Annals of Nuclear Medicine Vol. 12, No. 6, 323–331, 1998

^{123}I-MIBG myocardial scintigraphy in diabetic patients: Relationship with ^{201}Tl uptake and cardiac autonomic function

Shigeki NAGAMACHI,* Seishi JINNOUCHI,* Takeshi KUROSE,** Takashi OHNISHI,* Leo G. FLORES II,* Hiroshi NAKAHARA,* Shigemi FUTAMI,* Shozo TAMURA* and Shigeru MATSUKURA**

**Department of Radiology, Miyazaki Medical College*
***Third Department of Internal Medicine, Miyazaki Medical College*

Purpose: To investigate the influence of diabetic myocardial damage (suspected myocardial damage; SMD) diagnosed by ^{201}Tl-SPECT and diabetic cardiac autonomic neuropathy (AN) on myocardial MIBG uptake in patients with non-insulin-dependent diabetes mellitus (NIDDM).
Subjects and Methods: Eighty-seven diabetic patients divided into four subgroups: 23 with SMD (+) AN (+); 19 with SMD (+) AN (–); 27 with SMD (–) AN (+); 18 with SMD (–) AN (–), and 10 controls were studied. Both planar and SPECT images were taken at 30 minutes (early) and 3 hours (delayed) after ^{123}I-MIBG injection. The heart to mediastinum uptake ratio (H/M) and washout ratio of ^{123}I-MIBG (WR) were obtained from both planar images. On SPECT images, the total uptake score (TUS) was obtained by the 5 point score method by dividing the myocardium into 20 segments on visual analysis. Similarly, the difference between the ^{201}Tl image and the ^{123}I-MIBG image in TUS was taken as the difference in the total uptake score (ΔTUS) representing cardiac sympathetic denervation without SMD.
Results: On both early and delayed planar images, the mean H/M value in the subgroups of diabetic patients was significantly lower in the SMD (+) AN (+) group than in the control group, but among those subgroups, there was statistically significant difference between the SMD (+) AN (+) and SMD (–) AN (–) groups only on the delayed images. Regarding the WR value, there was no statistically significant difference among subjects. On SPECT image analysis, the diabetic subgroup with AN or SMD had statistically significant lower values for TUS than those of the control group. Among diabetics, there was a statistically significant differences between SMD [+] AN [+] and SMD [–] AN [–] on both early and delayed images. Similarly, the SMD [+] AN [–] group also had significantly lower values than those of SMD [–] AN [–] on early images. Regarding ΔTUS, there was a statistically significant differences between AN [+] subgroups and controls. Similarly, the mean value for ΔTUS was much higher in AN [+] subgroups than in AN [–] subgroups with or without SMD in diabetes mellitus.
Conclusion: ^{123}I-MIBG myocardial uptake is affected by both SMD and cardiac autonomic neuropathy. Based on the finding that ΔTUS was much higher in AN [+] subgroups and there was no statistically significant difference between SMD [+] AN [+] and SMD [–] AN [+] subgroups, a decrease in myocardial ^{123}I-MIBG uptake might progress independently of SMD.

Key words: ^{123}I-MIBG myocardial scintigraphy, NIDDM, diabetic myocardial damage, cardiac autonomic neuropathy

Received March 2, 1998, revision accepted September 3, 1998.

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

INTRODUCTION

ALONG WITH CARDIAC DENERVATION, cardiac autonomic neuropathy is a significant prognostic factor for diabetes mellitus.[1] Many studies have reported the usefulness of ^{123}I-MIBG scintigraphy in diabetic cardiac denervation.[2–10] In particular, diabetic patients with cardiac autonomic neuropathy (AN) had a considerably decreased uptake of MIBG when compared to diabetics without AN,[2,4] but the diagnostic value of ^{123}I-MIBG myocardial scintigraphy in diabetes is limited because reduced ^{123}I-MIBG uptake is considered to be caused not only by macroangiopathy[11] but also by microangiopathy.[2]

Diabetic cardiomyopathy is one of the major complications in patients with diabetes mellitus, being probably caused by microangiopathy.[12,13] Although its clinical criteria have not been determined yet, ^{201}Tl-SPECT is known as a useful method for diagnosing it.[14,15] Generally, ^{201}Tl-SPECT is often used to screen ischemia and reversible perfusion defects on exercise ^{201}Tl scintigraphy in conjunction with ST segment depression, which is a diagnostic finding.[16] Although coronary angiography should be used to confirm myocardial ischemia, it cannot be used routinely in some cases of diabetes with equivocal SPECT findings and negative exercise ECG. Although the exact mechanism is unknown, one of the main causes of such a phenomenon is considered to be diabetic cardiomyopathy induced by microangiopathy.[14,15] Since diabetic patients with such findings could not be asked to have further coronary angiogram for ethical reasons, it was decided to resort to careful course observation. Consequently, there had been no report regarding ^{123}I-MIBG myocardial uptake in patients with or without diabetic cardiomyopathy and cardiac autonomic neuropathy.

In the current study, we defined suspected myocardial damage (SMD) as a case with decreased ^{201}Tl uptake without significant ST depression on exercise ECG. All SMD patients had a normal echocardiogram and no history of myocardial ischemia. SMD was, therefore, considered to be mainly caused by diabetic cardiomyopathy.

