Annals of Nuclear Medicine Vol. 16, No. 1, 33–38, 2002

Serial change in ^{123}I-MIBG myocardial scintigraphy in non-insulin-dependent diabetes mellitus

Shigeki NAGAMACHI,* Seishi JINNOUCHI,* Takeshi KUROSE,** Ryuichi NISHII,* Keiichi KAWAI,*** Shigemi FUTAMI,* Shozo TAMURA* and Shigeru MATSUKURA**

**Department of Radiology, **Third Department of Internal Medicine, and ***Central Research Laboratories, Miyazaki Medical College*

Purpose: We performed ^{123}I-MIBG (MIBG) myocardial scintigraphy twice in patients with non-insulin-dependent diabetes mellitus (NIDDM) to investigate whether MIBG distribution was improved by pertinent clinical control. To determine the influential factors for MIBG distribution, we investigated the association between various clinical parameters and the serial change in MIBG uptake parameters. ***Patients and Methods:*** Twenty NIDDM patients with no cardiac disorders were evaluated. Planar images were taken at 30 minutes (early) and 3 hours (delayed) after MIBG injection. The heart-to-upper-mediastinum uptake ratio (H/M) and washout ratio (WR) were calculated as parameters for estimating cardiac sympathetic function. Patients were divided into two groups, eight in the improved group and twelve in the unimproved group, according to the serial change in H/M. The mean interval between the baseline and the follow up study was 2.1 ± 0.6 year. Differences between the means of the laboratory data in patients in both groups were compared for the baseline and the follow up study by using the paired t-test. As a means of determining the influential factors for a serial change of MIBG uptake, Fisher's exact test was performed to evaluate the association between the serial change in cardiac MIBG parameters and changes in other clinical parameters, such as blood sugar (BS) control, BS control method (insulin therapy), serum cholesterol control, and severity of diabetic complications. We also analyzed the association between the changes in $CV_{R\text{-}R}$ (coefficient variance of R-R intervals at rest ECG) or NCV (velocity of posterior tibial nerve) and those of other clinical parameters. Associations among these neurological parameters (MIBG parameters, $CV_{R\text{-}R}$ and NCV) were also analyzed. ***Results:*** Paired t-tests showed a significant decrease in fasting blood sugar and fructosamine in the improved group in the follow up study compared to those in the baseline study. Nevertheless, Fisher's exact test showed no significant association between FBS, HbA_{1C}, fructosamine and the improvement in cardiac MIBG uptake. The only significant association was observed between the serial change in H/M and the BS-control method (insulin therapy). Within the neurological parameters, a significant association was noted between the serial changes in H/M and $CV_{R\text{-}R}$. ***Conclusion:*** Although BS control was likely to be an important factor, it did not always ameliorate cardiac MIBG uptake. Based on the significant association between the BS-control method (insulin therapy) and MIBG uptake change, the severity of diabetes mellitus was likely to be a more influential factor. It was suggested that cardiac MIBG uptake could improve within the mild stage if controlled by diet therapy or an oral hypoglycemic agent in NIDDM.

Key words: follow-up ^{123}I-MIBG myocardial scintigraphy, NIDDM, serial change

Received February 28, 2001, revision accepted November 1, 2001.

For reprint contact: Shigeki Nagamachi, M.D., Department of Radiology, Miyazaki Medical College, Kihara 5200, Kiyotake-cho, Miyazaki 889–1692, JAPAN.

E-mail: snagama@post.miyazaki-med.ac.jp

INTRODUCTION

ALONG with cardiac denervation, cardiac autonomic neuropathy is a significant prognostic factor for diabetes mellitus.[1–3] Many studies have reported the usefulness of

^{123}I-MIBG (MIBG) scintigraphy in monitoring diabetic cardiac sympathetic nerve dysfunction.[4–16] Decreases in MIBG uptake have been reported to correlate with the body mass index (BMI), systolic blood pressure, disturbed left ventricular diastolic filling, and QT interval length. Diabetic patients with autonomic neuropathy (AN) have a considerably decreased MIBG uptake when compared to diabetics without AN,[4,6] but few studies have been performed to clarify whether a disturbed cardiac sympathetic nervous system can recover in diabetic patients. In insulin-dependent diabetes mellitus (IDDM), poor glycemic control constitutes an essential determinant in the progression of MIBG uptake, whereas the impact of glycemic control on the serial change in MIBG uptake has not been determined in non-insulin-dependent diabetes mellitus (NIDDM). Although a few limited studies with aldose reductase inhibitor have been reported,[10,11] the results have not been generally accepted.

