Effects of Metabolic and Myocardial Microcirculatory Abnormalities on the Pathogenesis of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus: A Prospective Study in Japanese Patients

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ABSTRACT

Background: In diabetic patients, cardiac autonomic neuropathy is an important factor affecting prognosis. Whether this condition in diabetic patients is caused directly by neurovisceral metabolic disorder and/or indirectly by microcirculation remains to be clarified.

Objective: The aim of this study was to determine whether cardiac sympathetic nerve dysfunction can be detected using adenosine triphosphate (ATP) testing, while also investigating the effects of metabolic and/or myocardial microcirculatory abnormalities on the pathogenesis of cardiac autonomic nerve dysfunction in patients with type 2 diabetes mellitus (DM-2) in Japan.

Methods: This prospective study was performed at the Division of Diabetology, Department of Internal Medicine, Toho University, Ohashi Hospital, Tokyo, Japan. Patients aged ≥ 18 years with DM-2 with no abnormalities on electrocardiography (ECG) or echocardiography were enrolled. An ATP thallium (Tl)-201 myocardial scintigraphy test (ATP test) and iodine (I)-123 metaiodobenzylguanidine (MIBG) scintigraphy were performed. ATP was administered by continuous IV infusion over 6 minutes at 0.16 mg/kg min. Five minutes after the ATP infusion was started, Tl-201 111 MBq IV was administered. Single-photon emission computed tomography (SPECT) imaging was begun immediately after the end of ATP infusion and was completed 3 hours after stress to show washout from stress to rest. I-123 MIBG 111 MBq IV was administered. A planar image from the front side and a SPECT image (early phase) was obtained 15 to 30 minutes later. After 3 hours, a planar image from the front side and a SPECT image (late phase) were obtained to show washout from stress to rest. The mean Tl washout rate (ATP-WR) and heart-to-mediastinum (H/M) ratio in the late-phase scintigraphic images and the washout rate of MIBG (MIBG-WR) in the left ventri-
The correlations of these measurements with the mean values of glycosylated hemoglobin (HbA1c) and fasting plasma glucose obtained from monthly measurements over the previous 6 and 24 months were determined.

**Results:** A total of 25 patients were enrolled (13 men, 12 women; mean [SD] age, 59.86 [8.28] years). Significant negative correlations between both ATP-WR and MIBG-WR and HbA1c were found \( r = -0.52 \; [P = 0.02] \) and \( -0.47 \; [P = 0.03] \), respectively. Although no correlation was found between ATP-WR values and the early phase H/M ratio, a significant positive correlation was observed between ATP-WR and H/M ratio \( r = 0.54; \; P = 0.02 \).

**Conclusions:** In the present study in Japanese diabetic patients without subjective signs of coronary artery disease and without abnormalities on ECG or echocardiography, ATP-WR, an indicator of myocardial blood flow, was correlated with myocardial sympathetic nerve dysfunction and 24-month glycemic control. However, sympathetic nerve dysfunction was not correlated with 24-month glycemic control. (Curr Ther Res Clin Exp. 2005;66:600–612) Copyright © 2005 Excerpta Medica, Inc.

**Key words:** cardiac sympathetic nervous dysfunction, ATP T1-201 myocardial scintigraphy, I-123 metaiodobenzylguanidine scintigraphy, glycemic control.

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**INTRODUCTION**

In diabetic patients, cardiac autonomic neuropathy, which is thought to be associated with sudden death and asymptomatic myocardial infarction, serves as an important factor affecting prognosis.1 The results of recent studies have attracted researchers’ attention.2–4 These studies suggested a relatively poor prognosis in diabetic patients with cardiac autonomic neuropathy in the absence of clinically detectable micro- and macrovascular complications. Thus, autonomic function tests might provide a guide to prognosis.

Whether cardiac autonomic neuropathy in diabetic patients is associated with neurovisceral metabolic disorder or myocardial microcirculatory disorder remains to be clarified.