Accordingly, the current study was undertaken to clarify how AN diagnosed by clinical autonomic nerve function tests and SMD influences cardiac ^{123}I-MIBG uptake in NIDDM.

MATERIALS AND METHODS

Population study

A total of 87 patients over 45 years of age with non-insulin-dependent diabetes mellitus (NIDDM), as defined by the criteria of the National Diabetes Group, and 10 age-matched controls were enrolled in this study. All subjects were asymptomatic and had normal cardiovascular physical examinations, normal rest 12-lead electrocardiograms (ECG), and normal echocardiograms.

To detect suspected diabetic myocardial damage (SMD), all subjects underwent exercise ^{201}Tl-myocardial scintigraphy and treadmill exercise ECG by the Bruce protocol.[17] SMD was defined as the presence of reversible decreased uptake on exercised ^{201}Tl myocardial SPECT without ST-segment depression on ECG. We neglected all patients with > 1 mm ST-segment depression on exercise ECG who are highly suspected of having silent myocardial ischemia.[16,18]

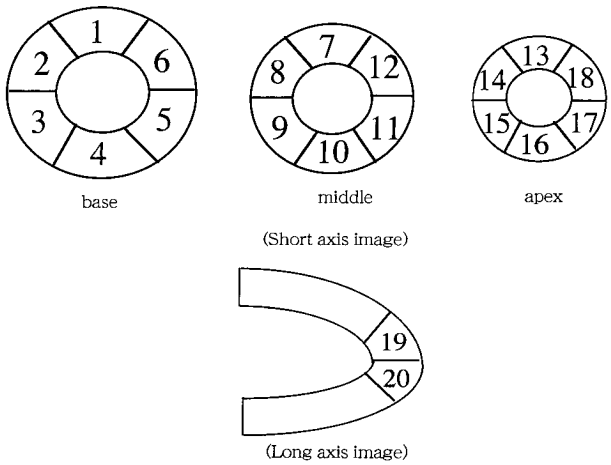


Fig. 1 Schematic presentation illustrating the left ventricular segmental analysis of myocardial SPECT images.

Consequently, there were 45 patients with normal ^{201}Tl myocardial SPECT, 42 diabetic patients who were clinically suspected of having diabetic myocardial damage (SMD (+)) as diagnosed by ^{201}Tl myocardial SPECT, and 10 normal controls.

To detect cardiac autonomic nerve dysfunction, the patients were evaluated for an abnormal blood pressure response to heart rate variability during a bedside maneuver.[2] The evaluation of heart rate variability was performed by quantitation of the coefficient of variation of R-R intervals ($CV_{R\text{-}R}$).[19–21] ECGs were recorded in the resting supine position, and the $CV_{R\text{-}R}$ (mean/SD × 100%) was calculated by processing 100 consecutive R-R intervals.[2] As the normal value for $CV_{R\text{-}R}$ is different in each generation,[21] the normal lower limits of volunteers were delimited as follows: 41–50 years: 2.2, 51–60 years: 1.9, and older than 60 years: 1.6. The value for each lower limit or less was defined as abnormal. All AN (+) patients met these $CV_{R\text{-}R}$ criteria. The AN (+) group had a high incidence of orthostatic hypotension (56.3% and 57.8%). Sweating abnormality (82.4% and 84.2%) and diabetic diarrhea (82.4% and 78.9%) were also frequently seen in the AN (+) group.

Finally, all patients were divided into four subgroups: 23 with SMD (+) AN (+); 19 with SMD (+) AN (−); 27 with SMD (−) AN (+); and 18 with SMD (−) AN (−). All subjects agreed to participate in the study approved by the Institutional Review Board of the Miyazaki Medical College.

Protocol for imaging

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. Both the patients and the normal control groups remained on their normal diets and drug regimens except for drugs that cause alterations in sympathetic activity. Both planar and SPECT studies were performed 30 minutes and 3 hours after ^{123}I-MIBG (111 MBq) injection by using a rotating gamma camera (ZLC7500, Shimadzu) equipped with a low-energy, parallel-hole, general-purpose collimator collecting 32 frames (each 45 sec) from the 45-degree right anterior oblique position to the 45-degree left posterior oblique position. The full photopeak of ^{123}I (159 keV, 15%) was used. Transaxial slices (12 mm thickness) were reconstructed with a Shepp-Logan convolution filter and a back-projection technique. No attenuation correction was applied.

The symptom-limited supine ergometer exercise test was done by starting the exercise at 25 watts and increasing it by 25 watts every 3 min while monitoring with a 12-lead electrocardiogram and blood pressure check. Exercise end points were the development of physical exhaustion, frequent premature ventricular contractions and exertional hypotension. At near maximal exercise, 111 MBq of ^{201}Tl-chloride was injected intravenously, and exercise was continued for another minute. The study was done at 1 week intervals after the ^{123}I-MIBG scintigraphy. ^{201}Tl-SPECT images were obtained with a rotating gamma camera (ZLC7500, Shimadzu) equipped with a low-energy, high-resolution, parallel-hole collimator centered on the 70 keV photo peak with a 15% window at 10 min

