Mechanism of Impaired Left Ventricular Wall Motion in the Diabetic Heart Without Coronary Artery Disease

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OBJECTIVE — To elucidate whether impairment of the myocardial free fatty acid (FFA) metabolism and small vessel abnormalities in the myocardium are etiologic or contributory factors of myocardial dysfunction in patients with NIDDM without any significant coronary artery disease.

RESEARCH DESIGN AND METHODS — We performed myocardial imaging with ^{123}I-labeled β-methyl-p-iodophenyl pentadecanoic acid (BMIPP), a branched analog of FFA, and dipyridamole-infusion ^{201}thallium scintigraphy (Dip) in nine patients who demonstrated left ventricular wall motion abnormalities without any significant coronary artery disease and in fifteen control cases. As an index of myocardial FFA metabolism, the heart-to-mediastinum count ratio (H/M) of BMIPP was calculated from the mean count in the regions of interest at the heart and the upper mediastinum.

RESULTS — Nine patients with reduced wall motion documented by left ventriculography (LVG) (hypokinetic group) demonstrated significantly lower BMIPP uptake (2.1 ± 0.2, mean ± SD) than fifteen patients with normal wall motion (normokinetic group) (2.3 ± 0.2, $P < 0.05$). Regional ventricular wall motion observed by LVG, regional BMIPP uptake, and regional redistribution phenomenon (RD) were evaluated for five regions of the left ventricle: anterior, septal, apical, lateral, and inferoposterior regions. Wall motion was abnormal in 24 out of 120 regions. Regional BMIPP uptake was reduced in 47 regions. RD in Dip was observed in 23 regions. In regional analysis, the existence of defect in the BMIPP image showed significant correlation with wall motion abnormality ($P < 0.01$), but there was no significant relationship between the RD in Dip and regional wall motion abnormality ($P = 0.16$). Myocardial biopsy specimens obtained from the right ventricle of 20 patients showed no pathologic changes, with the exception of two patients.

CONCLUSIONS — Our findings suggest that impairment of myocardial FFA metabolism rather than small vessel abnormalities in the myocardium is responsible for modest left ventricular dysfunction in patients with diabetes.

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Abbreviations: BMIPP, β-methyl-p-iodophenyl pentadecanoic acid; Dip, dipyridamole-infusion ^{201}thallium scintigraphy; FFA, free fatty acid; H/M, heart-to-mediastinum count ratio; LVG, left ventriculography; MIBG, metaiodobenzylguanidine; RD, redistribution phenomenon; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Systéme International (SI) units and conversion factors for many substances.

Since a specific type of cardiomyopathy related to diabetes (diabetic cardiomyopathy) was first described by Rubler et al. (1) in 1972, numerous investigations have reported cardiac dysfunction specific to diabetes. However, the pathogenesis of diabetic cardiomyopathy remains unclear, although several mechanisms including small vessel coronary artery disease (1–3) and metabolic alterations of the diabetic myocardium (4,5) have been proposed. Factor et al. (6) reported that hypertension might play an important role in the development of cardiomyopathy in patients with diabetes because of its adverse cumulative effects on the cardiovascular system.

We previously reported a case of hypertensive diabetic cardiomyopathy demonstrating left ventricular wall motion abnormality despite the coronary artery being normal (7). Our findings suggested that the myocardial free fatty acid (FFA) metabolism is impaired in the region with wall motion abnormality when compared with myocardial perfusion in general, and this impairment appears to be an etiologic or contributory factor to regional wall motion abnormality, together with small vessel disease. In the present study, to confirm this hypothesis, we studied nine patients who demonstrated left ventricular wall motion abnormalities without any coronary artery disease and fifteen control cases.

RESEARCH DESIGN AND METHODS

Patient population

A total of 24 patients were selected based on the criteria described below from 242 patients with NIDDM who underwent coronary angiography at Kansai Rosai Hospital during 1996 after complaining of chest pain suggesting effort angina. These 24 patients (13 men and 11 women, age 61 ± 11 years [34–71]) (mean ± SD [range]) did not have any lesion of the major epicardial arteries. All patients met the following criteria: 1) they were NIDDM patients according to World Health Organization (WHO) criteria and 2) they had no history or clini-