The current study was undertaken to clarify how myocardial MIBG distribution changes in a clinical follow-up of patients with NIDDM and to find the determinant factor influencing the changes in MIBG distribution. At the same time, the serial changes in the coefficient variance of the R-R interval of rest ECG ($CV_{R\text{-}R}$), nerve conducting velocity of the posterior tibial nerve (NCV), and MIBG uptake were evaluated.

MATERIALS AND METHODS

Twenty patients, all over 43 years of age and diagnosed with NIDDM by the criteria of the National Diabetes Group, were enrolled in this study. All subjects had a low probability of coronary artery disease based on the absence of cardiovascular symptoms, a normal resting ECG, a normal maximal exercise ECG, and a normal stress ^{201}Tl-chloride myocardial SPECT. Based on echocardiographic analysis, no subjects had evidence of left ventricular hypertrophy, and all had normal left ventricular function. All subjects agreed to participate in the study and signed an informed consent form approved by the Institutional Review Board of Miyazaki Medical College.

To block tracer uptake in the thyroid gland, each subject received 10 mg of potassium iodine 2 days before the investigation and 10 mg daily for 1 or 2 days afterwards. Patients remained on their normal diets and drug regimens except for drugs that could cause changes in sympathetic activity. Anterior planar images were obtained 15 minutes (early) and 4 hours (delayed) after ^{123}I-MIBG (111 MBq) injection by means of a rotating gamma camera (ZLC7500, Shimadzu) equipped with a Krypton collimator. Energy discrimination was provided by a 20% window centered on the 159 keV photopeak of ^{123}I.

For the semiquantitative analysis, the heart-to-upper-mediastinum uptake ratio (H/M) was calculated by the conventional ROI method on both early and delayed planar images, as previously reported.[4,17] After correction for the physical decay of ^{123}I, the tracer washout rate from the myocardium (WR) was calculated by the following formula.

$$WR = \frac{\text{early}\,([H]-[M]) - \text{delayed}\,([H]-[M])}{\text{early}\,([H]-[M])} \times 100\%$$

According to the serial change in H/M, we divided all patients into two groups: those whose H/M values were higher in the follow-up study than in the baseline study were placed in the improved group. The patients whose H/M values were lower in the follow-up study than in the baseline study were placed in the unimproved group. Because H/M is affected by the size of the heart,[17] the cardiac chamber size was confirmed by ^{201}Tl-SPECT to be unchanged between the baseline and the follow-up study.

The clinical characteristics, the mean laboratory data values and MIBG parameters in the baseline study for the two groups were compared (Table 1). All values are shown as the mean ± SD. In each group, means for each parameter in the baseline study data and the follow-up study data were compared (Table 2). Scheffe's F-test for multiple comparisons was applied to detect the statistically significant difference as defined by ANOVA. A comparison of serial data within one group was performed by means of Wilcoxon's matched-pairs signed-rank test. A value of $p < 0.05$ was considered statistically significant.

Non-parametric testing (Fisher's exact test) was also employed to evaluate whether the serial changes in MIBG parameters were independent of the change in other

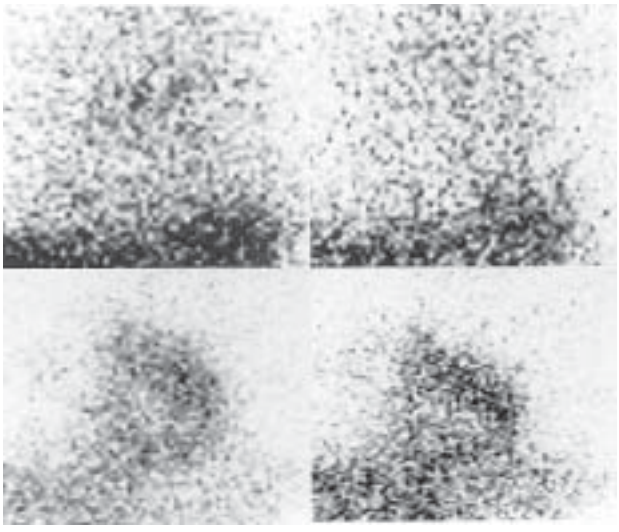

Fig. 1 A 58-year-old patient with NIDDM for 13 years. In the first study (*upper row*), myocardial MIBG uptake was not noted on either the early (*left*) or delayed image (*right*). H/M was 1.7 on the early and 1.8 on the delayed image. WR was 11.8%. In the follow-up study 2 years later (*lower row*), normal myocardial uptake was noted on both the early (*left*) and delayed images (*right*). H/M increased to 3.2 on the early and 3.1 on the delayed image. WR decreased to 3.1%.