Table 1

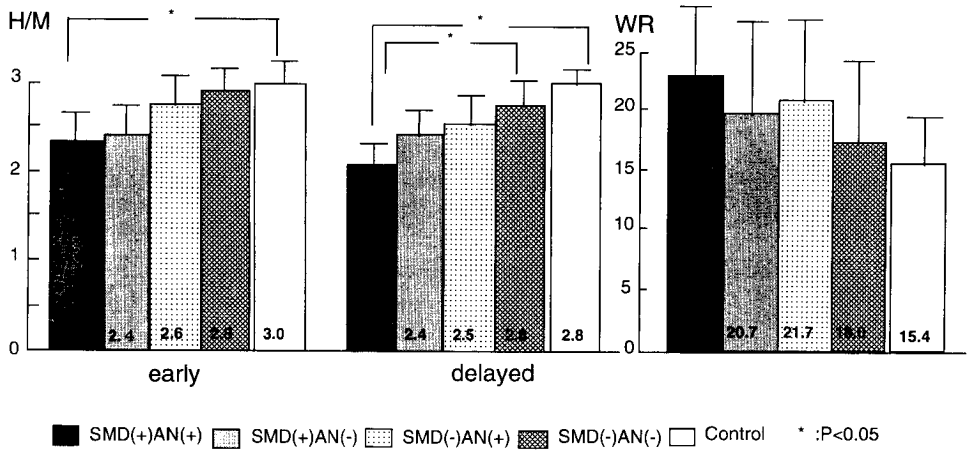
	AN (+) SMD (+) (n = 23)	AN (−) SMD (+) (n = 19)	AN (+) SMD (−) (n = 27)	AN (−) SMD (−) (n = 18)	Control (n = 10)
Age (yr)	57.0 ± 12.6	49.8 ± 16.4	54.6 ± 11.5	58.2 ± 11.9	56.1 ± 19.2
BMI (kg/m^2)	23.5 ± 3.5	23.0 ± 3.5	21.6 ± 3.8	22.0 ± 2.8	21.8 ± 4.2
Durations (yr)	14.5 ± 9.2	8.8 ± 5.8	13.6 ± 7.7	11.5 ± 6.3	/
FBS (mg/dl)	176.8 ± 71.7	103.3 ± 64.5	180.8 ± 66.5	157.1 ± 63.7	96.3 ± 23.5
HbA_{1C}	7.7 ± 1.6	9.1 ± 2.8	8.4 ± 1.6	7.5 ± 1.9	3.5 ± 1.2
Cholesterol (mg/dl)	223.5 ± 58.5	203.3 ± 49.4	215.2 ± 49.6	216.2 ± 45.8	198.6 ± 36.8
Triglycerides (mg/dl)	189.1 ± 102.7	140.7 ± 75.7	128.8 ± 52.3	134.4 ± 61.9	142.5 ± 12.5
Frucutosamine (μmol/l)	336.5 ± 99.7	418.3 ± 133.4	365.3 ± 108.3	340.3 ± 100.7	246.8 ± 36.8
Neuropathy (%)	83.3%	63.2%	85.2%	61.1%	/
Retinopathy (%)	82.6%	42.1%	77.8%	61.1%	/
Nephropathy (%)	78.3%	26.1%	59.3%	61.1%	/
Orthostatic hypotension	56.3%	0%	57.8%	0%	/
Sweating abnormality	82.4%	0%	84.2%	0%	/
Diabetic diarrhea	82.4%	0%	78.9%	0%	/

SMD: Suspected myocardial damage diagnosed by ^{201}Tl-SPECT, AN: Cardiac autonomic neuropahy diagnosed by $CV_{R\text{-}R}$, BMI: Body mass index, FBS: Fasting blood sugar, HbA_{1C}: Hemoglobion A_{1C}, Under line: There were significant difference between diabetes and control, *: $p < 0.01$

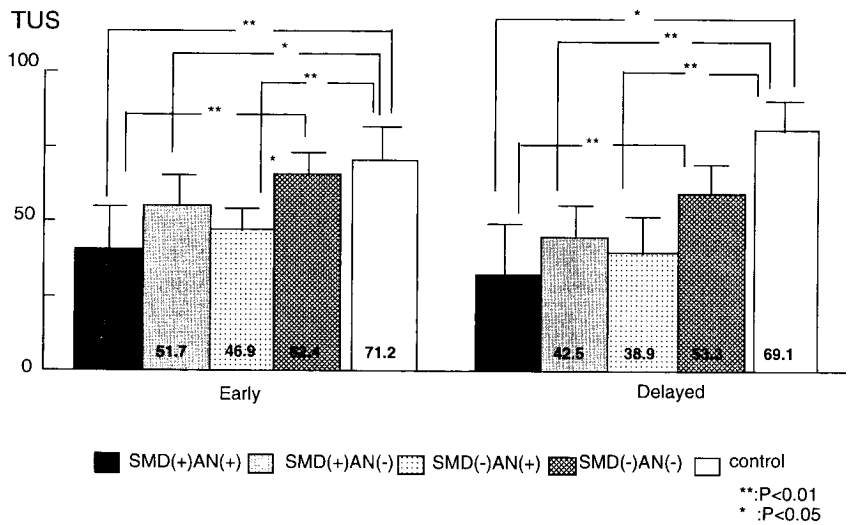
Table 2

	AN (+) SMD (+) (n = 23)	AN (−) SMD (+) (n = 19)	AN (+) SMD (−) (n = 27)	AN (−) SMD (−) (n = 18)	Control (n = 10)
LVEF (%)	66.6 ± 10.7	70.3 ± 17.3	72.4 ± 10.7	68.2 ± 11.7	75.3 ± 12.8
$CV_{R\text{-}R}$ (%)	1.1 ± 0.32	2.7 ± 0.77	1.1 ± 0.41	2.7 ± 0.77	3.2 ± 0.33
NCV (m/sec)	40.4 ± 5.7	43.0 ± 7.3	39.9 ± 6.5	42.9 ± 3.9	/