Isotopic myocardial blood flow scintigraphy may be one of the most useful methods of assessing myocardial microcirculatory disorder, but it does not allow a micro-level evaluation in patients with stenosis in the thick coronary arteries. Therefore, I performed adenosine triphosphate (ATP) thallium (TI)-201 myocardial scintigraphy5 in patients with no abnormal findings on electrocardiography (ECG) performed during rest and exercise to evaluate microcirculatory disorder based on the washout rates of TI. I also performed iodine (I)-123 metaiodobenzylguanidine (MIBG) scintigraphy5 to assess cardiac sympathetic nervous function. MIBG scintigraphy provides images of the presynapsis of cardiac sympathetic nerves, with excellent quantification capability and reproducibility.5

I assessed the correlations of cardiac autonomic neuropathy and myocardial microcirculatory disorder and glycemic control.6 Using ATP TI-201 and MIBG scintigraphy, I conducted the present study for the purposes of determining
whether cardiac sympathetic nerve dysfunction can be detected using ATP testing, while also investigating the effects of metabolic and/or myocardial microcirculatory abnormalities on the pathogenesis of cardiac autonomic nerve dysfunction in patients with type 2 diabetes mellitus (DM-2) in Japan.

PATIENTS AND METHODS

Male and female patients aged ≥18 years with DM-2 who were seen at the Division of Diabetology, Department of Internal Medicine, Toho University, Ohashi Hospital, Tokyo, Japan, between February 1997 and September 2000 were enrolled. Patients were excluded if they had poorly controlled hypertension (systolic/diastolic blood pressure, ≥160/≥100 mm Hg), chest pain, and/or abnormal findings on ECG or echocardiography on rest or exercise.

The study protocol was approved by the institutional review board at the hospital. Written informed consent was obtained from each patient. All patients who participated in the study were volunteers, and there was no compensation for participation.

Study Design

To assess cardiac sympathetic nerve function, ATP Tl-201 myocardial scintigraphy and I-123 MIBG scintigraphy were performed. Patients arrived for their clinic visits at their assigned times and underwent routine examination for DM-2.

ATP Tl-201 Myocardial Scintigraphy

While monitoring each patient's blood pressure, a catheter was inserted and ATP was administered by continuous IV infusion over 6 minutes at 0.16 mg/kg · min. Five minutes after the start of the ATP infusion, Tl-201 111 MBq IV was administered and flushed with 10 mL of physiologic saline. Early phase single-photon emission computed tomography (SPECT) imaging was begun immediately after the ATP infusion was completed. Three hours later, to show washout from stress to rest (3 hours after stress), late-phase SPECT images were obtained. The mean washout rate of Tl-201 in the left ventricle (ATP-WR) was calculated using a bull's-eye map created from 10 slices of short-axis SPECT images, as follows:

$$\text{ATP-WR} = \frac{\text{Count in early phase} - \text{Count in late phase}}{\text{Total count in early phase}}$$

I-123 MIBG Scintigraphy

After an interval of at least 3 days after ATP Tl-201 myocardial scintigraphy, I-123 MIBG 111 MBq IV was administered to each patient at rest. A frontal planar image and an early phase SPECT image were obtained 15 to 30 minutes later. Three hours later, to show washout from stress to rest (3 hours after stress), an additional frontal planar image and a late-phase SPECT image were obtained.
Using the planar images in the early and late phases, a heart-to-mediastinum (H/M) ratio, which indicates the MIBG uptake into the heart, was calculated. A depressed H/M ratio (<2.0%) could indicate: (1) low density of the sympathetic nerves; (2) impaired uptake of MIBG into the sympathetic nerve terminals (uptake-i); and/or (3) impaired microcirculation. The I-123 MIBG washout rate (MIBG-WR) in the entire left ventricle was calculated, using the region of interest (ROI) of the heart obtained from the frontal planar images in the early and late phases, as follows:

$$\text{MIBG-WR} = \frac{\text{ROI in early phase} - \text{ROI in late phase}}{\text{ROI in early phase}}$$

The 3-day interval between scintigraphy studies took into account the $t_{1/2}$ values of the radionuclides, T1 and I. The tolerability of the radioisotopes was not assessed because they have not been found to be associated with any clinically significant adverse reactions.

