Cardiac Iodine-123 Metaiodobenzylguanidine (^{123}I -MIBG) Scintigraphy Parameter Predicts Cardiac and Cerebrovascular Events in Type 2 Diabetic Patients Without Structural Heart Disease

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Background: Cardiac iodine-123 metaiodobenzylguanidine (^{123}I -MIBG) scintigraphy is an established method of assessment of cardiovascular sympathetic function. The aim of the present study was to investigate the long-term cardiovascular predictive value of cardiac ^{123}I -MIBG scintigraphy parameters in Japanese type 2 diabetic patients without structural heart disease.

Methods and Results: Cardiac ^{123}I -MIBG scintigraphy in 108 patients with type 2 diabetes who did not have structural heart disease, was evaluated. The washout rate (WR) was considered enhanced if it was $\geq 40\%$. Accurate follow-up information for 4.6 years was obtained in 54 enhanced WR patients (27 male; mean age, 61 ± 11 years) and in 54 sex- and age-matched preserved WR patients (27 male; mean age, 61 ± 10 years). Major adverse cardiac and cerebrovascular events (MACCE) were investigated. During follow-up, 10 enhanced WR patients developed MACCE including cardiac death, coronary revascularization, stroke, and congestive heart failure, while MACCE occurred in only 3 male patients. The Kaplan-Meier curves indicated that enhanced WR patients had higher incidence of MACCE than those with preserved WR ($P < 0.05$). Cox proportional hazards regression analysis showed that age and enhanced WR were independently associated with the incidence of MACCE (hazard ratio, 4.06; 95% confidence interval: 1.194–18.76, $P = 0.0237$).

Conclusions: Abnormal WR of cardiac ^{123}I -MIBG scintigraphy at baseline has long-term cardiovascular predictive value in Japanese patients with type 2 diabetes without structural heart disease. (*Circ J* 2012; **76**: 399–404)

Key Words: Autonomic nervous system; Cardiac ^{123}I -MIBG scintigraphy; Cardiovascular disease; Diabetes mellitus

Both myocardial perfusion and gated single-photon emission computed tomography (SPECT) show that event rates are higher among patients with larger perfusion defects and reduced ejection fraction or large ventricular volume despite the low incidence of cardiac events, in the J-ACCESS study.¹ Event rates were higher among diabetic patients, which would indicate the need for aggressive medical therapy. Therefore, myocardial perfusion SPECT is useful for risk stratification in the Japanese population.¹ Recently, a Japanese assessment of cardiac events and survival using quantitative gated SPECT (J-ACCESS 2) in patients with asymptomatic diabetes mellitus documented the short-term cardiac event rates.² Cardiac adrenergic nerve activity has been estimated by use of iodine-123 metaiodobenzylguanidine

(^{123}I -MIBG) as a noradrenaline analog.^{3,4} The autonomic imbalance, characterized by increased sympathetic activity and/or decreased parasympathetic activity, is strongly related to cardiovascular mortality. It has been reported that cardiac MIBG imaging provides prognostic information on patients with chronic heart failure.^{5–13} Few data are yet available, however, on whether the various parameters of cardiac MIBG imaging might be useful as a prognostic index for cardiac and cerebrovascular events in patients with type 2 diabetes. The objective of the present study was therefore to clarify the predictive value of cardiac MIBG imaging for major adverse cardiac and cerebrovascular events (MACCE) in patients with type 2 diabetes without structural heart disease.

Received August 23, 2011; revised manuscript received October 25, 2011; accepted October 26, 2011; released online November 30, 2011
Time for primary review: 16 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-0905

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Figure 1. Receiver-operating characteristic curve for the ability of wash-out rate (WR) to predict major adverse cardiac cerebrovascular events.