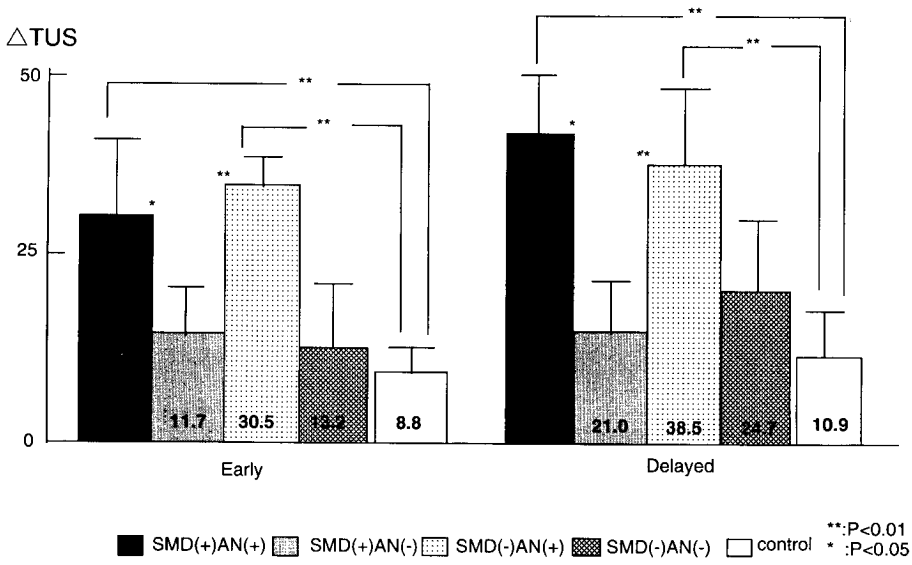
SMD: Suspected myocardial damage, AN: Cardiac autonomic neuropathy diagnosed by $CV_{R\text{-}R}$, LVEF: Left ventricular ejection fraction, NCV: Conduction velocities of posterior tibial nerve, *: $p < 0.01$



a



b



c

Fig. 2 Comparison of parameters of each indexes on planar images (a). Comparison of Total uptake score (TUS) on SPECT images (b). Comparison of the difference between TUS on ^{201}Tl-SPECT and ^{123}I-MIBG SPECT (ΔTUS) (c).

and 3 hr after ^{201}Tl injection. The camera was rotated over a 180° arc in an elliptical orbit about the patient's thorax at 6° increments for 30 seconds each. Data were transferred to a minicomputer (Scintipac 700A, Shimadzu) for further analysis.

Planar image analysis

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.[2] After correction for the physical decay of ^{123}I, the tracer washout rate from the myocardium (WR) was calculated by dividing the early minus delayed heart uptake count by the early heart uptake count.

SPECT image analysis

Visual analysis was done with 20 segments per study; three short-axis slice at the apical, mid, and basal levels and a vertical long-axis slice at the mid-ventricular level (Fig. 1). These SPECT images were also interpreted by three experienced observers who did not have the patient's clinical information. The degree of tracer uptake on each segment was scored as, normal 4, mildly decreased 3, moderately decreased 2, severely decreased 1 and defect 0. By Maeno's method, the sum of visual uptake scores on each segment was taken as the total uptake score (TUS). To account for a mismatch between the uptake of ^{123}I-MIBG and ^{201}Tl, the difference (ΔTUS) was calculated by using the following formulas.[22]

1. TUS (Total uptake score) = $\sum^{n=20}$ (Uptake score of each segment)
2. ΔTUS (TUS difference between exercise ^{201}Tl SPECT and MIBG SPECT)

   = $\sum^{n=20}$ (Uptake score of exercise ^{201}Tl – Uptake score of ^{123}I-MIBG on each segment)

Regarding reversible perfusion defects in ^{201}Tl scintigraphy, we determined them by one or more grade improvements in uptake on the delayed image as compared with those on the early image.

Statistics

Mean values for each parameter were compared among diabetic subgroups and controls. All values are presented as mean values ± s.d. Scheffe' F test for multiple comparisons was applied to detect the statistically significant difference as defined by ANOVA. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The clinical characteristics, diabetic status, and clinical laboratory data for each group are summarized in Table 1. There were no significant differences between diabetics and normal controls except for FBS, HbA_{1C} and Fructosamine. Although there were no statistically significant differences in the values for LVEF and NCV, $CV_{R\text{-}R}$ had a statistically significant lower value in AN (+) groups than in AN (–) groups (Table 2).

Planar image analysis

Only the SMD (+) AN (+) group had statistically significant lower H/M values than those of the controls in both early and delayed studies. Although SMD (+) AN (+) had a much lower H/M value than that of the SMD (–) AN (–) group on the delayed study (2.2 ± 0.3 versus 2.8 ± 0.2, $p < 0.05$), there was not a statistically significant differences between if and any of the other diabetic subgroups. With regard to the mean value for WR, no statistically significant difference was observed among the subgroups (Fig. 2a).