**SPECT Imaging**

A cardiofocal collimator (Multi-SPECT3, Siemens Medical Systems, Hoffman Estates, Illinois) was used for SPECT imaging. The collimator rotates 360°, with 30 seconds per projection at each 5° angle. Reconstruction was performed at an energy peak of 70 to 80 KeV with a 20% window. The data were acquired in a 125 x 125 matrix.

**Assessment of Glycemic Control**

Fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) values were determined within 1 month before and after ATP and MIBG scintigraphy. In each patient, means of monthly FPG and HbA1c values were calculated over 6 and 24 months before scintigraphy. The last FPG and HbA1c measurements were obtained at the last clinical check, within 2 weeks before the first scintigraphy.

Based on the FPG and HbA1c results, the following correlations were assessed:
1. ATP-WR and H/M ratio;
2. ATP-WR and MIBG-WR;
3. ATP-WR and glycemic control (FPG and HbA1c); and
4. Glycemic control, H/M ratio, and MIBG-WR.

**Tolerability**

Tolerability was assessed using blood pressure monitoring during scintigraphy.

**Statistical Analysis**

Correlation analyses were performed using simple linear regression, with StatView version 5 (SAS Institute Inc., Cary, North Carolina). $P < 0.05$ was considered statistically significant. Data are expressed as mean (SD).
RESULTS
Twenty-five patients were enrolled (13 men, 12 women; mean [SD] age, 59.86 [8.28] years). The baseline characteristics of the patients are shown in the table. The mean (SD) duration of DM diagnosis was 8.82 (5.42) years. Sixteen patients received oral hypoglycemic agents, and 5 patients had previously received dietary therapy alone. Of the 16 patients who had received hypoglycemic agents, 12 were treated with monotherapy with a sulfonylurea (SU); 4, with a combination of SU and an \( \alpha \)-glucosidase inhibitor; and 4, with intermedi-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age, mean (SD), y</td>
<td>59.86 (8.28)</td>
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<tr>
<td>Female</td>
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<td>BMI, mean (SD), kg/m(^2)</td>
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<td>Duration of diabetes diagnosis, mean (SD), y</td>
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<td>Oral hypoglycemic agent</td>
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<td>Sulfonylurea</td>
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<td>Sulfonylurea + ( \alpha )-glucosidase inhibitor</td>
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<td>Intermediate 70/30 insulin</td>
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<tr>
<td>Dietary</td>
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<tr>
<td>FPG, mean (SD) of 1 month, mg/dL</td>
<td>168.2 (48.3)</td>
</tr>
<tr>
<td>HbA(_{1c}), mean (SD) of 1 month, %</td>
<td>7.60 (1.11)</td>
</tr>
<tr>
<td>HbA(_{1c}), mean (SD) of 6 months, %</td>
<td>8.10 (1.58)</td>
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<tr>
<td>HbA(_{1c}), mean (SD) of 24 months, %</td>
<td>8.16 (1.83)</td>
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<td>Ejection fraction, mean (SD), %</td>
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<tr>
<td>Neuropathy†</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension†</td>
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</tr>
</tbody>
</table>

BMI = body mass index; FPG = fasting plasma glucose; HbA\(_{1c}\) = glycosylated hemoglobin.
*Some patients received >1 treatment.
†Some patients had >1 complication.
‡Eight patients had microalbuminuria (creatinine, 30–300 \( \mu \)g/mL) and 5 had proteinuria (creatinine, >300 \( \mu \)g/mL).
§Six patients had simple retinopathy and 5 had preproliferative retinopathy.
‖With absent tendon reflex or subjective symptoms.
§§Systolic/diastolic blood pressure \( \geq 140/\geq 90 \) mm Hg.
ate 70/30 insulin. Diabetic complications at baseline were as follows: hyperlipidemia, 14 patients; nephropathy, 13 (8 with microalbuminuria and 5 with proteinuria); retinopathy, 11 (6 with simple retinopathy and 5 with preproliferative retinopathy); and neuropathy (with absent tendon reflex or subjective symptoms), 10 patients. Mean (SD) FPG and HbA\textsubscript{1c} values at 1 month before or after ATP and MIBG scintigraphy were 168.2 (48.3) mg/dL and 7.60% (1.11%), respectively. Mean (SD) HbA\textsubscript{1c} values over 6 and 24 months before the study were 8.10% (1.58%) and 8.16% (1.83%), respectively.