Methods

Patient Selection

A total of 165 patients with type 2 diabetes mellitus, who were admitted to Oita University Hospital from 1998 to 2004 for blood glucose control, were recruited. Type 2 diabetes mellitus was defined as fasting plasma glucose concentration ≥ 126 mg/dl, 2-h plasma glucose concentration following a 75-g oral glucose load ≥ 200 mg/dl, or the self-reported use of anti-diabetic medication.¹⁴ None of the patients had organic heart disease as determined on physical examination, chest X-ray, 12-lead electrocardiogram (ECG), echocardiography, or ^{201}Tl cardiac scintigraphy. Myocardial ischemia was excluded by treadmill exercise ECG testing and ^{201}Tl SPECT. Essential hypertension was defined as diastolic blood pressure (BP) ≥ 90 mmHg, systolic BP ≥ 140 mmHg or self-reported use of anti-hypertensive medication.¹⁵ Patients treated with α - or β -adrenergic blocking agents, tricyclic anti-depressants or other serotonin reuptake inhibitors, anti-platelet agents or who had macroalbuminuria (≥ 500 mg/day) or abnormal plasma creatinine concentration (≥ 1.2 mg/dl) were also excluded from the study. Dyslipidemia was defined as fasting triglycerides > 200 mg/dl, or high-density lipoprotein (HDL) cholesterol ≤ 45 mg/dl in women and ≤ 35 mg/dl in men.¹⁵ Hyperuricemia was defined as uric acid > 6.0 mg/dl in women or > 7.0 mg/dl in men.¹⁶ Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 ml $\cdot$ min $^{-1}$ $\cdot$ 1.73 m $^{-2}$.¹⁷ Patients with an eGFR < 30 ml $\cdot$ min $^{-1}$ $\cdot$ 1.73 m $^{-2}$ were excluded. This investigation was conducted according to the Declaration of Helsinki. Prior informed consent in terms of gathering baroreflex sensitivity (BRS) measurements was obtained from all patients, and the study protocol was approved by the institutional review board of

Oita University.

Cardiac ^{123}I -MIBG Scintigraphy

Planar scintigraphy was performed at 15 min (early) and at 4 h (delayed) after the injection of 111 MBq of ^{123}I -MIBG using a rotating gamma camera (ZLC 7500; Siemens, Munich, Germany). Data were analyzed with computer-based analysis software (SCINTIPAC; Shimadzu, Kyoto, Japan). The anterior planar scintigraphy images were analyzed visually. For semiquantitative analysis, regions of interest were drawn over the whole heart and also a 10 $\times$ 10-mm area over the upper mediastinum on the early and delayed planar images to calculate the mean heart/mediastinum (H/M) ratio. After correcting for the physical decay of ^{123}I -MIBG, the percentage wash-out rate (WR) of the tracer from the myocardium was determined for the 4-h period. The WR was calculated from the initial and delayed images, as previously reported.^{18,19} At Oita University Hospital, the normal ranges for early H/M ratio, delayed H/M ratio, and WR are set at 2.0–2.7, 2.1–2.9, and 21–30%, respectively. WR cut-off values were determined from receiver operating characteristic curve (Figure 1). The best WR with the highest sensitivity and specificity to predict MACCE was 41.4%. Therefore, we defined enhanced WR as $\geq 40\%$. From 1998, accurate follow-up information for 3–10 years (mean, 4.6 ± 2.5 years) was obtained in 54 enhanced WR patients (27 women, 27 men, mean age, 61 ± 11 years) and 54 sex- and age-matched preserved WR patients (27 women, 27 men, mean age, 61 ± 10 years) selected from 111 patients with preserved WR.

Follow-up

Most of the follow-up for patients occurred at Oita University Hospital. Information was obtained from those patients whose

Table 1. Patient Clinical Characteristics

	Enhanced WR (n=54)	Preserved WR (n=54)	P value
Age (years)	61±11	61±10	NS
Gender (F/M)	54/54	54/54	NS
Body mass index (kg/m ²)	25±5	26±6	NS
Current smoker (%)	54	50	NS
Duration of diabetes (years)	10±7	11±8	NS
Fasting plasma glucose (mg/dl)	157±51	149±57	NS
Hemoglobin A _{1c} (%)	8.4±1.8	8.0±1.7	NS
Hypertension (%)	63	50	NS
Systolic BP (mmHg)	132±20	130±21	NS
Diastolic BP (mmHg)	71±13	69±11	NS
Heart rate (beats/min)	71±9	68±9	NS
Dyslipidemia (%)	76	69	NS
Hyperuricemia (%)	20	20	NS
eGFR (ml·min ⁻¹ ·1.73m ⁻²)	81±28	76±24	NS
H/M ratio (early)	2.1±0.5	2.2±0.3	NS
H/M ratio (delayed)	1.9±0.4	2.3±0.5	<0.0005
WR (%)	49±9	29±7	<0.0001

Data given as mean±SD.