SPECT image analysis

Mean TUS values were statistically of lower significance in diabetic subgroups than in control subjects on delayed MIBG images. Among diabetics, there was a statistically significant difference between the SMD (+) AN (+) group and the SMD (–) AN (–) group in both early (39.0 ± 8.7 versus 62.4 ± 6.5, $p < 0.01$) and delayed studies (28.9 ± 9.2 versus 53.3 ± 6.8, $p < 0.01$). More importantly, there was no statistically significant difference among diabetes with SMD or AN (Fig. 2b).

The mean value for the ΔTUS in AN (+) group was much higher than that of the control group on both early and delayed images. Among diabetics, the AN (+) group had a statistically much higher ΔTUS value than the SMD (+) AN (–) group (early: 28.8 ± 10.1 & 30.5 ± 8.7 versus 11.7 ± 7.8, $p < 0.05$ & $p < 0.01$, delay: 38.8 ± 12.3 & 38.5 ± 10.7 versus 21.0 ± 5.8, $p < 0.05$ & $p < 0.01$). More importantly, there was no statistically significant differences between the SMD (+) AN (–) group and the other groups (Fig. 2c).

A Representative Case (Fig. 3)

A 66-year-old female with NIDDM. In addition to a lower $CV_{R\text{-}R}$ of 0.65, the patient had symptoms of somatic autonomic neuropathy (i.e., orthostatic hypotension, diabetic diarrhea, and night-time sweating). Although the exercise ^{201}Tl SPECT showed perfusion defects with redistribution on the delayed image, there were no significant changes in the exercise ECG and echocardiography. Because of these findings the patient was put into the SMD (+) AN (+) group. Planar ^{123}I-MIBG myocardial scintigraphy showed severely decreased uptake of the heart with accelerated washout on the delayed image. H/M on the early and delayed images was 1.9 and 1.6 respectively, and WR was 37.9%. ^{123}I-MIBG SPECT showed a defect in the inferior wall and severely decreased uptake in both the lateral wall and septum on the early image.

