Coronary Microangiopathy in Type 2 Diabetic Patients: Relation to Glycemic Control, Sex, and Microvascular Angina Rather Than to Coronary Artery Disease

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Coronary microangiopathy is a major complication in diabetics. However, the presence of independent factors in association with coronary microangiopathy in patients with non–insulin-dependent diabetes mellitus (NIDDM) or the difference in coronary microangiopathy between diabetics with coronary artery disease (CAD) and those with microvascular angina is unclear. **Methods:** Nineteen patients with NIDDM and microvascular angina, 18 patients with NIDDM and CAD, and 17 age-matched control subjects were studied. Myocardial segments that were perfused by angiographically normal coronary arteries were studied. The baseline myocardial blood flow (MBF) and the MBF during dipyridamole administration were measured using PET and ^{13}N-ammonia, after which the myocardial flow reserve (MFR) was calculated to assess coronary microangiopathy. **Results:** The baseline MBF was comparable among NIDDM patients with microvascular angina, NIDDM patients with CAD, and control subjects. However, the MBF during dipyridamole administration was significantly lower in NIDDM patients with microvascular angina (126 ± 42.7 mL/min/100 g) than that in either NIDDM patients with CAD (210 ± 70.1 mL/min/100 g; $P < 0.01$) or control subjects (293 ± 159 mL/min/100 g; $P < 0.01$), as was the MFR (NIDDM with microvascular angina, 1.90 ± 0.73; NIDDM with CAD, 2.59 ± 0.81 [$P < 0.01$]; control subjects, 3.69 ± 1.09 [$P < 0.01$]). Multivariate stepwise regression analysis showed that, among the factors considered, glycemic control was independently related to the MFR ($r = 0.838$; $P < 0.05$). **Conclusion:** Glycemic control appears to be essential for coronary microangiopathy in NIDDM.

Key Words: hyperglycemia; non–insulin-dependent diabetes mellitus; flow reserve; atherosclerosis; coronary microangiopathy

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Coronary microangiopathy is an important pathophysiologic feature of diabetes (*1–6*). Insulin resistance, glycemic control, and lipid disorders are related to vascular angiopathy in diabetics (*7–15*). However, the specific role of these factors in coronary microangiopathy is unclear.

This coronary microangiopathy is often expressed as microvascular angina that is characterized by an angina with normal coronary angiography. The association of hyperinsulinemia in nondiabetics with microvascular angina without coronary artery disease (CAD) has been reported (*16*). However, the role of insulin resistance in such patients has not been clarified. Although coronary microangiopathy in diabetics has been studied, including that in patients with microvascular angina or with CAD (*4,5*), it has not been determined whether differences exist in the nature of the myocardial perfusion abnormality between these 2 groups of patients.

Recently, the relationship between glycemic control and reduced myocardial flow reserve (MFR) in patients with non–insulin-dependent diabetes mellitus (NIDDM) without evidence of myocardial ischemia has been reported (*17,18*). Because coronary angiography could not be performed in those asymptomatic patients, it is not known whether the reduced MFR in such patients is associated with coronary microangiopathy or macroangiopathy (*17,18*). Which factors are responsible for the coronary microangiopathy in NIDDM also remains uncertain.

This study was undertaken to determine the factors that are the principal contributors of the reduced MFR in angiographically normal coronary arteries in patients with NIDDM. Furthermore, we compared the MFR of patients with NIDDM having microvascular angina with the MFR of those having CAD, who were perfused by normal coronary arteries.

MATERIALS AND METHODS

Study Population

Thirty-seven patients with NIDDM (28 men, 9 women; mean age, 62.0 ± 8.08 y; age range, 42–68 y) with microvascular angina (n = 19) or CAD (n = 18) were studied. Seventeen normolipidemic, normoglycemic, asymptomatic age-matched volunteers (13 men, 4 women; mean age, 55.9 ± 10.4 y; age range, 38–68 y) without a history of heart disease or chronic disease were selected as control subjects. Diagnosis of microvascular angina was made