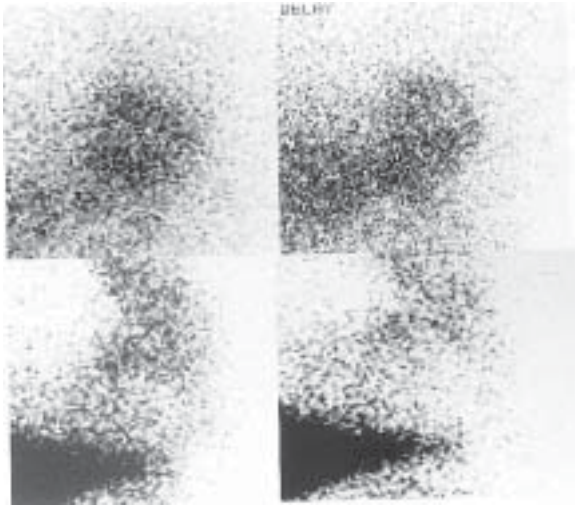

Fig. 2 A 47-year-old woman with NIDDM for 13 years. In the first study (*upper row*), normal myocardial MIBG uptake was noted. The value of H/M was 2.5 on the early (*left*) and 2.2 on the delayed image (*right*). WR was 12.0%. Two years later (*lower row*), myocardial MIBG uptake was unclear on both the early (*left*) and the delayed images (*right*). Both uptake parameters decreased to 1.9 and 1.5. WR was 21.1%.

clinical parameters. That is, we divided all patients into two categories according to each clinical parameter. Then the association between each clinical parameter and the change in MIBG distribution, whether improved or unimproved, was analyzed. The parameters were age (50≥ or 50<), gender, number of years from onset (≥10 years or <10 years), body mass index (BMI), hypertension, orthostatic hypotension, BS-control, BS-control method (insulin therapy), VB_{12} therapy. The relevance of glycemic controls was defined as well-controlled or poorly-controlled according to the change in HbA_{1C} and fructosamine during the observation period. The severity of both retinopathy and nephropathy was defined as follows: normal or simple retinopathy was categorized as mild, and preproliferative or proliferative retinopathy was categorized as severe. Similarly, stages 0 to IIIa nephropathy (Japanese Diabetic Society classification) were categorized as mild and stages IIIb to IV were categorized as severe. In terms of BMI, triglycerides and total cholesterol, we divided patients into improved and unimproved groups.

Corresponding analyses of clinical parameters and $CV_{R\text{-}R}$ or NCV were also done. In addition, associations among the serial changes in nerve-condition parameters were evaluated.

RESULTS

The representative improved case showed a remarkable increase in cardiac MIBG uptake on both early and delayed planar images in the follow-up study (Fig. 1). In contrast, the representative unimproved cases showed a notable decrease in cardiac MIBG uptake in the follow-up study (Fig. 2).

Table 1 Comparison of parameters between improved and unimproved group in the baseline study

	Improved (n = 8)	Unimproved (n = 12)
Male : Female	3 : 5	8 : 4
Age	58.8 ± 10.8	56.1 ± 7.9
Duration	13.0 ± 9.1	12.7 ± 2.5
BMI	24.5 ± 4.2	22.0 ± 2.0
HbA_{1C}	8.4 ± 1.4	7.9 ± 1.5
FBS	236.8 ± 115.8	204.4 ± 41.6
T-cho	234.9 ± 42.9	245.0 ± 25.2
TG	193.1 ± 140.7	180.3 ± 51.1
Fructosamine	336.9 ± 45.6	355.5 ± 124.1
NCV	42.6 ± 6.0	42.5 ± 5.3
$CV_{R\text{-}R}$	1.3 ± 0.8	1.7 ± 0.5
H/M-E	2.3 ± 0.5	2.4 ± 0.3
H/M-D	2.1 ± 0.5	2.1 ± 0.4
WR	25.7 ± 10.4	30.7 ± 9.2
Neuropathy	6 (75.0%)	12 (100%)
Retinopathy	5 (62.5%)	12 (100%)
Nephropathy	4 (50.0%)	12 (100%)
Hypertension	6 (75.0%)	7 (58%)
Hypotension	5 (62.5%)	8 (68%)
Insulin	2 (25.0%)	11 (92%)
Vitamin B_{12}	4 (50.0%)	6 (50%)