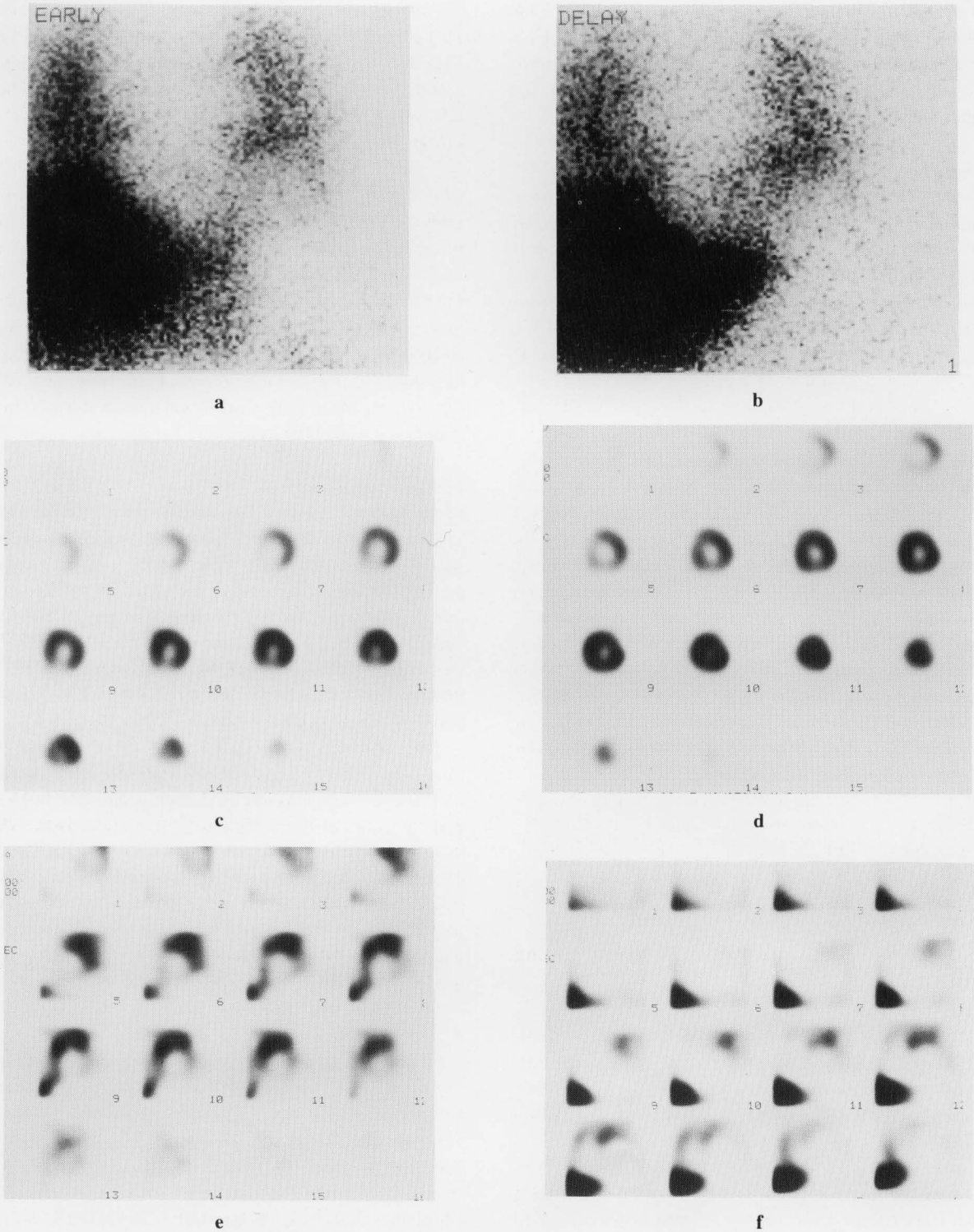


Fig. 3 A 66 year-old-woman in SMD (+) AN (+) group. Planar early image showed severely decreased ^{123}I-MIBG uptake of heart (a) with accerelated washout on the delayed image (b). Values of H/M on the early and delayed images were 1.9 and 1.6 respectively and WR was 37.9%. Stress ^{201}Tl SPECT showed decreased uptake in the inferior wall (c) with redistribution on the delayed image (d). ^{123}I-MIBG SPECT showed defect in inferior wall and severely decreased uptake both in lateral wall and septum on the early image (e). Delayed SPECT image showed striking washout with small amount of residual tracer in anterior wall (f). Values of TUS on the early and delayed images were 31 and 10. Values of ΔTUS were 28 and 49.

The delayed image showed striking washout with a small amount of residual tracer in the anterior wall. TUS values on the early and delayed images were 31 and 10. ΔTUS values of were 28 and 49.

DISCUSSION

The usefulness of ^{123}I-MIBG imaging for the assessment of cardiac sympathetic innervation is generally accepted.[23,24] A diabetic heart has also been reported to undergo denervated changes resulting in decreased ^{123}I-MIBG uptake,[2–10] but the cardiac complications caused by diabetic angiopathy restrict the clinical value of ^{123}I-MIBG. That is, cardiac ^{123}I-MIBG uptake is considered to be affected by both diabetic myocardial damage and cardiac autonomic nerve dysfunction.[2–6] Therefore, for the diagnosis of diabetic heart, conclusions cannot be reached with ^{123}I-MIBG myocardial scintigraphy alone.

To clarify the influence of SMD, all subjects undertook both ^{201}Tl-SPECT and ^{123}I-MIBG myocardial scintigraphy in the current study. As we expected, there was a statistically significant difference between SMD (+) AN (+) and controls in the H/M value. Among diabetic patients, a statistically significant differences was shown only between the SMD (+) AN (+) and the SMD (−) AN (−) groups on the delayed study. H/M is a simple method which allows the comparison of inter-individual and inter-institutional results by correcting for differences in the body geometry and attenuation of individual subjects. Nevertheless, it is sometimes difficult to make a ROI assignment on the planar image (i.e., heart uptake included that of the myocardium and activity of the overlying lung, posterior to the heart), particularly in diffusely decreased myocardial uptake such as that of a diabetic individual. This might explain the insignificant statistical difference among diabetics in the H/M value.[4]

WR is also a commonly used index for increasing sympathetic nerve activity related to norepinephrine storage ability. Although some reports indicated that WR increases in diabetes mellitus,[3] our previous data did not confirm this phenomenon.[2] The cardiac sympathetic nerve is frequently degenerated, and ^{123}I-MIBG sometimes accumulates less evenly on the early images. The absolute amount of tracer which is washed out between early and delayed images should be relatively small in such cases. This explains why some of the diabetic subgroups failed to establish statistical significance.

On the contrary, TUS was greatly affected by SMD and AN. As expected, the SMD (+) AN (+) group showed the most prominent change, but there was no statistical significance among the diabetic subgroups with AN or SMD. We could therefore confirm that both factors influence cardiac ^{123}I-MIBG uptake. TUS provides regional information about tracer uptake which is more reliable than that from the H/M in the evaluation of segmental analysis. Nevertheless, we could not determine whether the main cause of reduced ^{123}I-MIBG uptake is myocardial damage or cardiac autonomic neuropathy.

ΔTUS is an index representing the degree of myocardial sympathetic denervation without myocardial damage. Generally, the areas of reduced ^{123}I-MIBG uptake are larger than ^{201}Tl perfusion defects in myocardial ischemia.[25–27] Such lesions are considered to be viable but denervated.[27] Silent myocardial ischemia could also promote denervation in surrounding ischemic lesions,[9,11] but in the current study, there was no statistically significant difference between the SMD (+) AN (−) and SMD (−) AN (−) groups in the mean ΔTUS value. These results suggested that the reason for the decreased ^{201}Tl uptake in SMD was unlikely to be macroangiopathy but mainly microangiopahty. Under normal cardiac autonomic nerve conditions, the surrounding SMD tissues might not be prominently denervated.

Conversely, the subgroups with AN had much higher ΔTUS values than other groups. The findings suggested that decreased ^{123}I-MIBG uptake would progress even in the absence of SMD. Previously, Maeno et al.[22] reported that these mismatched segments had the potential for provoking ventricular tachycardia (VT) in patients with idiopathic dilated cardiomyopathy. Similarly, in NIDDM, such arrhythmia is one of the major complications.[28] The AN (+) group with higher ΔTUS, therefore, might have a potential risk of VT. ΔTUS could be a useful index to predict malignant arrhythmia in diabetes mellitus.

