Journal of Cardiology 22: 427–438, 1992

Systolic and diastolic left ventricular dysfunction in middle-aged asymptomatic non-insulin-dependent diabetics

Isao YASUDA
Koichi KAWAKAMI
Toshio SHIMADA
Keiichiro TANIGAWA*
Rinji MURAKAMI
Shiro IZUMI
Shigefumi MORIOKA
Yuzuru KATO*
Katsutoshi MORIYAMA

Summary

Radionuclide ventriculographic studies were performed at rest and during exercise in 15 middle-aged asymptomatic patients with non-insulin-dependent diabetes mellitus (NIDDM) whose mean age was 58.7±10.5 years (mean±SD), and in 10 age- and sex-matched normal control subjects. The patients had neither clinical evidence of cardiovascular diseases nor obvious perfusion defects during maximal exercise testing with thallium-201 myocardial scintigraphy. The average left ventricular ejection fraction (LVEF) at rest was 69.1±5.3% in the diabetic patients and 65.6±4.2% in the control subjects, and during exercise, the average LVEFs were 68.3±6.9% and 72.1±5.0%, respectively. The changes in LVEF during exercise were −0.7±7.6% in the diabetic group and +6.5±2.6% in the control group ($p<0.01$). However, the filling fraction during the first third of diastole at rest was significantly less in the diabetic group than in the control group ($p<0.05$), the time to peak filling rate (TPF) was longer, and the TPF/R-R, normalized by the R-R interval and expressed as a percentage, was greater in the NIDDM patients than in the control subjects. There was close correlation between the abnormal response of LVEF to exercise and the reduced early diastolic filling in the diabetic patients.

We concluded that 1) not only the response of LVEF to exercise but also the early left ventricular diastolic filling at rest are impaired in middle-aged asymptomatic NIDDM patients, and 2) some common factors could cause dysfunction of both the systolic and diastolic left ventricles in NIDDM patients, possibly latent global myocardial ischemia or metabolic myocardial disturbances.

島根医科大学 第四内科
*同 第一内科
出雲市塩冶町 89-1 (〒693)

The Fourth and *the First Departments of Internal Medicine, Shimane Medical University, Enya-cho 89-1, Izumo 693

Received for publication February 20, 1991; accepted August 22, 1991 (Ref. No. 38-PS142)

Key words
Non-insulin-dependent diabetic patients Radionuclide ventriculography Left ventricular systolic and diastolic dysfunction Latent global myocardial ischemia

Introduction

The incidence of congestive heart failure is relatively high in patients with diabetes mellitus[1-3] and an increasing number of studies have proved that cardiac dysfunction occurs in diabetic patients with normal coronary arteries[4,5], however, the causes of these abnormalities are still unclear. Some authors[6,7] have suggested the presence of a specific diabetic cardiomyopathy. Rubler et al[6] reported 4 adult-onset diabetics who had cardiomegaly and congestive heart failure in the absence of major coronary artery disease or hypertension. Hamby et al[7] observed a high incidence of diabetes mellitus in their series of patients with idiopathic cardiomyopathy. It has been proposed that the metabolic derangements of diabetes impair left ventricular function[4,8]. Several investigators have shown that abnormalities of left ventricular systolic[9-14] or diastolic[4,8,15-19] function or both[5] are common in diabetics even without coronary artery disease or clinical manifestations of congestive heart failure. Abnormalities of left ventricular function have been observed in diabetics at rest[4,9,20,21] and also during exercise[10-14]. Whether these abnormalities result from microangiopathy in the heart or from metabolic derangements inherent in diabetes mellitus remains unclear.

Previous studies to detect subclinical left ventricular dysfunction have been made mainly on young asymptomatic patients with insulin-dependent diabetes mellitus (IDDM). There are few reports dealing with left ventricular systolic and diastolic function in middle-aged asymptomatic patients with non-insulin-dependent diabetes mellitus (NIDDM)[14,16]. The present study is the first to examine the relationship between systolic and diastolic dysfunction in individual diabetics. If there is any relationship, it may prove that systolic and diastolic dysfunction in diabetics have some factors in common. In the present study, we used submaximal exercise testing combined with radionuclide ventriculography to investigate left ventricular systolic and diastolic function in middle-aged asymptomatic NIDDM patients without signs of ischemic heart disease or any other cardiovascular disease.

Methods

Study subjects

Fifteen middle-aged asymptomatic NIDDM patients, 8 males and 7 females, who ranged in age from 40 to 75 years and whose mean age was 58.7±10.5 years, were selected for the present study from 47 diabetics.

History, physical examination, electrocardiography at rest and chest radiography were used to exclude patients with cardiac or pulmonary disease, endocrine disorders or alchoholism, or patients receiving drugs which might affect their cardiac performance. The exclusion criteria for patients were excluded if they had any abnormalities on physical examination or by electrocardiography or chest radiography, a systolic blood pressure above 160 mmHg or a diastolic pressure above 95 mmHg, renal insufficiency, abnormal blood urea nitrogen or creatinine levels, or more than 20% excess over ideal body weight. Those who were suspected of having coronary artery disease were excluded from the results of maximal exercise testing with thallium-201 myocardial scintigraphy, as described below.