Duration: Duration from onset, BMI: Body mass index, FBS: Fasting blood sugar, T-cho: Total cholesterol, TG: Triglyceride, NCV: Nerve conducting velocity of posterior tibial nerve, $CV_{R\text{-}R}$: Coefficient variance of R-R interval, H/M-E: Heart to mediastinal uptake ratio of early image, H/M-D: Heart to mediastinal uptake ratio of delayed image, WR: Washout ratio, Hypotension: Orthostatic hypotension, Insulin: Controlled with insulin therapy, Vitamin B_{12}: Vitamin B_{12} medication

Regarding as laboratory data, there were no apparent differences between the improved group and the unimproved group in the baseline study. Prevalence of diabetic complications and insulin therapy were higher in the unimproved group (Table 1). In the improved group, the mean H/M value increased significantly and WR decreased significantly in the follow-up study. Both fasting plasma glucose and fructosamine significantly decreased. In the unimproved group, both H/M values significantly decreased in the follow-up study. Mean BMI, triglyceride, NCV and $CV_{R\text{-}R}$ significantly deteriorated (Table 2).

Fisher's exact test showed a significant association between the serial change in H/M, $CV_{R\text{-}R}$ and insulin therapy. NCV showed a significant association with triglyceride control (Table 3). Among nerve-condition parameters, only the serial change in $CV_{R\text{-}R}$ showed a significant association with H/M (Table 4).

Table 2 Comparison of parameters between baseline and follow up study

	Improved group (n = 8)		Unimproved group (n = 12)	
	baseline	follow up	baseline	follow up
H/M-E	2.3 ± 0.5	*3.3 ± 0.4	2.4 ± 0.3	*2.1 ± 0.3
H/M-D	2.1 ± 0.5	*2.9 ± 0.4	2.1 ± 0.4	*1.7 ± 0.5
WR	25.7 ± 10.4	*19.6 ± 9.1	30.7 ± 9.2	39.1 ± 12.3
NCV (m/sec)	42.6 ± 6.0	44.1 ± 5.9	42.5 ± 5.3	*38.3 ± 3.8
$CV_{R\text{-}R}$	1.5 ± 0.8	2.3 ± 1.6	1.7 ± 0.5	*1.2 ± 0.3
BMI (kg/m^2)	24.5 ± 4.2	23.9 ± 3.4	22.0 ± 2.0	*24.6 ± 1.7
HbA_{1C} (%)	8.4 ± 1.4	8.0 ± 1.9	8.1 ± 1.5	8.0 ± 2.1
Fructosamine	336.9 ± 45.6	*292.0 ± 58.7	355.5 ± 124.1	331.5 ± 101.3
FBS (g/d*l*)	236.8 ± 115.8	*153.6 ± 70.5	204.4 ± 41.6	201.6 ± 68.8
TG (mg/d*l*)	193.1 ± 140.7	161.8 ± 94.6	180.3 ± 51.1	*204.6 ± 36.5
T-cho	234.9 ± 42.9	213.6 ± 23.8	245.0 ± 25.2	266.4 ± 33.4

H/M-E: Heart to mediastinal uptake ratio of early image, H/M-D: Heart to mediastinal uptake ratio of delayed image, WR: Washout ratio, NCV: Nerve conduction velocity of posterior tibial nerve, $CV_{R\text{-}R}$: Coefficient variance of R-R interval, BMI: Body mass index, FBS: Fasting blood sugar, TG: Triglyceride, T-cho: Total cholesterol, * $p < 0.05$

Table 3 Association between change of neurological parameters and other clinical parameters

	Neurological parameters				
	H/M-E	H/M-D	WR	$CV_{R\text{-}R}$	NCV
Age	0.64	0.64	>0.99	0.35	0.34
Sex	0.36	0.36	>0.99	>0.99	>0.99
Duration	>0.99	>0.99	0.31	>0.99	0.31
BMI	0.4	0.4	0.06	>0.99	>0.99
Nephropathy	0.17	0.17	0.16	>0.99	0.65
Retinopathy	>0.99	>0.99	>0.99	>0.99	>0.99
Hypertension	0.64	0.64	>0.99	>0.99	>0.99
Hypotension	0.64	0.64	0.61	0.31	0.64
TG	0.17	0.17	0.65	0.14	0.007*
T-cho	0.65	0.65	>0.99	>0.99	0.65
BS	0.36	0.36	>0.99	0.61	>0.99
Insulin therapy	0.004*	0.004*	0.17	0.007*	0.06
VB_{12} therapy	0.67	0.67	>0.99	0.64	>0.99