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on the basis of the following criteria: positive findings by electrocardiographic exercise stress testing and anatomically normal coronary arteries. Details of coronary angiographic findings are given in Table 1, and general characteristics of the study subjects are summarized in Table 2. There were no significant differences among the 3 groups in terms of sex, body weight, height, body mass index (BMI), blood pressure at rest and during dipyridamole administration, heart rate at rest and during dipyridamole loading, and levels of plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride. Plasma fasting insulin concentration was comparable between subjects with NIDDM and microvascular angina without CAD and those with NIDDM and CAD. There was no significant difference in age between the age-matched control subjects (control group) and the total group of patients with NIDDM or those with NIDDM and microvascular angina. However, the mean age of patients with NIDDM and CAD was significantly higher than that of both control subjects and patients with NIDDM and microvascular angina. Plasma concentrations of fasting glucose (FBS) and hemoglobin A_{1c} (HbA_{1c}) levels averaged for the past 5 y from data gathered at regular clinic visits for diabetes were significantly higher in those with NIDDM than in control subjects. Data for control subjects were reviewed from those collected at visits to local health service centers. HbA_{1c} was assayed by the latex aggregation method (normal range, 4.3%–5.8%). FBS was measured after an overnight fast of >12 h. Plasma insulin concentrations were measured by radioimmunoassay (normal fasting range, 3–18 U/mL). Before the study, all participants were informed of the nature of the investigation, after which they agreed to participate in the study protocol, which was approved by the local ethics committee.

Patients with NIDDM. We made the diagnosis of NIDDM according to the following criteria: fasting glucose concentration > 7.3 mmol/L (140 mg/dL) and HbA_{1c} level > 6.5% before the initiation of therapy. All patients with NIDDM underwent coronary angiography and were proven to have 1 or 2 normal coronary arteries within the 3 major branches as diagnosed by 3 independent specialists (0% stenosis). Twelve NIDDM patients were treated with oral hypoglycemic agents, 21 patients were treated with diet therapy alone, and 4 patients who had apparently developed insulin resistance were treated with insulin. The latter 4 patients had become resistant to oral hypoglycemic agents after long-term therapy with these agents. Among the 37 patients with NIDDM, 19 with well-controlled essential hypertension were included, 10 of whom had diffuse left ventricular hypertrophy ([LVH]; wall thickness, >12 mm). The criteria of essential hypertension were systolic blood pressure (SBP) > 160 mm Hg or diastolic blood pressure (DBP) > 95 mm Hg (or both) with no specific cause. Of the 10 patients with LVH, 8 had microvascular angina. These patients were not included in other recent studies (*17–21*). The criterion of well-controlled diabetes was a HbA_{1c} level averaged over the previous 5 y of <8.0% and that of poorly controlled diabetes was a HbA_{1c} level averaged over the previous 5 y of ≥8.0%.

Control Group. The resting electrocardiogram was normal in all control subjects. All potential control subjects underwent a symptom-limited treadmill test, and those with typical chest pain or abnormal electrocardiogram indicating myocardial ischemia were excluded. In this study, cardiac normality in control subjects was not confirmed by coronary angiography, but these subjects were selected among those with a low probability of cardiac disease and can be considered to be appropriate as healthy control subjects as reported by Rozanski et al (*22*). Because of the difficulty in recruiting healthy control subjects for PET studies, PET data for all but 2 of these control subjects were those used for other studies (*17–21*).

TABLE 1
Coronary Angiographic Findings in Study Patients

Coronary angiographic findings	No.
Zero-vessel disease	
Microvascular angina	19
After PTCA to LAD	6
After PTCA to LCX	1
After PTCA to RCA	1
After CABG to LAD and LCX	1
One-vessel disease	
LAD	2
LCX	1
RCA	1
Two-vessel disease	
LAD and LCX	0
LAD and RCA	3
LCX and RCA	3
No. of patients with old myocardial infarction	3

PTCA = percutaneous transluminal coronary angioplasty; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; CABG = coronary artery bypass grafting.

Estimation of Insulin Resistance

Quantitative estimation of whole-body insulin resistance was made by obtaining the glucose disposal rate (GDR) during hyperinsulinemic euglycemic clamping (μmol/min/kg) using a previously reported method (*18*). In all patients, the glucose concentration became constant within 2 h after the initiation of insulin clamping.

Estimation of Major Complications of Diabetes

The presence and degree of retinopathy, neuropathy, and nephropathy, which are major complications of diabetes, were graded as follows after a review of clinical records: 0, none; 1, mild; 2, moderate; and 3, severe.