The duration of diabetes mellitus of the subjects ranged from 3 to 22 years, with a mean duration of 9.1±7.5 years. Six patients received oral antidiabetic agents, 4 were treated by diet alone, and 5 were treated with insulin 8 to 12 units per day. Glycosylated hemoglobin concentrations (normal values <8.0%) ranged from 8.5 to 15.6%, with a mean value of 10.4 ±2.0%. Two of 15 patients had proliferative retinopathy and 3 of them had proteinuria

Table 1. Clinical features of 15 diabetic patients

Case	Age (yrs) & sex	Duration of illness (yrs)	Treatment	Hgb A1 (%)	Retinopathy	Urinary protein
1	57 F	7	Diet	8.5	(−)	(−)
2	41 F	22	I	12.5	(−)	(−)
3	71 F	6	Diet	9.4	(−)	(−)
4	59 F	3	Diet	11.7	(−)	(−)
5	55 M	4	OA	11.4	(−)	(−)
6	74 M	20	I	10.2	(+)	(−)
7	66 M	20	I	15.6	(+)	(+)
8	60 F	9	OA	12.0	(−)	(−)
9	51 F	7	OA	10.4	(−)	(+)
10	56 M	7	OA	9.2	(−)	(−)
11	66 M	9	I	9.0	(−)	(+)
12	53 M	6	OA	8.8	(−)	(−)
13	41 M	11	OA	8.8	(−)	(−)
14	73 F	18	I	9.9	(−)	(−)
15	51 M	3	Diet	8.9	(−)	(−)

F=female; M=male; I=insulin; OA=oral agent; Hgb A1=glycosylated hemoglobin A1.

(**Table 1**).

Ten age- and sex-matched healthy control subjects consisting of 5 males and 5 females whose mean age was 61.7±14.4 years were also studied for comparison. None of the control subjects had evidence of heart disease, based on history, physical examination, electrocardiography and chest radiography. None presented any obvious perfusion defects on maximal exercise testing with thallium-201 myocardial scintigraphy and none had angina or significant ST shifts on their 12-lead electrocardiograms during exercise.

Myocardial scintigraphy

Subjects were studied in the postabsorptive state. A standard multistage exercise was performed with a motorized ergometer by simultaneous recording of a 12-lead electrocardiogram. The exercise load was begun at 20 W for one min, then increased by 20 W increments every min until symptoms such as leg fatigue occurred. One min before termination of the exercise, a bolus of 111 MBq thallium-201 was injected intravenously. Blood pressure and 12-lead electrocardiograms were recorded every min. Images were obtained twice within 5 min after exercise (early imaging) and 4 hours later (delayed imaging).

Radionuclide ventriculography

All patients underwent multigated radionuclide ventriculography with simultaneous electrocardiographic tracings. Twenty min after the intravenous administration of 148 MBq stannous pyrophosphate, 925 MBq technetium pertechnetate was injected intravenously for in vivo labeling of red blood cells. Imaging was performed in a supine position, using a mobile gamma camera equipped with a multipurpose collimator and built-in a computer system (General Electric, Starcam, 400 AC/T). Imaging was performed in the left anterior oblique projection. Eighty percent of the total workload on maximal exercise testing with thallium-201 myocardial scintigraphy was adopted as an appropriate workload. Each cardiac cycle was divided into 24 frames on a 64×64 matrix. Four hundred cardiac cycles at rest and at least 200 cardiac cycles during supine bicycle exercise were collected and stored by ECG gating. Ectopic beats were excluded from the data.

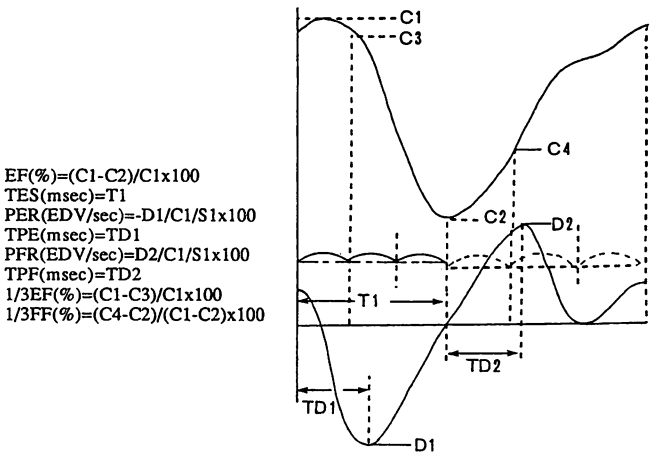

Fig. 1. Radionuclide ventriculographic measurements and calculations.

EF=ejection fraction; TES=time to end-systole; PER=peak ejection rate; TPE=time to peak ejection rate; PFR=peak filling rate; TPF=time to peak filling rate; FF=filling fraction; S1=sampling time; C1-C4=EDC and ESC counts at the 1/3 FF and 1/3 EF, respectively; D1, D2=maximum values of negative dv/dt during systole and positive dv/dt during diastole, respectively.

During exercise, stabilization of heart rate was achieved within one min and before data acquisition. Left ventricular time-activity curves obtained from the cardiac image sequence of variable left ventricular and background regions of interest exhibited excellent temporal resolution and were used to represent measurements of relative left ventricular changes with time throughout the average cardiac cycle. Left ventricular time-activity curves were reconstructed from the first 4 Fourier harmonics. First derivative curves (dv/dt) of these time-activity curves were obtained throughout the entire cycle with a computer. A maximum value of negative dv/dt during systole was defined as the peak ejection rate. A maximum value of positive dv/dt during diastole was defined as the peak filling rate. The following indexes were obtained from the time-activity and first derivative curves (**Fig. 1**).