H/M: Heart to mediastinum uptake ratio, E: Early, D: Delayed WR: Washout ratio, $CV_{R\text{-}R}$: Coefficient variance of R-R interval, BMI: Body mass index, TG: Triglyceride, T-cho: Total cholesterol, BS: Blood sugar, *: statistically significant

Table 4 Association among neuronal parameters

	H/M-E	H/M-D	WR	$CV_{R\text{-}R}$	NCV
H/M-E		0.001*	0.06	0.007*	0.17
H/M-D	0.001*		0.06	0.007*	0.17
WR	0.06	0.06		0.3	0.3
$CV_{R\text{-}R}$	0.007*	0.007*	0.3		0.14
NCV	0.65	0.65	0.3	0.14	

H/M: Heart to mediastinum uptake ratio, E: Early, D: Delayed, WR: Washout ratio, $CV_{R\text{-}R}$: Coefficient variance of R-R interval, NCV: Nerve conduction velocity of posterior tibial nerve, *: statistically significant

DISCUSSION

The current study demonstrated that cardiac ^{123}I-MIBG distribution improved in patients with NIDDM. The result was not in accordance with the previous report, which stated that diabetic cardiac autonomic neuropathy is an irreversible complication.[18,19] Three major factors which could explain the decreased MIBG uptake in NIDDM were considered[13]: suppressed type 1 uptake, an accelerated release from storage vesicles, and a decreased number of cardiac sympathetic nerve endings or storage vesicles. Theoretically, both the first and the second factors are reversible so that an improvement in MIBG distribution could be established by therapy which improved sympathetic nerve storage vesicle function. The third factor is irreversible and will continue as the disease progresses. Whether cardiac MIBG uptake improves would be determined by a balance of the condition of such factors.

Nevertheless, the most effective method for improving MIBG uptake remains unknown. Several glycemic control factors, such as HbA_{1C} or fructosamine, have been reported to be effectual for regulating both diabetic macroangiopathy and microangiopathy.[20–22] Strict control of HbA_{1C} or FBS is known to be effective for primary prevention of coronary artery disease.[21] Cardiac microangiopathy is also known to improve with strict glycemic control,[20,22] but improvement of cardiac microangiopathy does not always indicate an improvement in sympathetic nerve function.

As glycemic control in the improved group was better at the time of the follow up study than the baseline study, glycemic control was probably important for the improvement of cardiac MIBG uptake. But some cases categorized in the unimproved group showed a decrease in H/M despite a marked drop in HbA_{1C}. Because of no

significant association between glycemic control and serial change in H/M, normoglycemic condition was unlikely to be the absolute factor for the improvement of MIBG uptake. Rather, the severity of diabetes was considered to be more important, based on the significant association between the BS control method (i.e. insulin therapy) and serial change in MIBG. As most of the unimproved cases need insulin therapy, cardiac MIBG uptake was suggested to be an irreversible condition. With the progression of diabetes mellitus, the number of cardiac sympathetic nerve should decrease and they may not be repaired by glycemic control. Rigorous glycemic control, therefore, might be effective only in limited conditions.

Age, gender, BMI, orthostatic hypotension, cholesterol, triglyceride, retinopathy, and nephropathy were not associated. Although several studies have demonstrated that a defect in MIBG uptake is correlated with BMI,[23] HT,[13] and orthostatic hypotension,[4] the modification of these parameters did not lead to the recovery of cardiac MIBG uptake. In contrast, one patient in the unimproved group had new-onset hypertension[13] which is a well-known pivotal factor. These parameters might be only deterioration factors for MIBG distribution.

Diabetic cardiac autonomic neuropathy is now treated by ARI administration,[10,11,24,25] but it has not been confirmed to be effective in patients with severe NIDDM. We had no cases treated with ARI. In the current study, we used the alternate drug vitamin B_{12},[26] but no significant association with MIBG parameters was noted. Although vitamin B_{12} acts to heal damaged nerves via various mechanisms, including acceleration of folic acid metabolism, synthesis of lecithin and acetylcholine,[27,28] it appears ineffectual in repairing destroyed nerves.