WR, washout ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; H/M, heart/mediastinum.

follow-up was performed by a general practitioner. Information on the patients who were hospitalized in other departments was also obtained. For the patients who died, the cause of death was documented with the help of the patients' family and general practitioner.

The endpoint was defined as the appearance of MACCE, which included cardiovascular mortality, non-fatal myocardial infarction, coronary revascularization through angioplasty or bypass, stroke, and congestive heart failure requiring admission. Using this combined criterion, only the first event was taken into account in statistical analysis.

Statistical Analysis

Data are presented as mean±SD. Chi-square test was used for categorical variables, and the analysis of variance (ANOVA) test was used for continuous variables. Differences between 2 groups were analyzed using Student's t-test. Kaplan-Meier MACCE-free analysis was used to compare MACCE-free times between the enhanced WR group and the preserved WR group. Univariate and multivariate Cox proportional hazard regression was performed to identify independent predictors (risk factors) for MACCE. Risk factors entered into the risk model included age, gender, body mass index, smoking status, duration of diabetes, fasting plasma glucose, hemoglobin A_{1c}, hypertension, dyslipidemia, hyperuricemia, eGFR, early H/M ratio and delayed H/M ratio, and WR. Results are given as hazard ratios (HR) with 95% confidence intervals (95%CI). P<0.05 was considered significant. Multivariate Cox regression analysis was performed only for variables with significant univariate impact. All calculations were performed with JMP version 9.0.0 (SAS, Cary, NC, USA), running under Windows 7 (Microsoft, Redmond, WA, USA).

Results

Patient Characteristics

Baseline patient characteristics of the preserved WR group and the enhanced WR group are presented in **Table 1**. The delayed H/M ratio was higher in the preserved WR group than

Table 2. Frequency of Endpoints

	Enhanced WR group (n=54)	Preserved WR group (n=54)
Cardiac death	0	1
Non-fatal myocardial infarction	0	0
Coronary revascularization	3	1
Stroke	6	1
Congestive heart failure	1	0
Total	10	3

WR, washout ratio.

in the enhanced WR group (P<0.0005). No significant difference was observed in terms of age, body mass index, duration of diabetes, fasting plasma glucose or hemoglobin A_{1c}, blood pressure, heart rate, eGFR, or early H/M ratio. With regard to gender, current smoker, hypertension, dyslipidemia, or hyperuricemia, the number of patients was not different between the 2 groups.

Patient Outcome

During the follow-up, 5 patients died (4.6%). Of the 5 deaths, 1 was due to a cardiac cause, while 4 were attributed to non-cardiac causes. All causes in the mortality rate were not significantly different between the preserved WR group and the enhanced WR group. There were no significant differences in total cardiac mortalities between the 2 groups.

Univariate and Multivariate Predictors of MACCE

During the follow-up, 13 patients presented with MACCE (12.0%). Of the 13 MACCE, 1 was attributed to cardiac death, 0 were attributed to non-fatal myocardial infarction, 4 were attributed to coronary revascularization, 7 were attributed to stroke, and 1 was attributed to congestive heart failure (**Table 2**). The MACCE were observed more frequently in the enhanced WR group (18.5%) than in the preserved WR group (5.6%; P<0.05). Results of univariate and multivariate Cox proportional hazards regression analysis of the MACCE