Systolic phase indexes: 1) Ejection fraction=(EDC−ESC)/(EDC−BG)×100, where EDC, ESC and BG are end-diastolic, end-systolic and background counts, respectively. 2) Left ventricular ejection time (msec)=the time interval between the electrocardiographic R wave and the frame with minimum counts at which the dv/dt value was zero. 3) 1/3 ejection fraction=ejection fraction during the first third of systole. 4) Peak ejection rate (EDV/sec)=peak ejection rate normalized to end-diastolic counts, where EDV is end-diastolic volume. 5) Time to peak ejection rate (msec)=the time interval between the electrocardiographic R wave and the peak negative dv/dt.

Diastolic phase indexes: 1) Peak filling rate (EDV/sec)=peak filling rate normalized to end-diastolic counts. 2) Time to peak filling rate (msec)=the time interval between the end-systolic and the peak positive dv/dt. 3) 1/3 filling fraction=filling fraction during the first third of diastole.

Statistical analysis

All variables of the control subjects and diabetic patients were compared using the unpaired t-test, and all variables obtained at rest and during exercise were compared by the paired t-test. A p value of less than 0.05 was considered statistically significant. All data were expressed as means±standard deviations.

Table 2. Indexes at rest and peak exercise

	At rest		At peak exercise			
	HR (beats/min)	SBP (mmHg)	HR (beats/min)	SBP (mmHg)	PRP ($\times 10^4$)	TWL (watts)
Control subjects (n=10)	62±11	129±14	123±33	178±18	2.2±0.8	441±231
Diabetics (n=15)	67±9	135±18	124±25	199±37	2.5±0.9	485±230

Values are means±SD.
HR=heart rate; SBP=systolic blood pressure; PRP=pressure-rate product; TWL=total workload.

Results

1. Exercise capacity

There was no difference between the diabetic and control groups with respect to heart rate and blood pressure at rest. Termination of exercise was determined by signs of exhaustion, such as leg fatigue, in all subjects. None experienced chest pain, myocardial scintigraphic defects or electrocardiographic changes. Both groups attained similar total workloads, peak heart rates, peak blood pressures and pressure-rate products. There was no significant difference between the diabetic and control groups with regard to exercise capacity (**Table 2**).

2. Ejection fraction

No regional wall motion abnormalities in phase and amplitude analysis of the radionuclide ventriculography were observed in any subjects in either group at rest or during exercise. The left ventricular ejection fraction (LVEF) was 60% or more in all NIDDM patients. The average LVEF at rest was 69.1±5.3% in the NIDDM patients and 65.6±4.2% in the control subjects, and it was higher in the diabetic group than in the control group, but the difference was not significant. During exercise, the average LVEF changed to 68.3±6.9% in the former and 72.1±5.0% in the latter, but the difference also was not significant. LVEF of the control group increased significantly with exercise ($p<0.01$), however, that of the diabetic group remained unchanged (**Fig. 2**).

The average change in LVEF with exercise was −0.7±7.6% in the diabetic group and +6.5±2.6% in the control group, with the difference being significant ($p<0.01$) (**Fig. 3**). If a normal response of LVEF to exercise can be defined as an increase of more than 4% during exercise, 12 of the 15 NIDDM patients (80%) and 2 of the 10 control subjects (20%) were considered abnormal.

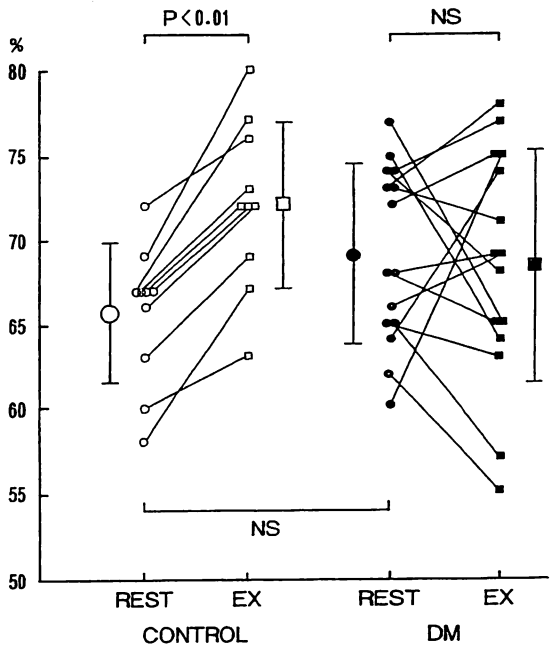

Fig. 2. The response of LVEF to exercise.
The average LVEF at rest was 69.1±5.3% in the NIDDM patients and 65.6±4.2% in the control subjects. On exercise, the average LVEF changed to 68.3±6.9% and 72.1±5.0%, respectively. LVEF of the control group increased significantly ($p<0.01$), but that of the diabetic group did not.

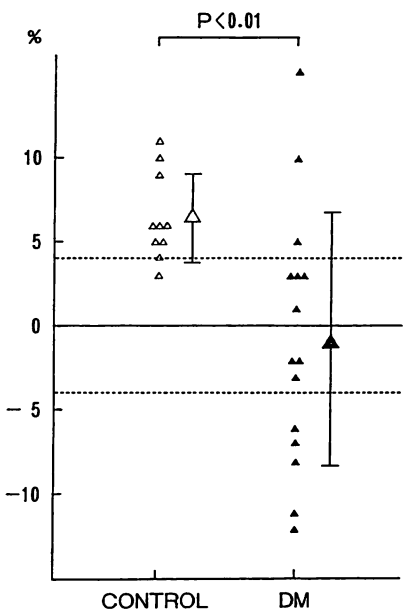

Fig. 3. Average change in LVEF with exercise.
The average change in LVEF with exercise was −0.7±7.6% in the diabetic group and +6.5±2.6% in the control group with the differences being significant. If a normal response of LVEF to exercise was defined as an increase of more than 4% during exercise, 12 of 15 NIDDM patients (80%) and 2 of 10 control subjects (20%) were regarded abnormal.