PET

The regional baseline myocardial blood flow (MBF) and the MBF during dipyridamole loading were measured using PET and ^{13}N-ammonia. Twenty-four hours before the PET study, all medications were withheld and caffeine intake was stopped because caffeine intake can alter the MBF (*23*). Cigarette smoking was stopped on the day of the PET study because cigarette smoking can reduce the MFR (*24*). Myocardial flow images were obtained using a Headtome IV scanner (Shimadzu Corp., Kyoto, Japan). This scanner has 7 imaging planes; in-plane resolution is 4.5 mm at full width at half maximum (FWHM) and the z-axial resolution is 9.5 mm at FWHM. Effective in-plane resolution is 7 mm after using a smoothing filter. The sensitivities of the Headtome IV scanners are 14 and 24 kcts/s for direct and cross planes, respectively.

After acquiring transmission data to correct for photon attenuation before obtaining images, 740–1110 MBq ^{13}N-ammonia were injected, and dynamic PET and static PET were performed for 2 and 8 min, respectively. After waiting 45 min to allow for decay of

TABLE 2
General Characteristics of Study Subjects

Characteristic	Control subjects	NIDDM patients		
		With MVA	With CAD	All
n (M/F)	17 (13/4)	19 (16/3)	18 (12/6)	37 (28/9)
Age (y)	55.9 ± 10.4	58.9 ± 8.57	65.3 ± 6.33*	62.0 ± 8.08
BW (kg)	60.7 ± 7.81	65.6 ± 11.6	62.1 ± 8.75	65.2 ± 9.22
Height (cm)	164 ± 11.3	166 ± 7.60	160 ± 8.63	163 ± 8.60
BMI	23.4 ± 4.10	24.5 ± 2.7	24.3 ± 2.95	24.5 ± 2.76
At rest				
SBP (mm Hg)	129 ± 12.3	132 ± 19.8	144 ± 19.1	139 ± 20.2
DBP (mm Hg)	76.8 ± 7.34	77.7 ± 8.60	77.7 ± 13.2	79.0 ± 10.5
HR (bpm)	67.1 ± 13.9	67.5 ± 8.31	60.3 ± 12.7	65.2 ± 10.8
RPP	8892 ± 1692	9017 ± 2075	8523 ± 1732	9067 ± 1856
After DP				
SBP (mm Hg)	123 ± 11.7	129 ± 19.5	135 ± 24.1	134 ± 20.6
DBP (mm Hg)	76.4 ± 7.40	71.1 ± 9.42	71.0 ± 16.8	71.2 ± 13.2
RPP	9564 ± 1012	10,423 ± 2366	9427 ± 1420	9673 ± 1578
FBS (mmol/L)	4.82 ± 0.49	10.4 ± 2.50†	9.00 ± 2.24†	9.72 ± 2.37†
HbA_{1c} (%)	5.51 ± 0.23	8.40 ± 1.10†	7.90 ± 1.80†	8.3 ± 1.4†
TC (mmol/L)	5.01 ± 0.56	4.62 ± 0.727	4.89 ± 0.740	4.77 ± 0.694
HDL (mmol/L)	1.46 ± 0.66	1.06 ± 0.240	1.14 ± 0.266	1.10 ± 0.27
TG (mmol/L)	1.28 ± 0.45	1.37 ± 0.906	1.47 ± 0.959	1.51 ± 0.97
LDL (mmol/L)	2.99 ± 0.50	2.84 ± 1.03	3.07 ± 0.728	2.89 ± 0.89
FI (mIU/L)	—	8.07 ± 5.03	6.50 ± 6.98	7.29 ± 6.32

*$P < 0.01$ versus MVA.
†$P < 0.01$ versus controls.
MVA = microvascular angina; n = number of study patients; BW = body weight; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; RPP = rate pressure products; DP = dipyridamole; FBS = fasting plasma glucose concentration; HbA_{1c} = hemoglobin A_{1c}; TC = total cholesterol; HDL = high-density lipoprotein cholesterol; TG = triglycerides; LDL = low-density lipoprotein cholesterol; FI = fasting plasma insulin concentration.

the radioactivity of ^{13}N-ammonia, dipyridamole (0.56 mg/kg) was administrated intravenously. Five minutes after dipyridamole administration, 740–1110 MBq ^{13}N-ammonia were injected and, at exactly the same time, a second dynamic scan was obtained for 2 min and a static scan was obtained for 8 min. The dynamic scan was obtained every 15 s (8 times) during the 2-min period, and dynamic data were obtained for 7 slices. Only 1-channel electrocardiographic monitoring in limb leads was made during PET scanning.