Table 3. Association of Baseline Characteristics With MACCE

	Univariate P value	Multivariate HR	95%CI	P value
Age (years)	0.0179*	1.07	1.004–1.151	0.0378*
Female gender	0.0526			
Body mass index (kg/m ²)	0.0102*	1.11	0.997–1.251	0.0562
Current smoker	0.1418			
Duration of diabetes (years)	0.1541			
Fasting plasma glucose (mg/dl)	0.4784			
Hemoglobin A _{1c} (%)	0.4968			
Hypertension (%)	0.1581			
Dyslipidemia (%)	0.0346*	2.74	0.471–51.88	0.2968
Hyperuricemia (%)	0.0049**	1.89	0.451–7.504	0.3720
eGFR (ml·min ⁻¹ ·1.73m ⁻²)	0.0661			
H/M ratio (early)	0.6449			
H/M ratio (delayed)	0.5188			
Enhanced WR	0.0265*	4.06	1.194–18.76	0.0237*

*P<0.05; **P<0.005.

CI, confidence interval; eGFR, estimated glomerular filtration rate; H/M, heart/mediastinum; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; WR, washout ratio.

are presented in Table 3. Univariate analysis indicated that age, body mass index, dyslipidemia, hyperuricemia and enhanced WR were associated with MACCE. On multivariate analysis using those risk factors, age (HR, 1.07; 95%CI: 1.004–1.151; P=0.0378) and enhanced WR (HR, 4.06; 95%CI: 1.194–18.76; P=0.0237) independently predicted the incidence of MACCE (Table 3).

Kaplan-Meier MACE-Free Estimation

MACCE-free ratio as evaluated on Kaplan-Meier analysis was significantly lower in the enhanced WR group than in the preserved WR group (log-rank 4.73, P=0.0296; Figure 2).

Discussion

In the present study, 108 Japanese type 2 diabetic patients were followed for a mean period of 4.6 years, and MACCE

developed in 13 patients. The most important finding is that abnormal WR can accurately predict cardiovascular events in patients with type 2 diabetes without structural heart disease/severe complications. MACCE-free ratio as evaluated on Kaplan-Meier analysis was significantly lower in the enhanced WR group than in the preserved WR group.

Autonomic imbalance, characterized by increased sympathetic activity and/or decreased parasympathetic activity, is strongly related to cardiovascular mortality. The relationship between cardiovascular autonomic neuropathy and the incidence of cardiovascular events, however, has been poorly investigated in type 2 diabetic patients. There have been few Japanese reports. Previously, we suggested that baseline assessment of BRS using the phenylephrine method might be a long-term cardiovascular predictor in type 2 diabetic patients without structural heart disease/severe complications.²⁰ We discussed cardiovascular autonomic neuropathy from the view-

point of BRS, reflecting parasympathetic activity. Sympathetic abnormalities may be also involved, which were evaluated in the present study.

Nagamachi et al reported the prognostic value of ^{123}I -MIBG cardiac imaging and heart rate variability over a period of 7.2 years in 144 patients with type 2 diabetes mellitus. The H/M ratio of the cardiac MIBG parameter was useful for predicting cardiac events and long-term mortality in type 2 diabetes mellitus. Regarding prognostic indicators for death, both cardiac autonomic neuropathy (CAN) and delayed H/M ratio were significant independent predictors.⁵ The survival rate was significantly lower in type 2 diabetes patients with an abnormal delayed H/M ratio (<1.7) than in those without it, which appears to be similar to the average delayed H/M ratio of 1.9 in the present enhanced WR group. WR, however, could not predict cardiovascular events in the Nagamachi et al study.⁵ Their patients were slightly younger, less obese, and more often women than the present patients. One of the reason for the differences in results might be the differences in patient characteristics. Cardiovascular events were associated with gender differences in cardiac autonomic function in Japanese type 2 diabetic patients without structural heart disease in a previous study.²¹

In J-ACCESS-2, according to multivariate Cox regression analysis, summed stress score ≥ 9 on stress $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT, and current smoking were independent predictors of cardiac events.² Matsuo et al have previously documented that an excellent prognosis was associated with a normal stress SPECT in asymptomatic diabetic patients without structural heart disease.²² The present study showed that cardiac ^{123}I -MIBG scintigraphic findings could predict cardiac and cerebrovascular events in type 2 diabetic patients without structural heart disease, similarly to stress myocardial perfusion imaging.