Statistically, there was no correlation between an abnormal response of LVEF to exercise and the various clinical variables, such as age, duration of diabetes, glycosylated hemoglobin concentration, diabetic complications, heart rate or blood pressure at rest or during exercise, pressure-rate product, total workload or ejection fraction at rest in the NIDDM patients.

Ejection fraction during the first third of systole (1/3 EF) at rest was significantly higher in the diabetic group (25.5±6.5%) than in the control group (19.9±3.1%) ($p<0.01$) (**Table 3**).

Among the NIDDM patients, 7 diabetic patients with 1/3 EF of more than 25% (patients 3, 4, 5, 6, 7, 8 and 10) had higher glycosylated hemoglobin concentrations (11.4%) than did the other 8 patients with 1/3 EF of 25% or less (9.6%). Global LVEF at rest was 73.3±2.8%

Table 3. Radionuclide ventriculographic data

		Control subjects (n=10)	Diabetics (n=15)
EF (%)	Re	65.6±4.2	69.1±5.3
	Ex	72.1±5.0[a]	68.3±6.9
dEF (%)		+6.5±2.6	−0.7±7.6**
TES (msec)	Re	373±38	371±41
	Ex	296±25[a]	289±33[a]
TES/R-R (%)	Re	38.3±6.9	41.5±3.7
	Ex	47.8±5.4[a]	49.2±5.7[a]
PER (EDV/sec)	Re	3.46±0.45	3.48.0.41
	Ex	4.25±1.05[b]	4.17±0.80[a]
TPE (msec)	Re	163±21	150±22
	Ex	118±33[a]	100±35[a]
TPE/R-R (%)	Re	16.6±2.7	16.9±2.7
	Ex	18.8±5.3	17.2±6.9
PFR (EDV/sec)	Re	2.81±0.56	3.02±0.74
	Ex	4.97±1.14[a]	5.43±1.18[a]
TPF (msec)	Re	159±56	181±52
	Ex	128±39	123±26[a]
TPF/R-R (%)	Re	16.1±5.5	20.4±7.2
	Ex	20.2±4.2	21.1±3.2
1/3 EF (%)	Re	19.9±3.1	25.5±6.5**
	Ex	29.8±6.0[a]	27.3±5.9
1/3 FF (%)	Re	45.9±12.1	35.5±14.1*
	Ex	24.4±6.8[a]	18.7±7.6[a]

Values are means±SD.
* $p<0.05$; ** $p<0.01$, compared with the values of the control group.
[a] $p<0.05$; [b] $p<0.01$, compared with the values at rest.
EF=ejection fraction; dEF=change in LVEF with exercise; TES=time to end-systole; TES/R-R=TES normalized by the R-R interval and expressed as a percentage; PER=peak ejection rate; TPE=time to peak ejection rate; TPE/R-R=TPE normalized by the R-R interval and expressed as a percentage; PFR=peak filling rate; TPF=time to peak filling rate; TPF/R-R=TPF normalized by the R-R interval and expressed as a percentage; 1/3 EF=ejection fraction during the first third of systole; 1/3 FF=filling fraction during the first third of diastole; Re=rest; Ex=exercise.

Table 4. Radionuclide ventriculographic data of each patient

Case	EF (%)		dEF (%)	1/3 EF (%)	1/3 FF (%)	TPF (msec)	TPF/R-R (%)
	At rest	On exercise		At rest			
1	68	65	−3	25	32	220	23.5
2	64	74	10	21	50	116	12.6
3	77	65	−12	28	30	280	27.1
4	75	64	−11	39	18	288	37.5
5	74	68	−6	27	31	165	20.9
6	73	78	5	27	48	153	12.5
7	68	69	1	31	52	135	12.6
8	72	75	3	35	41	144	16.6
9	62	55	−7	24	10	198	25.1
10	74	77	3	28	40	132	12.5
11	73	71	−2	25	55	152	16.7
12	65	63	−2	17	11	210	29.0
13	60	75	15	16	41	148	16.8
14	66	69	3	23	32	170	21.0
15	65	57	−8	17	42	210	21.0

Abbreviations: see Table 3.

and 65.4±3.9%, respectively ($p<0.05$) (**Table 4**).

3. Diastolic filling

Left ventricular diastolic filling at rest was also impaired in the NIDDM patients. The filling fraction during the first third of diastole (1/3 FF) at rest was significantly lower in the diabetic group (35.5±14.1%) than in the control group (45.9±12.1%) ($p<0.05$). The time required to attain peak filling rate (TPF) at rest was longer in the NIDDM patients than in the control subjects. This remained true even when the TPF was normalized by the R-R interval and expressed as a percentage (TPF/R-R). The peak filling rate (PFR) was slightly higher in the diabetic group than in the control group. The 1/3 FF differed significantly between the 2 groups and the other indexes showed no statistically significant difference (**Table 3**).