Determination of MBF and MFR

The regional MBF was calculated according to the 2-compartment model (*25,26*). This model has been validated (*25,26*) and has been used frequently in studies of MBF and MFR (*17–21,23,24*). Metabolites of ^{13}N-ammonia can be negligible during the first 90 s after infusion of ^{13}N-ammonia (*27*). The time–activity curve of the left ventricular cavity was used as an input function. Tracer spillover was corrected by least-squares nonlinear regression analysis to calculate the MBF with the assumption that myocardial radioactivity and left ventricular radioactivity were influenced by each other. Details are given in recent articles (*17,19,20*).

All data were corrected for dead-time effects to reduce error to <1%. To avoid the influence of the partial-volume effect associated with the object's size, recovery coefficients obtained from experimental phantom studies in our laboratory were used. The recovery coefficient was 0.8 when myocardial wall thickness was 10 mm. For correction of the partial-volume effect, specialists in our hospital measured wall thickness with 2-dimensional echocardiography. The recovery coefficients were taken into consideration when measuring the MBF.

To determine the MBF, regions of interest were placed at the septum, anterior wall, lateral wall, and inferoposterior wall on the transaxial images as reported (*17,19,20*). In this investigation, only segments that were perfused by angiographically normal coronary arteries were studied. Segments that were perfused by coronary artery bypass grafts were excluded because reduced MRF in such segments has been reported (*28*). Static ^{13}N-ammonia images were also obtained from PET and analyzed visually by 3 independent specialists who had no other information on the patients. The MFR was determined as follows: MFR = regional MBF during DP administration/regional baseline MBF.

Statistics

The MBF at rest, MBF during dipyridamole loading, MFR, body weight, SBP, DBP, height, BMI, and lipid parameters were compared in the 3 groups using ANOVA; individual data were then analyzed by the 2-tailed unpaired Student t test. Values are expressed as the mean ± SD. $P < 0.05$ was considered significant. Multivariate stepwise regression analysis was undertaken to examine which factors were independently related to MFR: age, baseline MBF, average FBS, average HbA_{1c}, FBS at the time of PET, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, duration of diabetic state, plasma insulin concentration during PET, GDR, and the existence of microvascular angina.

RESULTS

Hemodynamic and Electrocardiographic Responses to Dipyridamole Administration

No significant differences in SBP at rest and during dipyridamole administration and rate pressure product (RPP) were found between the groups (Table 2). During dipyridamole administration, typical chest pain or chest oppression accompanied by electrocardiographic changes was observed in 24 study patients. Because of difficulty in recording the electrocardiogram in the precordial leads during PET, a detailed description of electrocardiographic response to dipyridamole was not possible.

Baseline MBF, MBF During Dipyridamole Administration, and MFR

The baseline MBF was comparable among patients with NIDDM having microvascular angina (78.7 ± 18.8 mL/min/100 g), those having CAD (81.8 ± 16.2 mL/min/100 g), and control subjects (78.2 ± 33.3 mL/min/100 g). However, the MBF during dipyridamole administration was significantly lower in NIDDM patients with microvascular angina (126 ± 42.7 mL/min/100 g) than that in both NIDDM patients with CAD (210 ± 70.1 mL/min/100 g; $P < 0.01$) and control subjects (293 ± 159 mL/min/100 g; $P < 0.01$). The MBF during dipyridamole administration in those with NIDDM with CAD was also significantly lower compared with that in control subjects ($P < 0.05$).

The MFR was significantly lower in all NIDDM patients (2.24 ± 0.83) than that in control subjects (3.69 ± 1.09; $P < 0.01$). The MFR in patients with NIDDM and microvascular angina (1.90 ± 0.73) was significantly lower than that in both control subjects ($P < 0.01$) and patients with NIDDM and CAD (2.59 ± 0.81; $P < 0.05$). The MFR in patients with NIDDM and CAD was also significantly lower than that in control subjects ($P < 0.01$). There were no significant differences in average FBS, average HbA_{1c}, baseline MBF, and blood pressure between the 2 patient subgroups (Tables 2 and 3). However, the mean age of patients with NIDDM and CAD (65.3 ± 6.33 y) was significantly higher than that of patients with microvascular angina (58.9 ± 8.57; $P < 0.05$).