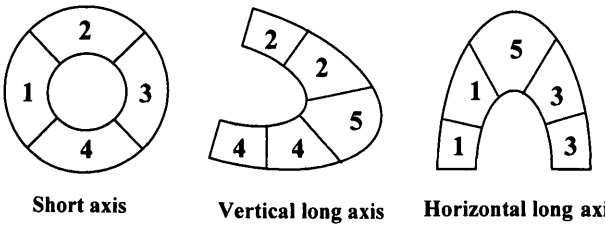

Figure 1—*Relation between scintigraphic images and five segments of the left ventricle. 1, septal; 2, anterior; 3, lateral; 4, inferoposterior; 5, apical.*

cal evidence of myocardial infarction, coronary bypass surgery, valvular or congenital heart disease, and other myocardial diseases, which might cause left ventricular wall motion abnormality with normal coronary arteries, including myocarditis, idiopathic cardiomyopathy, myocardial involvement in systemic disease, or alcoholic cardiomyopathy. Of the patients, 14 had arterial hypertension diagnosed according to WHO criteria (160/95 mmHg) and had been treated with antihypertensive drugs. Six patients were treated with Ca antagonists and eight with ACE inhibitor. All patients were included in the study after they had given their written informed consent.

Study design

Patients were selected after coronary arteriography and cineangiographic left ventriculography (LVG). All underwent dipyridamole-infusion ^{201}thallium scintigraphy (Dip) to assess small coronary artery disease. Myocardial SPECT imaging with ^{123}I-labeled β-methyl-p-iodophenyl pentadecanoic acid (BMIPP) was performed to assess the myocardial FFA metabolism within 1 week after Dip.

Coronary arteriography and cineangiographic LVG

Selective coronary arteriography was performed using standard techniques. Two experienced observers who were unaware of the results of the radionuclide examinations assessed the status of the coronary arteries retrospectively and independently. A ≥50% reduction in the diameter in a major epicardial branch was considered significant. Discrepancies between the observers were resolved by consensus. Contrast LVG was performed in 30° right anterior oblique projection and 60° left anterior oblique projection. Three experienced observers without knowledge of the patient's scan findings or clinical history scored the regional wall motion at the five myocardial segments by using a 5-point grading system (3, normal; 2, hypokinesis; 1, severe hypokinesis; 0, akinesis; −1, dyskinesis). Differences of opinion concerning the angiographic results were resolved by consensus. The left ventricular ejection fraction was calculated from a monoplane angiogram in 30° right anterior oblique projection by means of the area-length method (8).

Endomyocardial biopsy

Of the 24 patients, 20 agreed to endomyocardial biopsy and gave their written informed consent. Biopsy specimens were obtained from the right ventricle with a Cordis bioptome (Cordis, Miami, FL) introduced percutaneously through a right internal jugular vein puncture. Three specimens were obtained from different sites. Stains with hematoxylin-eosin (H-E) and periodic acid-Schiff (PAS) were performed regularly.

Dipyridamole-infusion ^{201}thallium scintigraphy

The method of Dip was described previously (9). Briefly, all patients fasted at least 8 h, and methyl xanthines (theophylline, caffeine, etc.) were not allowed during this period. Dipyridamole was administered intravenously via an antecubital catheter at a dose of 0.14 mg · kg^{-1} · min^{-1} for 4 min. The 12-lead electrocardiogram (ECG), heart rate, and blood pressure were recorded before and at 1-min intervals during the dipyridamole-infusion test. Three minutes following infusion, ^{201}thallium (111 MBq) was administered intravenously. Ten minutes after the administration of ^{201}thallium, data acquisition for SPECT was started using a rotating gamma camera equipped with a low-energy general all-purpose collimator (Starcam 3000 XR/T, General Electronic Medical System, Milwaukee, WI). Delayed images were obtained after 4 h. The camera was rotated over 180° from the 45° left posterior oblique to the 45° right anterior oblique position, and contiguous transverse tomograms of ^{201}thallium encompassing the entire heart were reconstructed. Vertical long-axis, short-axis, and horizontal long-axis tomograms were then derived from the SPECT data. Initial and delayed images were evaluated by three independent observers without knowledge of the patient's cardiac catheterization or clinical data. Regional ^{201}thallium uptake was analyzed in the five segments shown in Fig. 1. The scintigrams were classified as normal if no defects were observed and as displaying redistribution phenomenon (RD) if the initial defects were resolved completely or in part on the delayed scan. Interobserver differences in interpretation were resolved by consensus.