No statistical correlation was observed between 1/3 FF, TPF or TPF/R-R in the NIDDM patients and the various clinical variables, such as age, duration of diabetes, glycosylated hemoglobin concentration, presence of retinopathy or nephropathy, heart rate or blood pressure at rest or during exercise, pressure-rate product, total workload or ejection fraction at rest.

Among the NIDDM patients, the average change in LVEF with exercise was −5.4±5.3% in 7 diabetic patients with 1/3 FF of less than 35% at rest (patients 1, 3, 4, 5, 9, 12 and 14), while that of the other 8 patients with 1/3 FF of 35% or more at rest was +3.4±7.0% ($p<0.05$). LVEF decreased with exercise in 6 diabetic patients with 1/3 FF of less than 35% at rest, except for patient 14. Similarly, the average TPF at rest was longer and the average TPF/R-R at rest was greater in 7 diabetic patients with reduced early diastolic filling than in the other 8 patients, 219±49 vs 149±28 msec ($p<0.01$) and 26.3±5.8 vs 15.2±3.1% ($p<0.01$), respectively. LVEF at rest and glycosylated hemoglobin concentrations were not significantly different between these 2 subgroups of the NIDDM patients; 69.6 vs 68.6% and 10.0 vs 10.8%, respectively (**Table 4**).

Discussion

Coronary artery disease is one of the most well-known diabetic complications[22,23]. Coronary angiography is an accurate and practical diagnostic procedure, but it must be used very carefully since it is an invasive procedure. We carefully selected the patients who were free of cardiovascular disease or factors other than diabetes that might alter left ventricular function. Maximal exercise testing combined with thallium-201 myocardial scintigraphy was used to exclude coronary artery disease from this study. However, it is somewhat difficult to detect three-vessel coronary artery disease with global myocardial ischemia even by maximal exercise testing with thallium-201 myocardial scintigraphy.

In the present study, there was no significant difference between the exercise capacities of the NIDDM patients and the control subjects. The results of our previous studies indicated that LVEF was maintained at rest, but decreased or did not increase during exercise in 80% of the NIDDM patients but in 20% of the control subjects. This difference in the incidence of abnormal LVEF responses to exercise between our study and previous studies (42–72%)[10–14] may be due to different background of the 2 diabetic populations. Our patient group consisted of middle-aged asymptomatic NIDDM. The value of the average change in LVEF with exercise in the control group ($6.5 \pm 2.6\%$) was also lower than that in the control group of the previously reported studies (10–15%)[10–14]. The abnormal LVEF response to exercise may be related to the use of a supine bicycle during exercise.

Subclinical impairment of left ventricular function in asymptomatic diabetic patients has been suggested based on the findings of echocardiography[9,16–20], systolic time intervals[4,9,16] and radionuclide ventriculography[10–16], but the causes of these abnormalities remain unclear. In fact, various factors have been considered capable of producing impairment of left ventricular function in asymptomatic diabetic patients, such as metabolic factors[4], microangiopathy[6,7,18,21], neuropathy[15] and latent coronary artery disease[23]. However, since these factors are often present simultaneously in diabetic patients, it is difficult to assess each factor's contributions.

A decrease in LVEF on exercise is a sensitive index of coronary artery disease[24,25]. Diffuse global microvascular circulation disturbance is present in various organs in diabetes due to microangiopathy or hyperviscosity of the blood. The shift to the left of the oxygen hemoglobin dissociation curve by glycosylated hemoglobin is partly due to the reduction in the oxygen supply to the myocardial cells, as well as cells of other organs affected by diabetes mellitus[26–28]. One possible explanation of an abnormal LVEF response to exercise could be latent global myocardial ischemia not due to coronary artery disease, because it is very difficult to detect global myocardial ischemia and three-vessel coronary artery disease on maximal exercise testing with thallium-201 myocardial scintigraphy.

In the NIDDM patients, no statistical correlation was observed between an abnormal LVEF response to exercise and the various clinical variables, such as age, duration of diabetes, glycosylated hemoglobin concentration, retinopathy or nephropathy, heart rate or blood pressure at rest or on exercise, pressure-rate product, total workload or ejection fraction at rest. Reasons for these findings could be as follows: 1) equivocal onset of NIDDM, 2) the relatively wide range of ages, and 3) inclusion of few severely complicated diabetic patients; only 2 patients with retinopathy and 3 with proteinuria.

Several investigators have reported a condition of cardiac hyperfunction[29–32] or tissue hyperperfusion in the kidneys[33], brain[34], retina[35] and subcutaneous tissue[36], particularly under poor metabolic control. We consider that there was cardiac hyperfunction in the NIDDM patients, especially in those with poor metabolic control, according to the results of radionuclide ventriculography. The 1/3 EF at rest was significantly higher in the diabetic group than in the control group ($p < 0.01$). Although there was no

