rate variability- *J Jpn Diab Soc* 1992; **35**: 17–23
 15. Morozumi T, Isida Y, Tani A, Sato H, Matsuyama T, Ozaki H, Hori M, Kitabatake A, Kamada T, Kimura K, Nakamura Y, Kozuka T: Clinical significance of I-123 MIBG myocardial scintigraphy for evaluating the severity of congestive heart failure. *Jpn J Nucl Med* 1991; **28**: 271–280
 16. Neubauer B, Chrstensen NJ: Norepinephrine, epinephrine and dopamine contents of the cardiovascular system in long-term diabetes. *Diabetes* 1976; **25**: 6–10
 17. Nakajo M, Shimabukuro K, Yoshimura H, Yonekura R, Nakabeppu Y, Tanoue P, Shinohara S: Iodine-131-metaiodobenzylguanidine intra-and extravesicular accumulation in the rat heart. *J Nucl Med* 1986; **27**: 84–89
 18. Dae MW, De Marco T, Botvinick EH, O'Connell JW, Hattner RS, Huberty JP, Yuen-Green MS: Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts: Implications for clinical studies. *J Nucl Med* 1992; **33**: 1444–1450
 19. Shiga K, Sugihara H, Inoue T, Fujita N, Ogawa F, Nakagawa T, Otsuki K, Umamoto I, Taniguchi Y, Nakagawa M: The distribution and kinetics of ¹²³I-MIBG in normal human hearts. *Jpn J Nucl Med* 1993; **30**: 1359–1367
 20. Gill JS, Hunter GJ, Gane G, Camm AJ: Heterogeneity of the human myocardial sympathetic innervation: In vivo demonstration by ¹²³I-labeled metaiodobenzylguanidine scintigraphy. *Am Heart J* 1993; **126**: 390–398
 21. Kobayashi H, Terada S, Kanaya S, Kashikura K, Momose M, Hosoda S, Kusakabe K: Artifactual defect of inferior myocardium on ¹²³I-metaiodobenzylguanidine myocardial SPECT: Characteristic findings and preventive method on phantom study. *Jpn J Nucl Med* 1994; **31**: 359–366
 22. Hirosawa K, Tanaka T, Kishida K, Bunko H: Clinical evaluation of ¹²³I-MIBG for assessment of sympathetic nervous system in the heart (Multi-center clinical trial). *Jpn J Nucl Med* 1991; **28**: 461–476
 23. Gohl K, Feistel H, Weikl A, Bachmann K, Wolf F: Congenital myocardial sympathetic dysinnervation (CMSD) - a structural defect of idiopathic long QT syndrome. *PACE* 1991; **14**: 1544–1553