As expected, a significant association was noted only between the changes in H/M and $CV_{R\text{-}R}$ among the neurological parameters. Because $CV_{R\text{-}R}$ indicates a parasympathetic nerve condition, both factors could behave similarly.[16] In contrast, there was a discrepancy between the serial change in H/M and conduction velocity of the posterior tibial nerve. Although the severity of peripheral nerve disorder is known to be associated with diabetic retinopathy, glycemic control, and the duration of diabetes,[29] the current study showed no correlation between NCV and these diabetes-related clinical factors, except for triglycerides. The authors do not yet have an explanation for the significant association between NCV and triglyceride control.

No association between WR and H/M could be explained as follows: In the case of a severely damaged cardiac sympathetic nerve, only a little MIBG accumulated on the early images. Consequently, the absolute amount of tracer, which was washed out between the early and delayed images, was small, resulting in a normal WR value even in severe cardiac autonomic neuropathy.

Regarding cardiac function, there is some disagreement about the correlation between cardiac dysfunction and decreased ^{123}I-MIBG uptake.[16,30] Probably due to the short follow-up time, LVEF did not change significantly during the observation period. Longer-term follow up may reveal a correlation between the change in MIBG parameters and cardiac function.

In conclusion, abnormal myocardial MIBG uptake of NIDDM was considered to be reversible under the limited condition of control by diet therapy or an oral hypoglycemic agent. It would improve in association with pertinent glycemic control.

REFERENCES

1. Ewing DJ, Cambell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980; 49: 95–108.
2. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. *JAMA* 1974; 229: 1749–1754.
3. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 1987; 64: 751–754.
4. Nagamachi S, Jinnouchi S, Nakahara H, Flores LG, Ohnishi T, Hoshi H, et al. ^{123}I-MIBG myocardial scintigraphy in diabetic patients: Relationship to autonomic neuropathy. *Nucl Med Commun* 1996; 17: 621–632.
5. Mäntysaari M, Kuikka J, Mustonene J, Tahvanainen K, Vanninen E, Länsimies E, et al. Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [^{123}I]metaiodobenzylguanidine. *Diabetes* 1992; 41: 1069–1075.
6. Kim SJ, Lee JD, Ryu YH, Jeon P, Shim YW, Yoo HS, et al. Evaluation of cardiac sympathetic neuronal integrity in diabetic patients using iodine-123 metaiodobenzyl guanidine. *Eur J Nucl Med* 1996; 23: 401–406.
7. Ziegler D, Weise F, Langen KF, Piolot R, Boy C, Hübinger A, et al. Effects of glycemic control on myocardial sympathetic innervation assessed by [^{123}I] metaiodobenzylguanidine scintigraphy: a 4-year prospective study in IDDM patients. *Diabetologica* 1998; 41: 443–451.
8. Hattori N, Tamaki N, Hayashi T, Masuda I, Kudoh T, Tateno M, et al. Regional abnormality of iodine-123-MIBG in diabetic hearts. *J Nucl Med* 1996; 37: 1985–1990.
9. Dubois EA, Kam KL, Somsen GA, Boer GJ, Bruin K, Batink HD, et al. Cardiac iodine-123 metaiodobenzylguanidine uptake in animals with diabetes mellitus and/or hypertension. *Eur J Nucl Med* 1996; 23: 901–908.
10. Utsunomiya K, Narabayashi I, Nakatani Y, Tamura K, Onishi S. I-123 MIBG cardiac imaging in diabetic neuropathy before and after Epalrestat therapy. *Clin Nucl Med* 1999; 24: 418–420.
11. Utsunomiya K, Narabayashi I, Tamura K, Nakatani Y, Saika Y, Onishi S, et al. Effects of aldose reductase inhibitor and vitamin B_{12} on myocardial uptake of iodine-123 metaiodobenzylguanidine in patients with non-insulin dependent diabetes mellitus. *Eur J Nucl Med* 1998; 25: 1643–1648.
12. Langer A, Freeman MR, Josse RG, Armstrong PW. Metaiodobenzylguanidine imaging in diabetes mellitus: Assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial

ischemia. *J Am Coll Cardiol* 1995; 25: 610–618.
13. Tamura K, Utsunomiya K, Nakatani Y, Saika Y, Onishi S, Iwasaka T. Use of iodine-123 metaiodobenzylguanidine scintigraphy to assess cardiac sympathetic denervation and the impact of hypertension in patients with non-insulin-dependent diabetes mellitus. *Eur J Nucl Med* 1999; 26: 1310–1316.
14. Nagamachi S, Jinnouchi S, Flores II LG, Ohnishi T, Futami S, Nakahara H, et al. ^{123}I-MIBG lung uptake in patients with diabetes mellitus. *KAKU IGAKU (Jpn J Nucl Med)* 1997; 34: 797–805.
15. Nagamachi S, Jinnouchi S, Kurose T, Ohnishi T, Flores II LG, Nakahara H, et al. ^{123}I-MIBG myocardial scintigraphy in diabetic patients: Relationship with ^{201}Tl uptake and cardiac autonomic function. *Ann Nucl Med* 1998; 12: 323–331.
16. Ito T, Azuma S, Hisada K. Studies of the relationship between decreased myocardial ^{123}I-Metaiodobenzylguanidine (MIBG) uptake and clinical examination findings in patients with non-insulin dependent diabetes mellitus. *J Japan Diab Soc* 1998; 41: 1063–1071.
17. Hattori N, Schweiger M. Metaiodobenzylguanidine scintigraphy of the heart: what we learnt clinically? *Eur J Nucl Med* 2000; 27: 1–6.
18. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function test: 10 years experience in diabetes. *Diabetes Care* 8: 491–498.
19. Watkins PJ. Natural history of the diabetic neuropathies. *Q J Med* 1990; 77: 1209–1218.
20. Yokoyama I. Improvement of myocardial flow reserve after successful improvement of hyperglycemia in non-insulin dependent diabetes (NIDDM) was more prominent in NIDDM with coronary artery disease rather than in NIDDM with chest pain syndrome. *J Nucl Med* 1999; 40: 168.
21. Minemawari Y, Tanaka S. A clinical significance of blood glucose control in coronary arteriosclerotic disease with abnormal glucose tolerance. *J Japan Diab Soc* 1999; 42: 735–742.
22. Yokoyama I, Yonekura K, Ohtake T, Yang W, Shin WS, Yamada N. Coronary microangiopathy in type 2 diabetic patients: Relation to glycemic control, sex, and microvascular angina rather than to coronary artery disease. *J Nucl Med* 2000; 41: 978–985.
23. Mäntysaari M, Kuikka J, Mustonen J, Tahvanainen K, Vanninen E, Lansimies E, et al. Measurement of ^{123}I-myocardial metaiodobenzyl-guanidine for studying cardiac autonomic neuropathy in diabetes mellitus. *Clin Auton Res* 1996; 6: 163–169.
24. Kurata C, Okayama K, Wakabayashi Y, Shouda S, Mikami T, Tawarahara K, et al. Cardiac sympathetic neuropathy and effects of aldose reductase inhibitor in streptozotocin-induced diabetic rats. *J Nucl Med* 1997; 38: 1677–1680.
25. Terashima H, Hama K, Yamamoto R, Tsuboshima M, Kikkawa R, Hatanaka I, et al. Effects of a new aldose reductase inhibitor on various tissues *in vitro*. *J Pharmacol Exp Ther* 1984; 229: 226–230.
26. Utsunomiya K, Tamura K, Nakatani Y, Saika Y, Karime S, Ohnishi S. Effects of Mecobalamine on myocardial uptake of I-123 MIBG in patients with non insulin dependent diabetes mellitus (II). *Jpn Pharmacol Ther* 1997; 25: 305–308.
27. John MS, Scott JM, Weir DG. The methyl folate trap. *Lancet* 1981; II: 337.
28. Watanabe T, Kaji R, Oka N, Bara W, Kimura J. Ultra-high dose methylcobalamin promotes nerve regeneration in experimental acrylamide neuropathy. *J Neural Sci* 1994; 122: 140–143.
29. Hayakawa T. An investigation of diabetic polyneuropathy by microneurography: Comparison of the data with motor nerve conduction velocity. *J Japan Diab Soc* 1999; 42: 335–340.
30. Nagaoka H, Izuka T, Kubota S, Kato N, Suzuki T, Inoue T, et al. Depressed contractile response to exercise in diabetic patients in the absence of cardiovascular disease: Relationship to adrenergic cardiac dysinnervation. *Nucl Med Commun* 1997; 18: 761–770.