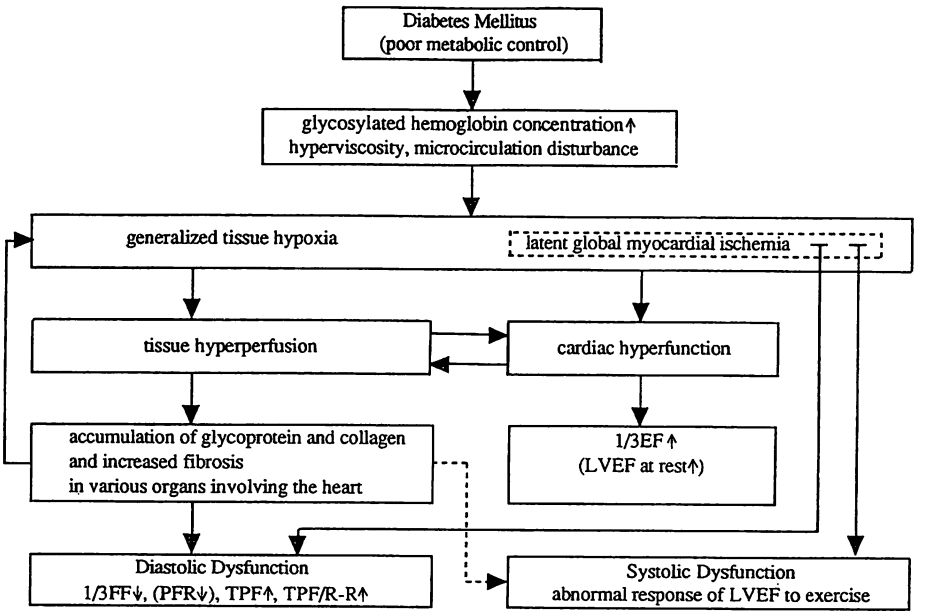

Fig. 4. Schematic diagram showing the mechanism of systolic and diastolic left ventricular dysfunction in the middle-aged asymptomatic NIDDM patients.
Abbreviations: see Table 3.

statistically significant difference, the value of LVEF at rest was higher in the diabetic group (69.1%) than in the control group (65.6%).

Thuesen et al[22] suggested that cardiac hyperfunction is not a consequence of an increase in the myocardial contractile state, but rather is secondary to a reduced afterload. Cardiac hyperfunction, particularly in early systole, in our diabetic patients may support the findings of their report. Parving et al[37] suggested that hyperperfusion and decreased precapillary resistance play a role in the genesis of diabetic microangiopathy, because hyperperfusion and decreased precapillary resistance result in increased hydrostatic capillary pressure and extravasation of plasma proteins.

We also observed impairment of left ventricular diastolic function at rest in the NIDDM patients. The prolonged isovolumic relaxation period reported in the previous studies[5,18,19] might affect early diastolic filling and show a diminished early diastolic filling fraction. We suspect that reduced early diastolic filling may result in prolongation of the time required to attain peak filling rate. In fact, the 1/3 FF at rest was significantly lower in the diabetic group than in the control group ($p<0.05$). Accordingly, the TPF at rest was longer and the TPF/R-R normalized by R-R interval and expressed as a percentage was larger in the NIDDM patients than in the control subjects. However, the PFR in the NIDDM patients was not lower than that of the control subjects, which differed from the results of the previous studies[15-17]. This difference may be attributed to the differences in the study population.

Although abnormalities of diastolic function have frequently been observed, the pathogenesis of these abnormalities has not been determined. Regan et al[4] reported the accumulation of periodic acid-Schiff (PAS) staining material (glycoprotein) in the interstitium. The accumulation of cholesterol and triglycerides in myocardial cells and glycoprotein and collagen in the myocardial interstitium[4,8,28] may lead to a decrease in left ventricular compliance,

and increased fibrosis of the myocardial interstitium[13,29] may result in greater stiffness of the myocardium. These histological changes may impair relaxation or distensibility of the left ventricle in early diastole.

Latent global myocardial ischemia may also play a role in left ventricular diastolic dysfunction. Radionuclide analysis of diastolic filling in patients with coronary artery disease has been found to be a highly sensitive technique for detecting diastolic abnormalities preceding the appearance of systolic abnormalities[40-43].

In the present study, close correlation was observed between an abnormal response of LVEF to exercise and reduced early diastolic filling among the NIDDM patients. This suggests that there may be some common factors between these systolic and diastolic abnormalities. It is very difficult to provide direct evidence of latent global myocardial ischemia, but we suggest the possible mechanism of systolic and diastolic left ventricular dysfunction in the middle-aged asymptomatic NIDDM patients as shown in **Fig. 4**.

Despite the normal ejection fraction at rest in the NIDDM patients, left ventricular diastolic filling was already impaired in the diabetic patients in the present study as well as in the previous studies[16,17], suggesting that abnormalities in left ventricular diastolic function may be an earlier sign of diabetic myocardial disease than impaired systolic function at rest.

Few patients in the present study had severe diabetic complications. Different results might have been obtained using another subset group of diabetic patients with, for example, severe complications or differing degrees of metabolic control.

Our study had some limitations. Our patient group was heterogeneous. However, it is very difficult to select a homogeneous subgroup of NIDDM, because the onset of NIDDM is equivocal and various factors are often present simultaneously. We used hemoglobin A1 concentration as an index of metabolic control level with NIDDM.

Further studies are necessary to elucidate the factors and mechanisms responsible for systolic and diastolic left ventricular dysfunction in diabetics.