The MFR in men with NIDDM (n = 28; 2.07 ± 0.60) was significantly lower than that in women with NIDDM (n = 9; 2.76 ± 1.22; $P < 0.05$), whereas age was comparable between the sexes, as were the baseline MBF and SBP and DBP at rest (Table 4). The MFR in men with NIDDM and microvascular angina (n = 16; 1.79 ± 0.62) was significantly lower than that in men with NIDDM and CAD (n = 12; 2.43 ± 0.34; $P < 0.05$), although the patients with NIDDM and CAD were significantly older. However, no such difference was observed in female NIDDM patients.

The MFR (1.52 ± 0.436) in 10 NIDDM patients with LVH was significantly lower than that in NIDDM patients without LVH (2.17 ± 0.69; $P < 0.05$), whereas the baseline MBF in NIDDM patients with LVH (105 ± 27.6) was significantly higher than that in NIDDM patients without LVH (81.4 ± 14.6; $P < 0.01$). However, the MBFs during dipyridamole administration were comparable between those with and without LVH (158 ± 50.7 versus 182 ± 57.6). Furthermore, the percentage of patients with LVH was higher among those with microvascular angina (8/19; 47.4%) than those with the CAD group (2/20; 10%).

MFR and Hypertension

No significant difference was found in the MFR between NIDDM patients with essential hypertension (n = 19; 2.02 ± 0.83) and those without essential hypertension (n = 18; 2.46 ± 0.85). The baseline SBP in NIDDM patients with hypertension (150 ± 21.8 mm Hg) was significantly higher than that in NIDDM patients without hypertension (127 ± 13.5 mm Hg; $P < 0.05$). The baseline RPP in hypertensive NIDDM patients (9606 ± 2226) was significantly higher than that in normotensive NIDDM patients (8082 ± 1520; $P < 0.05$). The SBP during dipyridamole administration was also significantly higher in those hypertensive NIDDM patients (140 ± 18.9 mm Hg) than that in normotensive subjects (123 ± 20.5 mm Hg; $P < 0.05$). However, the RPP during dipyridamole administration in hypertensive NIDDM patients (10,524 ± 1248) tended to be higher than that of those normotensive NIDDM patients (9399 ± 2041), but the difference was statistically insignificant. The MFR in diabetic patients without hypertension was significantly reduced compared with that in control subjects ($P < 0.01$), as was that in hypertensive diabetic patients ($P < 0.05$).

MFR and Insulin Resistance

No significant difference was found in the MFR between patients with severe insulin resistance (GDR, <5 mg/min/kg [<26 μmol/min/kg]; n = 17; MFR, 2.17 ± 0.74) and those with mild insulin resistance (GDR, ≥5 mg/min/kg [>26 μmol/min/kg]; n = 20; MFR, 2.33 ± 1.10).

TABLE 3
Comparison Between NIDDM Patients with Microvascular Angina and Those with CAD

NIDDM patients	HbA_{1c} (%)	FBS (μmol/min/kg)	GDR (μmol/min/kg)	At rest		
				MBF (mL/min/100 g)	SBP (mm Hg)	DBP (mm Hg)
With MVA	8.4 ± 1.1	10.44 ± 2.50	29.1 ± 11.0	78.7 ± 18.8	130 ± 18.9	74.6 ± 9.23
With CAD	7.9 ± 1.8	9.00 ± 2.24	25.9 ± 11.5	81.8 ± 16.2	143 ± 18.0	76.0 ± 13.1

MVA = microvascular angina.

TABLE 4
Comparison Between Sex of NIDDM Patients with Microvascular Angina and Those with CAD

Sex	HbA_{1c} (%)	FBS (μmol/min/kg)	GDR (μmol/min/kg)	At rest MBF (mL/min/100 g)	At rest SBP (mm Hg)	At rest DBP (mm Hg)	Age (y)
M	8.5 ± 1.2	10.5 ± 2.27	29.5 ± 12.2	79.5 ± 21.3	136 ± 20.0	77.3 ± 10.8	62.1 ± 9.42
F	7.6 ± 1.2	7.94 ± 1.46	22.2 ± 6.77	79.9 ± 17.8	143 ± 19.5	72.3 ± 11.8	62.2 ± 5.03

MFR and Hyperglycemia

The MFR in the well-controlled patients with NIDDM (n = 16; HbA_{1c}, <8%; MFR, 2.81 ± 0.95) was significantly higher than that in the poorly controlled patients (n = 21; HbA_{1c}, ≥8%; MFR, 1.85 ± 0.76; $P < 0.01$). Significant differences in the average FBS and HbA_{1c} were also noted between these 2 groups (Table 5). The baseline MBF tended to be lower in the well-controlled group than that in the poorly controlled group, but the difference was statistically insignificant ($P = 0.0727$). Insulin resistance was comparable between patients with CAD and patients with microvascular angina, as were the SBP, age, and plasma lipid fractions (Table 5).