In contrast, stroke occurred more frequently than cardiac events during the present follow-up. Similarly, Anan et al showed that the presence of cerebral white matter lesions in patients with type 2 diabetes was associated with both cardiovascular autonomic function assessed using percentage WR from ^{123}I -MIBG cardiac imaging, and insulin resistance.²³ The pathogenic mechanism underlying the association between CAN and stroke remains unclear. It has been suggested, however, that a change in the sympathetic and parasympathetic balance may occur in the cerebral vasculature due to the defective autoregulation of the cerebral blood flow associated with diabetes, and may increase the susceptibility to stroke.^{24,25} Alternatively, endothelial dysfunction might be involved. Schnell noted that endothelial-dependent vasodilatation in the coronary artery is reduced in proportion to the magnitude of cardiac sympathetic dysfunction, when assessed on ^{123}I -MIBG scintigraphy.²⁶ The author hypothesized that cardiac sympathetic dysinnervation in diabetes mellitus leads, via decreased NO activity, to subsequent reduction of coronary blood flow reserve and impairment of vascular performance of the diabetic heart.²⁶ Such an impairment of vascular performance might have occurred in cerebral arteries in the present type 2 diabetic patients who developed MACCE.

Cardiac sympathetic nerve activity evaluated on 1-time ^{123}I -MIBG scintigraphy during the stable period has prognostic value in patients with chronic heart failure.^{5–12} Kasama et al showed that the survival rate of patients with a delta-WR (^{123}I -MIBG scintigraphy before leaving the hospital and 6 months after discharge) of $<-5\%$ was significantly higher for those with a baseline WR of $<50\%$. On multivariate analysis, delta-WR $\geq 5\%$ was only incremental predictor of cardiac death on

serial ^{123}I -MIBG imaging. Kasama et al analyzed data from chronic heart failure patients.¹³ In contrast, The present patients had type 2 diabetes without structural heart disease. Nevertheless, in both studies, enhanced WR of ^{123}I -MIBG scintigraphy could predict cardiovascular events. The prognostic predictive value of cardiac ^{123}I -MIBG scintigraphy parameters should be evaluated in more pathologic conditions. Taken together, it is suggested that repeated cardiac ^{123}I -MIBG scintigraphy is required in type 2 diabetic patients, especially whose WR is $\geq 40\%$. The impact of serial diabetic control condition on ^{123}I -MIBG scintigraphy parameters should also be evaluated.

Several limitations should be considered in the present study. First, because we enrolled patients without severe complications, the incidence of MACCE was small, which might have made it difficult to analyze the data. For instance, although the delayed H/M ratio was significantly higher in the preserved WR group than in the enhanced WR group, the delayed H/M ratio did not predict incidence of the MACCE. Second, clinical manifestations of diabetic autonomic neuropathy involve many different sites, including cardiovascular, gastrointestinal, genitourinary, metabolic, sudomotor, and papillary. Because we did not quantitatively evaluate other autonomic neuropathy, the association between ^{123}I -MIBG cardiac imaging and other systemic autonomic neuropathy remains unclear. Third, some previous studies have demonstrated that abnormal myocardial perfusion SPECT could predict for the risk of cardiovascular events among asymptomatic diabetic patients 1–3 years after registration.^{27,28} Therefore, it remains unclear whether the present single baseline assessment of ^{123}I -MIBG cardiac imaging can really predict remote development of MACCE. In addition, we could not precisely evaluate serial changes in diabetic status including plasma glucose level and HbA_{1c} during follow-up. Finally, in the present study, we compared the data between a preserved WR group and an enhanced WR group. In other words, comparison with normal control subjects was not done.

Conclusion

The present results demonstrate that the abnormally increased WR of cardiac ^{123}I -MIBG scintigraphy at baseline has long-term cardiovascular predictive value in Japanese patients with type 2 diabetes without structural heart disease. Intensive management should be considered in this patient group.

Disclosures

There is no financial support for the present study.

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