要　約

インスリン非依存型糖尿病患者における左室収縮能および拡張能障害について

島根医科大学　第四内科，*第一内科

安田　勲，川上興一，島田俊夫，*谷川敬一郎，村上林児，泉　司郎，盛岡茂文，*加藤　譲，森山勝利

インスリン非依存型糖尿病患者における左室収縮能および拡張能について，運動負荷心プールシンチグラフィーを用いて検討した．対象は，心肺疾患，高血圧を除外し，運動負荷心筋シンチグラムにて陰影欠損が認められなかった糖尿病患者15例(男性8例，女性7例，平均年齢 58.7±10.5歳)である．対照は健常者10例(男性5例，女性5例，平均年齢 61.7±14.4歳)である．

安静時左室駆出率は対照群，糖尿病群それぞれ65.6±4.2，69.1±5.3% で，両群間に有意差を認めなかったが，運動負荷時にはそれぞれ 72.1±5.0，68.3±6.9% へと変化し，対照群では運動負荷により左室駆出率が有意に上昇したが，糖尿病群では有意差を認めなかった．さらに，両群の安静時と亜最大運動負荷時左室駆出率変化は，対照群 +6.5±2.6% に対し，糖尿病群は −0.7±7.6% で，両群間に有意差 ($p<0.01$) を認め，左室収縮予備能の低下が示唆された．一方，安静時左室拡張早期における 1/3 充満率において，対照群の 45.9±12.1% に対し糖尿病群では 33.9±14.9% で，有意の低下 ($p<0.05$) を認めた．また，TPF (time to peak filling rate) およびそれを R-R 間隔で補正した TPF/R-R においても，糖尿病群は延長の傾向を認め，左室拡張能，殊に拡張早期の能動的弛緩障害が示唆された．また，糖尿病群において，左室収縮予備能の低下を示す群と安静時左室拡張早期の充満率低下を示す群との間に，密接な相関が認められた．

インスリン非依存型糖尿病患者において，左室収縮予備能の低下および拡張能障害をともに認めた．両者に共通する要因として，代謝障害および組織学的変化に基づく瀰漫性の心筋虚血が関与している可能性がある．また，左室拡張早期の充満率低下は安静時において既に認められ，拡張早期の障害を良く反映し，糖尿病患者の心機能障害にとってより良い指標となり得ると考えられる．

References

1) McKee PA, Castelli WP, McNamara PM, Kannel WB: The natural history of congestive heart failure: The Framingham study. N Engl J Med **285**: 1441–1445, 1971
2) Kannel WB, Hjortland M, Castelli WP: The role of diabetes in congestive heart failure: The Framingham study. Am J Cardiol **34**: 29–34, 1974
3) Kannel WB, McGee DL: Diabetes and cardiovascular disease: The Framingham study. JAMA **241**: 2035–2038, 1979
4) Regan TJ, Ettinger PO, Khan MI, Jesrani MU, Lyons MM, Oldewurfel HA, Weber M: Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. Circ Res **35**: 222–227, 1974
5) Ahmed SS, Jaferi GA, Narang RM, Regan TJ: Preclinical abnormality of left ventricular function in diabetes mellitus. Am Heart J **89**: 153–158, 1975
6) Rubler SR, Dluglash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol **30**: 595–602, 1972
7) Hamby RI, Zoneraich S, Sherman L: Diabetic cardiomyopathy. JAMA **229**: 1749–1754, 1974
8) Regan TJ, Lyons MM, Ahmad SS, Levinson GE, Oldewurtel HA, Ahmed MR, Halder B: Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest **60**: 884–899, 1977
9) Zoneraich S, Zoneraich O, Rhee JJ: Left ventricular performance in diabetic patients without clinical heart disease: Evaluation by systolic time intervals and echocardiography. Chest **72**: 748–751, 1977
10) Vered Z, Batler A, Segal P, Liberman D, Yerushalmi Y, Berezin M, Neufeld HN: Exercise-induced left ventricular dysfunction in young men with asymptomatic diabetes mellitus (diabetic cardiomyopathy). Am J Cardiol **54**: 633–637, 1984
11) Mildenberger RR, Bar-Shlomo B, Druch M, Jablonsky G, Morch JE, Hilton D, Keushole AB, Forbath N, McLaughlin PR: Clinically unrecognized ventricular dysfunction in young diabetic patients. J Am Coll Cardiol **4**: 234–238, 1984
12) Margonato A, Gerundini P, Vicedomini G, Gilardi MC, Pozza G, Fazio F: Abnormal cardiovascular response to exercise in young asymptomatic diabetic patients with retinopathy. Am Heart J **112**: 554–560, 1986
13) Fisher BM, Gillen G, Lindop GBM, Dargie HJ, Frier BM: Cardiac function and coronary arteriography in asymptomatic type 1 (insulin-dependent) diabetic patients: Evidence for a specific diabetic heart disease. Diabetologia **29**: 706–712, 1986
14) Mustonen JN, Uusitupa MIJ, Tahvanainen K, Tarwar S, Laakso M, Lansimies E, Kuikka JT, Pyorala K: Impaired left ventricular systolic function during exercise in middle-aged insulin-dependent and noninsulin-dependent diabetic subjects without clinically evident cardiovascular disease. Am J Cardiol **62**: 1273–1279, 1988
15) Kahn JK, Zola B, Juni JE, Vinik AI: Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. J Am Coll Cardiol **7**: 1303–1309, 1986
16) Uusitupa M, Mustonen J, Laakso M, Vainio P, Lansimies E, Talwar S, Pyorala K: Impairment of diastolic function in middle-aged type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetic patients free of cardiovascular disease. Diabetologia **31**: 783–791, 1988
17) Ruddy TD, Shumak SL, Liu PP, Barnie A, Seawright SJ, McLaughlin PR, Zinman B: The relationship of cardiac diastolic dysfunction to concurrent hormonal and metabolic status in type 1 diabetes mellitus. J Clin Endocrinol Metab **66**: 113–118, 1988
18) Shapiro LM, Leatherdale BA, MacKinnon J, Fletcher RF: Left ventricular function in diabetics: 2. Relation between clinical features and left ventricular function. Br Heart J **45**: 129–132, 1981
19) Shapiro LM: Echocardiographic features of impaired ventricular function in diabetes mellitus. Br Heart J **47**: 439–444, 1982
20) Seneviratne BIB: Diabetic cardiomyopathy: The