^{123}I-BMIPP scintigraphy

All patients underwent myocardial SPECT imaging with ^{123}I-BMIPP at rest using the rotating gamma camera equipped with a low-energy general all-purpose collimator (Starcam 3000 XR/T). ^{123}I-BMIPP (111 MBq; Nihon Medi-Physics, Nishinomiya, Hyogo, Japan) was injected intravenously at rest in an overnight fasting state. Static acquisition was performed over 15 min, followed by the acquisition for myocardial SPECT using the same protocol as ^{201}thallium. Cardiac ^{123}I-BMIPP uptake was evaluated twice by two independent observers unaware of the clinical status of the patients. Left ventricular activity was measured on a manually drawn region of interest over the whole left ventricle, and the mean heart count per pixel (*H*) was generated. Another 7 × 7 pixel region of interest was set over the upper mediastinum area, and the mean count per pixel (*M*) was generated. The heart-to-mediastinum count ratio (H/M) was then computed to quantify cardiac ^{123}I-BMIPP uptake. Regional BMIPP uptake was analyzed in the five segments as for Dip (Fig. 1). The scintigrams were classified as normal if no defects were observed and as having a defect if no tracer distribution or reduced tracer distribution was observed. Interobserver differences in interpretation were resolved by consensus. The inter- and intra-observer variability in calculating the H/M ratio, which was previously calculated, was 95.5 and 90.6%, respectively.

The control value of cardiac BMIPP uptake was determined for 9 subjects (4 men, 5 women; age 54 ± 8 [38–62] years) showing no sign of cardiac disease after clinical, electrocardiographic, and echocardiographic examinations.

Table 1—*Clinical characteristics of patients with abnormal left ventriculogram (hypokinetic group) and normal left ventriculogram (normokinetic group)*

	Hypokinetic group	Normokinetic group	*P* value
n	9	15	—
Sex (M/F)	6/3	7/8	0.3
Age (years)	57 ± 11	64 ± 8	0.09
BMI (kg/m²)	21.1 ± 1.9	23.1 ± 2.4	0.04
Duration of diabetes (years)	12.1 ± 5.8	11.3 ± 8.5	0.81
Fasting plasma glucose (mmol/l)	159.3 ± 48.0	136.1 ± 41.2	0.22
HbA_{1c} (%)	8.9 ± 2.0	8.1 ± 2.2	0.38
Total cholesterol (mmol/l)	5.09 ± 0.60	5.39 ± 0.96	0.21
Hypertension (%)	44.4	46.7	0.63
Nephropathy (%)*	11.1	13.3	0.69
Neuropathy (%)†	44.4	33.3	0.83
Retinopathy (%)‡	33.3	33.3	0.68

Data are *n*, means ± SD, or %. *Diagnosed by the presence of microalbuminuria; †diagnosed by the absence of ankle-jerk deep tendon reflex; ‡diagnosed by the existence of microaneurysms, dot and blot hemorrhages, multiple hard exudates, neovascularization, or fibrotic changes alone or in any combination.

Statistical analysis

Data are expressed as means ± SD unless otherwise specified. The statistical significance of differences in mean values between two groups was analyzed with the unpaired Student's *t* test, or with the unpaired Wilcoxon's *t* test. One-way analysis of variance (ANOVA) test was used to compare differences of BMIPP uptake among the three groups. Correlations between two variables were examined using linear regression analysis. *P* values < 0.05 (two-sided) were considered to be statistically significant. Frequency data were analyzed by the χ^2 test or Fisher's exact test.

RESULTS — The clinical characteristics of the patients in the groups with hypokinetic or normokinetic left ventricles are shown in Table 1. Abnormal left ventricular wall motion was observed in 9 of 24 patients (hypokinetic group). The remaining 15 patients had normal left ventricular wall motion (normokinetic group). There were no significant differences in characteristics between the two groups, except for BMI. Medical control of diabetes did not differ between the two groups. The left ventricular ejection fraction evaluated by LVG was lower in the hypokinetic group (61 ± 12%) than the normokinetic group (72 ± 12%, $P < 0.05$, Fig. 2). All patients revealed <25% reduction in diameter in a major epicardial branch by coronary arteriography.

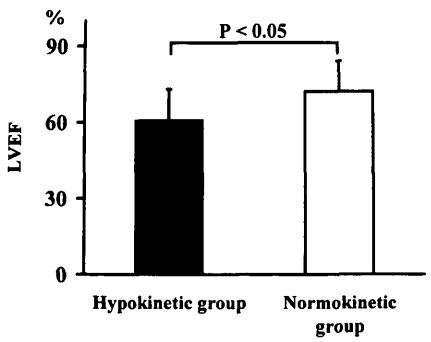

Figure 2—*Left ventricular ejection fraction (LVEF) between two groups.*

The H/M ratio of BMIPP in the hypokinetic group (2.1 ± 0.2) was significantly lower than that in normokinetic group (2.3 ± 0.2, $P < 0.05$, Fig. 3), and also significantly lower than the control subjects (2.4 ± 0.3). Furthermore, the H/M ratio was significantly correlated with the left ventricular ejection fraction ($r = 0.60$, $P < 0.05$, Fig. 4).