**ATP and MIBG Scintigraphy**

On ATP scintigraphy, no changes on ECG were observed during the ATP treatment. No local loss was observed in the early or late-phase images on ATP or MIBG SPECT imaging, indicating no abnormalities in blood flow or sympathetic nerve distribution. Mean (SD) ATP-WR was 36.6% (10.0%) (normal range, 40%-50%). Mean (SD) MIBG H/M ratio in the early and late-phase images were 2.01% (0.20%) and 2.05% (0.29%), respectively (normal range, 2%-3%). Figures 1 and 2 show MIBG activity in 2 patients. Although no correlation was found between ATP-WR values and the early phase H/M ratio, a positive correlation was found between ATP-WR and late-phase H/M ratio ($r = 0.54$; $P = 0.02$) (Figure 3). The mean (SD) MIBG-WR was 34.0% (6.7%) (normal range, 20%-30%). A negative correlation was observed between ATP-WR and MIBG-WR ($r = -0.52$; $P = 0.02$) (Figure 4).

**Glycemic Control**

Mean (SD) FPG and HbA\textsubscript{1c} values at 1 month before and after ATP and MIBG scintigraphy were 168.2 (48.3) mg/dL and 7.60% (1.11%), respectively. Although no correlation was found between FPG or HbA\textsubscript{1c} at the time of the treatment (within 1 month), a negative correlation was found between ATP-WR and mean HbA\textsubscript{1c} during the 6 months before the study ($r = -0.47$; $P = 0.03$), and between ATP-WR and mean HbA\textsubscript{1c} during the previous 24 months ($r = -0.51$; $P = 0.02$) (Figure 5).

No correlation was found between either MIBG H/M ratio (early and late-phase images) and MIBG-WR and either FPG or HbA\textsubscript{1c} within 1 month of treatment. No correlation was found between mean HbA\textsubscript{1c} during the 6 and 24 months before scintigraphy.

**Tolerability**

None of the patients had abnormal blood pressure values during the study.

**DISCUSSION**

Diabetic neuropathy, retinopathy, and nephropathy are complications unique to DM. Although the latter two occur many years after the onset of DM, diabetic neuropathy often occurs in a relatively early stage of the disease. Despite the
Figure 1. Myocardial metiodobenzylguanidine (MIBG) activity in a diabetic patient with preserved thallium (TI)-201 washout. (A) Polar maps of TI-201 activity in the left ventricle myocardium with adenosine triphosphate stress and at rest (3 hours after stress) (left, early phase; right, late phase). There was no perfusion defect. The lower panels show polar map of TI-201 washout from stress to rest (3 hours after stress). The mean washout rate of TI-201 was 49.5%. (B) Iodine-123 MIBG myocardial scintigraphy delayed planar anterior image of the chest obtained 4 hours after IV injection of nuclear agent. The mean isotope count at region of interest over the heart (H) and mediastinum (M) were measured, and the H/M ratio was 2.8. The MIBG washout rate from early (15 minutes after injection) to delayed imaging was 32.4%.

High prevalence of neuropathy in patients with DM, research concerning this complication seems to lag behind that concerning diabetic retinopathy and nephropathy due to less awareness of a deteriorated quality of life and a poor survival prognosis. In addition, the mechanisms of structural and physiologic disorders associated with diabetic neuropathy have not been clarified. Based on a literature search of MEDLINE (key terms: diabetic neuropathy, peripheral neuropathy, and autonomic neuropathy; years: 1970–2004), although many cases of peripheral neuropathy, such as motor and sensory nerve dysfunction, have been reported, reports of autonomic neuropathy are relatively limited. Only a few studies have assessed whether these dysfunctions affect each other, and if they do, how they interact with each other. In addition, a method of assessment of early autonomic neuropathy has not yet been established.