As we expected, the ΔTUS score was higher in delayed images owing to accelerated washout. Such lesions with prominent ^{123}I-MIBG washout were considered not to be degenerated but in the dysfunctional state, namely remaining nerves which are activated to compensate for the loss of quantity.[6] Because diabetic neuropathy is reversible if treated in the early stage, early detection is very important to achieve a better prognosis.[29,30] The difference between early and delayed images in ΔTUS might therefore reflect the amount of dysfunctional sympathetic nerves and could be a useful index for indicating treatment.

STUDY LIMITATIONS

The influence of aging is one factor. Tsuchimochi et al. reported that inferior wall uptake of ^{123}I-MIBG decreases with aging in individuals without cardiac disease, especially men.[31] Although there were no statistically significant differences among the five subgroups in mean age, elderly subjects in the current study probably had a lower cardiac ^{123}I-MIBG uptake.

A second limitation is that the exact cause of the low uptake on ^{201}Tl SPECT was not clarified. Because of the normal exercise ECG and normal UCG, the low uptake of ^{201}Tl in the current study was unlikely to be related to coronary artery involvement. However, depression of the ST segment on exercise ECG is not the perfect index with

which to diagnose myocardial ischemia.[32] Diabetic neuropathy interferes with afferent cardiac nerves leading to loss of noxious perception and resulting in the high incidence of silent myocardial ischemia in diabetes.[9] The SMD group, therefore, might include some cases of silent myocardial ischemia but our current data were different from those in previous reports showing that the areas of reduced ^{123}I-MIBG uptake are larger than ^{201}Tl perfusion defects in myocardial ischemia.[25–27] If some cases of SMI were included, there might be fewer cases in the current study. Nevertheless, sensitivity and specificity of the visually analyzed ^{201}Tl-SPECT for identification of coronary artery disease are both around 80%.[33] Coronary angiography should, therefore, be recommended for precise diagnosis.

Another limitation is the possibility of altered ^{201}Tl uptake induced by sympathetic denervation. Experimentally, myocardial sympathetic denervation is reported to increase rest myocardial blood flow,[34] but the influence of sympathetic denervation on myocardial blood flow is still controversial.[35] Because ^{201}Tl myocardial SPECT is usually performed for the screening of myocardial ischemia when we evaluate ^{123}I-MIBG myocardial scintigraphy, future studies are required to elucidate how sympathetic denervation alters the myocardial blood flow.

Nakajo et al. found that the cardiac ^{123}I-MIBG accumulation was inversely correlated with plasma concentrations and the rate of urinary excretion catecholamine in a rat model.[36] Conversely, it has been reported that the increase in the circulating norepinephrine concentration is not the only factor involved in the decrease of ^{123}I-MIBG uptake.[4,37] The current study did not determine the plasma catecholamine concentration. Further studies should be done to clarify the relationship between circulating norepinephrine and impaired neuronal norepinephrine reuptake in the decrease in ^{123}I-MIBG.

CONCLUSION

Both cardiac autonomic nerve dysfunction diagnosed by $CV_{R\text{-}R}$ and myocardial damage diagnosed by ^{201}Tl low uptake were important factors in myocardial ^{123}I-MIBG uptake in NIDDM.

Based on the result that there was a significantly higher ΔTUS value in the AN (+) group than in the AN (−) group and a statistically insignificant difference between SMD (+) AN (+) and SMD (−) AN (+), decreased MIBG uptake might progress independently of diabetic myocardial damage.

REFERENCES

1. Ewing DJ, Cambell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 49: 95–108, 1980.
2. 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 Commu* 17: 621–632, 1996.
3. 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* 41: 1069–1075, 1992.
4. 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* 23: 401–406, 1996.
5. Katono E, Owada K, Takeda H, Techigawara M, Watanabe N, Maruyama Y. Usefulness of myocardial imaging by ^{123}I-MIBG in assessment of diabetic neuropathy. *Jpn J Nucl Med* 30: 1235–1239, 1993.
6. 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* 37: 1985–1990, 1996.
7. 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* 23: 901–908, 1996.
8. Abe N, Kashiwagi A, Shigeta Y. Usefulness of cardiac ^{125}I-metaiodobenzylguanidine uptake for evaluation of cardiac sympathetic nerve abnormalities in diabetic rats. *J Japan Diab Soc* 35: 113–119, 1992.
9. Matsuo S, Takahashi S, Yoshida S, Tohru I, Nakamura Y, Mitsunami K, et al. Characteristics of regional sympathetic innervation in diabetic patients with silent myocardial ischemia assessed by ^{123}I-metaiodobenzyl guanidine imaging. *Jpn J Nucl Med* 33: 493–499, 1996.
10. 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* 25: 610–618, 1995.
11. Matsuo S, Takahashi M, Nakamura Y, Kinoshita M. Evaluation of cardiac sympathetic innervation with iodine-123-metaiodobenzylguanidine imaging in silent myocardial ischemia. *J Nucl Med* 37: 712–717, 1996.
12. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. *JAMA* 229: 1749–1754, 1974.
13. Rubler S, Dlugash J, Yuceoglu YZ, Kumal T, Branwood AM, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 30: 595–602, 1972.
14. Mizuno S, Genda A, Nakayama A, Igarashi Y, Takeda R. Myocardial involvement in diabetic patients evaluated by exercise thallium-201 scintigraphy and cardiac catheterization. *J Cardiogr* 15: 427–437, 1985.
15. Amano K, Sakamoto T, Oku J, Fujinami K, Sugimoto T. Diabetic cardiomyopathy in mild diabetics: evaluation by thallium-201 scintigraphy and exercise radionuclide ventriculography. *J Cardiogr* 16: 907–917, 1986.
16. Langer A, Freeman MR, Josse RG, Steiner G, Armstrong PW. Detection of silent myocardial ischemia in diabetes mellitus. *Am J Cardiol* 67: 1073–1078, 1991.
17. Bruce RA. Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. *Ann Clin Res* 3: 323–332, 1971.
18. Koistinen MJ. Prevalence of asymptomatic myocardial