preclinical phase. Br Med J **1**: 1444–1446, 1977
21) Sanderson JE, Brown DDJ, Rivellese A, Kohner E: Diabetic cardiomyopathy?: An echocardiographic study of young diabetics. Br Med J **1**: 404–407, 1978
22) Gorcia MJ, McNamara PM, Gordon T, Kannel WB: Morbidity and mortality in diabetics in the Framingham population. Diabetes **23**: 105–111, 1974
23) Abenavoli T, Rubler S, Fisher VJ, Axelrod HI, Zuckerman KP: Exercise testing with myocardial scintigraphy in asymptomatic diabetic patients. Circulation **63**: 54–64, 1981
24) Caldwell JH, Hamilton GW, Jorensen SG, Richtie JL, Williams PL, Kennedy YW: The detection of coronary artery disease with radionuclide techniques: A comparison of rest-exercise thallium imaging and ejection fraction response. Circulation **61**: 610–619, 1980
25) Okada RD, Boucher CA, Strauss HW, Pohost GM: Exercise radionuclide approaches to coronary artery disease. Am J Cardiol **46**: 1188–1204, 1980
26) Ditzel J: Oxygen transport impairment in diabetes. Diabetes **25** (Suppl 2): 832–838, 1976
27) Ditzel J, Standl E: The problem of tissue oxygenation in diabetes mellitus: 1. Its relation to the early functional changes in the microcirculation of diabetic subjects. Acta Med Scand **49** (Suppl): 578, 1975
28) Ditzel J: Impaired oxygen release caused by alterations of the metabolism in the erythrocytes in diabetes. Lancet I: 721–723, 1972
29) Mathiesen ER, Hilsted J, Feldt-Rasmussen B, Bonde-Petersen F, Christensen NJ, Parving H-H: Effect of metabolic control on hemodynamics in short-term insulin-dependent diabetic patients. Diabetes **34**: 1301–1305, 1985
30) Goldweit RS, Borer JS, Jovanovic LG, Drexler AJ, Hochreiter CA, Devereux RB, Peterson CM: Relation of hemoglobin A1 and blood glucose to cardiac function in diabetes mellitus. Am J Cardiol **56**: 642–646, 1985
31) Thuesen L, Sandahl-Christiansen J, Falstie-Jensen N, Christensen CK, Hermansen K, Mogensen CE, Henningsen P: Increased myocardial contractility in short-term type 1 diabetic patients: An echocardiographic study. Diabetologia **28**: 822–826, 1985
32) Thuesen L, Christiansen JS, Mogensen CE, Henningsen P: Cardiac hyperfunction in insulin-dependent diabetic patients developing microvascular complications. Diabetes **37**: 851–856, 1988
33) Christiansen JS, Gammelgaard J, Tronier B, Svendsen PA, Parving HH: Kidney function and size in diabetics before and during initial insulin treatmint. Kidney Int'l **21**: 683–688, 1982
34) Dandona P, Wollard ML, James IM, Newburry P, Beckett AG: Instability of cerebral blood flow in insulin-dependent diabetics. Lancet II: 1203–1205, 1979
35) Kohner EM, Hamilton AM, Saunders SJ, Suttcliff BA, Bulpitt CJ: The retinal blood flow and diabetes. Diabetologia **11**: 27–33, 1975
36) Gundersen HJG: Peripheral blood-flow and metabolic control in juvenile diabetes. Diabetologia **10**: 225–231, 1974
37) Parving HH, Viberti GC, Keen H, Christiansen JS, Lassen NA: Hemodynamic factors in the genesis of diabetic microangiopathy. Metabolism **32**: 943–949, 1983
38) Ledet T: Diabetic cardiopathy: Quantitative histologic studies of the heart from young juvenile diabetes. Acta Pathol Microbiol Scand (A) **84**: 421–428, 1976
39) Genda A, Mizuno S, Nunoda S, Nakayama A, Igarashi Y, Sugihara N, Namura M, Takeda R, Bunko H, Hisada K: Clinical studies on diabetic myocardial disease using exercise testing with myocardial scintigraphy and endomyocardial biopsy. Clin Cardiol **9**: 375–382, 1986
40) Bonow RO, Bacharach SL, Green MV, Kent KM, Rosing DR, Lipson LC, Leon MB, Epstein SE: Impaired left ventricular diastolic filling in patients with coronary artery disease: Assessment with radionuclide angiography. Circulation **64**: 315–323, 1981
41) Mancini GBJ, Slutsky RA, Norris SL, Bhargava V, Ashburn WL, Higgins CB: Radionuclide analysis of peak filling rate, filling fraction, and time to peak filling rate. Am J Cardiol **51**: 43–51, 1983
42) Poliner LR, Farber SH, Glaeser DH, Nylaan L, Verani MS, Roberts R: Alteration of diastolic filling rate by exercise radionuclide angiography: A highly sensitive technique for the detection of coronary artery disease. Circulation **70**: 942–950, 1984
43) Miller TR, Fountos A, Biello DR, Ludbrook PA: Detection of coronary artery disease by analysis of ventricular filling. J Nucl Med **28**: 837–843, 1987