Possible causes of neuropathy include a reduced number of nerve fibers, wallerian degeneration, and the slow reproduction of nerve fibers, which are considered to be associated with hyperglycemia. It has been reported that
Myocardial metaiodobenzylguanidine (MIBG) activity in a diabetic patient with preserved thallium (TI)-201 washout. (A) Polar maps of TI-201 activity in the left ventricle myocardium with adenosine triphosphate stress and at rest (3 hours after stress) (left, early phase; right, late phase). There was no perfusion defect. The lower panels show polar map of TI-201 washout from stress to rest (3 hours after stress). The mean washout rate of TI-201 was 17.2% and diffusely slow compared with that of the patient in Figure 1. (B) Iodine-123 MIBG myocardial scintigraphy delayed planar anterior image of the chest obtained 4 hours after IV injection of nuclear agent. The mean isotope count at region of interest over the heart (H) and mediastinum (M) were measured, and the H/M ratio was 2.1. The MIBG washout rate from early (15 minutes after injection) to delayed imaging was 44.2%. These findings show a decreased uptake of MIBG to the myocardial sympathetic nerve ends and increased washout compared with that of the patient in Figure 1, suggesting impaired function of the cardiac sympathetic nerves.

Hyperglycemia induces metabolic abnormalities, such as intracellular accumulation of sorbitol,\textsuperscript{10,11} accelerated production of advanced glycation end products,\textsuperscript{10,12} and abnormal protein kinase C activity.\textsuperscript{13} Researchers have started to investigate the involvement of vascular insufficiency in the development and progress of neuropathy.\textsuperscript{9} A cardiac microcirculatory disorder might be associated with cardiac autonomic neuropathy.

Diabetic patients with coronary artery disease (CAD) are generally considered to have a poorer prognosis compared with nondiabetic patients with CAD for various reasons, including the following: high risk for cardiac failure\textsuperscript{14}; diffuse coronary artery lesions extending to the peripheral branches, which can cause cardiac failure\textsuperscript{15}; and the presence of diabetic cardiomyopathy.\textsuperscript{16} Some
Figure 3. Correlation of adenosine triphosphate thallium-201 washout rate (ATP-WR) and iodine-123 metaiodobenzylguanidine (MIBG) heart-to-mediastinum (H/M) ratio ($r = 0.54; P = 0.02$).

Figure 4. Correlation of adenosine triphosphate thallium-201 washout rate (ATP-WR) and iodine-123 metaiodobenzylguanidine washout ratio (MIBG-WR) ($r = -0.52; P = 0.02$).
patients have DM-related cardiac dysfunction in which a diastolic filling is inhibited by deteriorated wall motion of the left ventricle (even without significant stenosis on coronary angiography at the first hospital visit), suggesting a role for sympathetic nerve dysfunction in cardiac dysfunction. 17

Ischemic heart disease (IHD) is the most frequently reported cause of DM-related death. For this reason, and because of the difficulty in detecting thoracic symptoms in diabetic patients, physicians are encouraged to examine whether IHD is developing without subjective symptoms. Without subjective symptoms, patients might not be aware of the disease, or patients might have difficulty understanding the necessity of diagnostic assessments, especially if these assessments include invasive testing. 5 Furthermore, in many diabetic patients, the presence of retinopathy and/or nephropathy might prevent them from undergoing exercise testing. 5 For these reasons, I consider ATP TI-201 myocardial scintigraphy, a drug-loading test, to be most suitable for the detection of IHD in diabetic patients. ATP TI-201 scintigraphy and nuclear methods using a 13N-ammonia tracer are useful for assessing myocardial blood flow. A diffuse slow washout of TI in the cardiac muscle generally indicates triple vessel disease. However, in patients with no stenosis on coronary angiography, a diffuse slow washout of TI in the cardiac muscle might indicate cardiac myocyte dysfunction or myocardial microcirculatory abnormality.