ischaemia in diabetic subjects. *BMJ* 301: 92–95, 1990.
19. Ueda N. Detection of diabetic autonomic neuropathy—Utilization of power spectral analysis of heart rate variability. *J Japan Diab Soc* 35: 17–23, 1992.
20. Hashimoto J, Hata M, Kondou M, Hirota A, Shima K. Normal reference values and prediction equation of autonomic nerve functions based on variations in the R-R interval in electrocardiographs. *J Japan Diab Soc* 30: 167–173, 1987.
21. Mori Y, Anzai K, Tashiro E, Takata T, Ohkubo K, Futata T, et al. Squatting test for the evaluation of diabetic cardiovascular autonomic neuropathy. *J Japan Diab Soc* 39: 857–865, 1996.
22. Maeno M, Ishida Y, Shimonagata T, Hayashida K, Toyama T, Hirose Y, et al. The significance of $^{201}Tl/^{123}I$-MIBG (Metaiodobenzylguanidine) mismatched myocardial regions for predicting ventricular tachycardia in patients with idiopathic dilated cardiomyopathy. *Jpn J Nucl Med* 30: 1221–1229, 1993.
23. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthrone NH, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 22: 21–31, 1981.
24. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jackes Jr S. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 28: 1620–1624, 1987.
25. Stanton MS, Tuli MM, Radtke NL, Heger JJ, Miles WM, Mock et al. Regional sympathetic denervation after myocardial infarction in humans detected noninvasively using I-123 metaiodobenzylguanidine. *J Am Coll Cardiol* 14: 1519–1526, 1989.
26. McGhie AL, Corbett JR, Akers MS, Kurkarni P, Sills MN, Kremers M, et al. Regional cardiac adrenergic function using I-123 metaiodobenzylguanidine tomographic imaging after acute myocardial infarction. *Am J Cardiol* 67: 236–242, 1991.
27. Ishida Y, Maeno M, Hirose Y, Takahashi N, Katabuchi T, Oka H, et al. Characteristic of regional sympathetic dysfunction in acute ischemic myocardium assessed by ^{123}I-Metaiodobenzylguanidine imaging: Impairment of myocardial norepinephrine uptake of retention. *Jpn J Nucl Med* 32: 631–642, 1995.
28. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 64: 751–754, 1987.
29. Brismar T, Sima AA, Greene DA. Reversible and irreversible nodal dysfunction in diabetic neuropathy. *Ann Neurol* 21: 504–507, 1987.
30. Ganguly PK, Beamish RE, Dhalla KS, Innes IR, Dhalla NS. Norepinephrine storage, distribution and release in diabetic cardiomyopathy. *Am J Physiol* 252: E734–E739, 1987.
31. Tsuchimochi S, Tamaki N, Tadamura E, Kawamoto M, Fujita T, Yonekura Y, et al. Age and gender differences in normal myocardial adrenergic neuronal function evaluated by Iodine-123-MIBG imaging. *J Nucl Med* 36: 969–974, 1995.
32. Bogaty P, Guimond J, Robitaille NM, Rousseau L, Simard S, Rouleau JR, et al. A reappraisal of exercise electrocardiographic indexes of the severity of ischemic heart disease: angiographic and scintigraphic correlates. *J Am Coll Cardiol* 29: 1497–1504, 1997.
33. Maddahi J, Rodrigues E, Kiat H, et al. Detection and evaluation of coronary artery disease by thallium-201 myocardial perfusion scintigraphy. In *Cardiac SPECT Imaging*, Depuey EG, Berman DS, Garcia EV, eds., New York, Raven Press, pp. 103–120, 1994.
34. Holtz J, Mayer E, Bassenger E. Demonstration of a-adrenergic coronary control in different layers of canine myocardium by regional myocardial sympathetictomy. *Pflugers Arch* 187–194, 1977.
35. Stevens MJ, Dayanikli F, Raffel DM, Allman KC, Sandforf T, Feldman EL, et al. Scintigraphic assessment of regionalized defects in myocardial sympathetic innervation and blood flow regulation in diabetic patients with autonomic neuropathy. *J Am Coll Cardiol* 31: 1575–1584, 1998.
36. Nakajo M, Shimabukuro K, Yoshimura H, Yonekura R, Nakabeppu Y, Tanoue T, et al. Iodine-131 Metaiodobenzylguanidine. Intra- and Extra-vesicular accumulation in the rat heart. *J Nucl Med* 27: 84–89, 1986.
37. Merlet P, Valette H, Rande JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 33: 471–477, 1992.