In the regional analysis, 24 of 120 regions showed regional wall motion abnormality in LVG. The BMIPP uptake was reduced in 47 regions (Table 2). The existence of defect in the BMIPP image showed significant correlation with wall motion abnormality ($P < 0.01$). Redistribution phenomenon in Dip was observed in 23 regions (Table 3). There were no regions that showed fixed thallium defects, and there was no significant relationship between the RD in Dip and regional wall motion abnormality ($P = 0.16$).

Pathological findings of endomyocardial biopsy specimens

Histologic examination of endomyocardial biopsy specimens obtained from the right ventricle revealed some thickening of the walls of arterioles in two patients (one showed normal wall motion and another abnormal wall motion in the left ventricle). There was no evidence of an increase in interstitial fibrous tissue or any other pathological findings. The remaining 18 patients did not show any pathological findings.

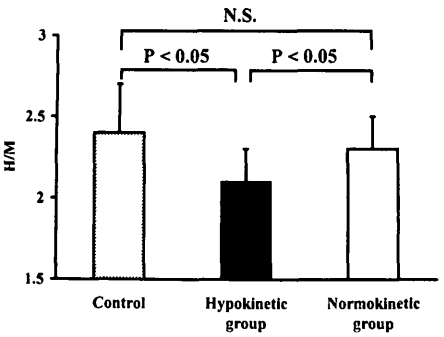

Figure 3—*BMIPP uptake in hypokinetic and normokinetic groups and in control subjects.*

CONCLUSIONS — Cardiovascular disease is the most common cause of death in patients with diabetes over the age of 30 years (10). Several factors can account for this increased incidence, including atherosclerosis of the coronary arteries and macroangiopathy. However, a substantial number of diabetic patients without evidence of ischemic, hypertensive, or valvular heart disease may still develop cardiac dysfunction and congestive heart failure, suggesting the presence of a specific cardiomyopathy related to diabetes, which has been termed "diabetic cardiomyopathy." Previous experimental, pathological, and clinical studies have shown that the specific cardiac dysfunction in diabetes might be caused by small vessel disease, interstitial

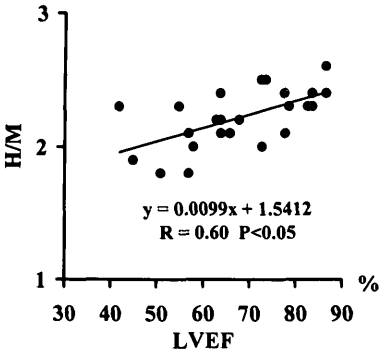

Figure 4—*Correlation between the H/M ratio in BMIPP images and left ventricular ejection fraction (LVEF).*

Table 2—*Relationship between defects in BMIPP and regional wall motion abnormality*

	Wall motion abnormality		
	+	−	Total
Defect (+)	16	31	47
Defect (−)	8	65	73
Total	24	96	120

$\chi^2 = 9.52$, $P < 0.01$.

fibrosis, metabolic derangement in the myocardium, and autonomic nervous system dysfunction. Hamby et al. (2) noted an increased incidence of diabetes in patients with idiopathic cardiomyopathy. They reported that autopsy findings of three diabetic subjects revealed patent large coronary arteries, but small vessel changes in the myocardium, and concluded that diabetic individuals could develop myocardial disease without large coronary artery involvement, possibly caused by pathological changes in the small artery vessels. Rubler et al. (1) reported substantial myocardial hypertrophy and fibrosis in their original series of four patients with diabetic cardiomyopathy. Factor et al. (3) reported thickening and proliferation of the capillary basement membranes and microaneurysms in the heart of diabetic patients. Thus, small vessel disease might be an etiologic or contributory factor of diabetic cardiomyopathy.

In the present study, histologic examination of endomyocardial biopsy specimens from 20 patients revealed the presence of arteriolar thickening only in two patients. One of them showed abnormal left ventricular wall motion, but no increase of interstitial fibrosis. The remaining 18 patients did not show any pathological findings such as small vessel abnormalities, substantial myocardial hypertrophy, or an increase of interstitial fibrosis. Histologic examination of endomyocardial biopsy may be less sensitive for detecting myocardial microcirculation abnormalities than dipyridamole-infusion ^{201}thallium because the myocardial specimens are small and come from only a part of the whole heart and they do not necessarily reflect the histology and pathology of the left ventricle. Thus, errors of interpretation may arise.