In conventional assessment of cardiac autonomic neuropathy, the RR interval is assessed using ECG 18 or 24-hour ambulatory blood pressure monitoring, and

Figure 5. Correlation of adenosine triphosphate thallium-201 washout rate (ATP-WR) and glycemic control as measured by the mean of monthly glycosylated hemoglobin (HbA1c) concentrations over 24 months before scintigraphy ($r = -0.51; P = 0.02$).
Ewing's test results are quantified. In recent years, I-123 MIBG scintigraphy using nuclear medical techniques has been used for the assessment of cardiac sympathetic nerve function. MIBG, considered to have uptake, storage, and release mechanisms similar to those of norepinephrine, is mainly taken into norepinephrine-retaining granules by the norepinephrine reuptake mechanism (uptake-1) at the sympathetic nerve endings, thus allowing them to remain there without any metabolism for a relatively long period of time. Therefore, reuptake by uptake-1 is thought to reflect the distribution and function of the sympathetic nerves. MIBG allows imaging of sympathetic nerve activity. Increased MIBG-WR indicates that MIBG taken into the secretory granule tends to easily disappear over time. Diabetic patients lacking MIBG uptake are suspected to have some dysfunction that results in a decreased ability to store and maintain norepinephrine within the granule. This decreased ability might be associated with a microcirculatory disorder, based on the fact that the sympathetic nervous system regulates myocardial contractile force and microvascular tonus.

Although it has been found that metabolic and/or microcirculatory abnormalities involve extracardiac autonomic or peripheral nerve disorders, the purpose of the present study was to determine whether these abnormalities play a role in the pathogenesis of cardiac autonomic nerve dysfunction. I found a correlation between the 2 nuclear medical scintigraphic methods and between the results of ATP testing and glycemic control over 24 months. These results suggest that sustained hyperglycemia does not appear to have a direct relation to the autonomic nervous system but might be related to myocardial microcirculatory abnormalities, which, in turn, are related to autonomic nerve dysfunction. These results suggest that microcirculatory disorders related to poor glycemic control might, in turn, contribute to cardiac sympathetic nerve dysfunction.

In diabetic patients with poor glycemic control over the long term, IHD and cardiac autonomic neuropathy might be suspected, even if no abnormalities are found on resting ECG or echocardiography. Diabetic patients undergoing ATP testing for IHD and having a slow TI washout might have some degree of myocardial sympathetic nerve dysfunction. Therefore, these patients should be followed up carefully to provide appropriate hypoglycemic treatment.

I cannot rule out the possibility of IHD in all of the patients in the present study because I did not perform coronary angiography. However, with the high sensitivity of the nuclear medical testing, I do not believe that I failed to detect significant stenosis. As a result, I suggest that ATP TI-201 scintigraphy might have an important role in assessing cardiac function in diabetic patients. In addition, the correlation between ATP-WRs and long-term glycemic control (HbA1c over the previous 24 months) lends support to the importance of glycemic control from the early stages of DM.

The present study had the following limitations: no sympathetic tests or coronary angiography were performed, a small sample size was used, and no controls were provided. Further investigations are scheduled, including sympathetic tests and coronary angiography using a larger sample size.
The findings from this study reaffirm the importance of glycemic control in diabetic patients. Diabetic patients with a slow T1 washout rate could be complicated with myocardial microcirculatory abnormalities and cardiac sympathetic nerve dysfunction even without any known coronary arterial lesions. Therefore, in these patients, careful attention should be paid to preventing cardiac failure and sudden death.

CONCLUSIONS
In the present study in Japanese diabetic patients without subjective signs of CAD and without abnormalities on ECG or echocardiography, ATP-WR, an indicator of myocardial blood flow, was correlated with myocardial sympathetic nerve dysfunction and 24-month glycemic control. However, sympathetic nerve dysfunction was not correlated with 24-month glycemic control.

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