To detect possible defects in myocardial microcirculation, we used Dip. Gould et al. (11–13) reported that dipyridamole given intravenously could lead to coronary vasodilatation in normal vessels, but fixed coronary stenoses prevented or attenuated this response. This difference in the degree of coronary vasodilatation between normal vessels and the stenotic vessels can be detected by abnormal thallium uptake when the radionuclide is injected during the peak of the vasodilative effect by dipyridamole. Redistribution occurs in areas of viable, but hypoperfused myocardial regions, comparable to that observed with exercise scintigraphy. Thus, Dip plays a clinically useful role in the noninvasive detection of coronary artery disease (14). It has also been reported to enable detection of abnormal coronary flow reserve, possibly caused by abnormalities of small coronary vessels (15,16). We used this method in the current study, but found no significant relationship between the RD in Dip and regional wall motion abnormality. These results indicate that small vessel disease does not cause regional left ventricular dysfunction in patients with modest dyskinesis. However, we do not deny the possibility that the addition of small vessel disease progresses left ventricular dysfunction.

Radiolabeled FFAs are considered to be clinically suitable agents for assessing myocardial metabolism because they are the preferred energy substrate for the myocardium under physiological conditions. BMIPP is a branched free fatty analog and was developed for imaging of the myocardial metabolism of FFA because it is metabolized more slowly than straight-chain FFA (17,18). Myocardial accumulation of ^{123}I-BMIPP has been also reported to be observed mainly in the triglyceride fraction (19) and to be associated with the synthesis of triglyceride (20). Moreover, myocardial accumulation of ^{123}I-BMIPP has also been reported to be closely correlated with the intercellular concentration of ATP (18). Therefore, ^{123}I-BMIPP may reflect myocardial energy production, which has a close relationship with left ventricular function. In fact, in this study, there was a significant correlation between the H/M ratio of BMIPP and the ejection fraction among all the subjects. The myocardial ^{123}I-BMIPP uptake of the patients with left ventricular dysfunction was less than that of patients without it. The presence of a defect in the BMIPP image showed significant correlation with wall motion abnormality. These results suggest that impairment of the myocardial FFA metabolism is an etiologic or contributory factor to left ventricular wall motion abnormality.

In regional wall motion analysis, both regional BMIPP uptake defect and RD in Dip were observed, not only in regions with abnormal wall motion but also in those without abnormality. Moreover, there was no significant relationship between the RD in Dip and regional wall motion abnormality. Thus, the wall motion abnormalities detected by left ventriculograms are not necessarily concordant with the changes detected by scintigraphic assessments. There might be inherent limitations in the comparison of regional wall motion abnormalities in two-dimensional ventriculography with three-dimensional SPECT imaging. One of the limitations of this study is that scintigrams only allow relative assessments.

We also need to consider the possible role of autonomic nervous system dysfunction in diabetic cardiomyopathy. Previous studies have documented the association of sympathetic nervous system dysfunction with congestive heart failure. Depletion of myocardial cathecholamines is known to occur in patients with heart failure (21), and this has also been reported in diabetic patients without congestive heart

Table 3—*Relationship between the redistribution phenomenon in Dip and regional wall motion abnormality*

	Wall motion abnormality		
	+	−	Total
Redistribution (+)	7	16	23
Redistribution (−)	17	80	97
Total	24	96	120

$\chi^2 = 1.94$, $P = 0.16$.

failure (22). Autonomic neuropathy has been shown to impair the cardiovascular responses to exercise in diabetic patients (23). Zola et al. (24) have reported a significant relationship between the left ventricular ejection fraction and the extent of cardiac autonomic neuropathy. Although a positive relationship has been reported between cardiac autonomic dysfunction and left ventricular dysfunction, the findings of other investigators (25,26) have not confirmed this. ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy has been considered to be useful for imaging the myocardial sympathetic nerve function (27–29). ^{123}I-MIBG myocardial scintigraphy was performed for all patients included in this study and all showed defects, but no correlations were found with wall motion (data not shown).

The interaction between diabetes and hypertension on the myocardium should also be considered. Factor et al. (6) have reported that diabetic cardiomyopathy might result from the combination of diabetes and hypertension. The animal model of hypertensive diabetic cardiomyopathy has shown similarities for both dysfunction aspects (30) and pathologic changes (31) seen in humans. In our study, the ratio of hypertensive patients did not differ between the two groups and we could not detect any effect of hypertension on the left ventricular dysfunction in our subjects.

In summary, the present study suggests that impairment of myocardial FFA metabolism rather than small vessel abnormalities in the myocardium may cause modest left ventricular regional dysfunction in patients with diabetes. However, the relatively small number of patients in this study limit the interpretation of our data, and further studies are needed to understand the mechanism of impaired left ventricular wall motion in the diabetic heart.

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