Relationship Between MFR and Glycemic Control, Insulin Resistance, Fasting Insulin Concentration, and Plasma Lipid Fractions

The MFR correlated with the average FBS for the previous 5 y ($P < 0.01$; $r = -0.61$) (Fig. 1). A significant inverse correlation between the MFR and the average HbA_{1c} was found for the previous 5 y ($P < 0.01$; $r = -0.54$) (Fig. 2). However, no significant relationship was found between the MFR and GDR or between the MFR and plasma concentrations of total cholesterol, triglycerides, LDL, HDL, and age. Multivariate stepwise regression analysis showed that, among the factors considered (HbA_{1c}, FBS, and existence of microvascular angina), the average FBS ($F = 11.1$) was independently related to the MFR ($r = 0.838$; $P < 0.05$).

Other Major Complications

Severity scores of retinopathy, neuropathy, and nephropathy were significantly higher in those patients with microvascular angina than those in patients with CAD (1.2 ± 0.87 versus 1.7 ± 0.39 [$P < 0.01$]; 0.36 ± 0.51 versus 0.087 ± 0.29 [$P < 0.05$]; and 0.64 ±1.03 versus 0.087 ± 0.29 [$P < 0.05$], respectively).

DISCUSSION

Factors That Reduce MFR

A relationship between the MFR and the severity of coronary stenosis has been reported (*29*). However, recent investigations have suggested that the MFR can be reduced in a variety of coronary risk factors, including hyperlipidemia (*19–21,30–33*) and diabetes (*4–6*). Because several factors contributed to diabetic angiopathy, controversy exists concerning the factors that could contribute to coronary microangiopathy in diabetic patients. Although CAD or microvascular angina is frequently associated with NIDDM, whether there is a difference in the degree of coronary microangiopathy between the 2 remains uncertain. The results of this study show that the MFR in angiographically normal coronary arteries in NIDDM patients was highly related to glycemic control.

Possible Mechanism for Reduced MFR in Angiographically Normal Coronary Arteries in NIDDM

Coronary microangiopathy might be an essential factor for the reduced MFR in anatomically normal coronary arteries in NIDDM. However, an impaired blood flow response to dipyridamole through flow-mediated vasodilation (endothelial dysfunction) (*34*) or angiographically undetectable balanced diffuse atherosclerosis, as has been shown in diabetics (*35*), may be minor factors responsible for the reduced MFR in NIDDM.

Lipid disorders (*19–21,30–33*), aging (*36*), or male gender (*19*) can reduce the MFR. However, the effect of such factors can be negated in this study; the lipid fractions and percentage of male subjects were comparable among the 3 study groups, and no significant relationships were found between the MFR and such factors. Although the age of patients with CAD was significantly higher than that of patients with microvascular angina, reduction of the MFR was significantly greater in those with microvascular angina than that in those with CAD. Thus, age could not explain the results.

The association of hyperinsulinemia with microvascular angina among nondiabetics also has been reported (*16*), suggesting that hyperinsulinemia may be related to coronary microangiopathy in nondiabetics with microvascular angina. However, no significant relationship was found between the MFR and the degree of insulin resistance. This result is consistent with that reported previously (*17*). The lack of hyperinsulinemia may be a factor. It has been suggested that insulin resistance is highly related to coronary macroangiopathy rather than microangiopathy (*5,14*). Our results support this speculation.

Patients with NIDDM and Microvascular Angina or CAD

In this study, only segments perfused by anatomically normal coronary arteries were studied. A reduced MFR of greater severity was noted in patients with NIDDM and microvascular angina than that in those with CAD. This finding could be attributed to the fact that CAD is a macrovascular abnormality (with the possibility of the coexistence of microangiopathy) and that the reduced MFR

TABLE 5
Comparison Between Well-Controlled NIDDM Patients and Poorly Controlled NIDDM Patients

NIDDM patients	HbA_{1c} (%)	FBS (μmol/min/kg)	GDR (μmol/min/kg)	At rest							
				MBF (mL/min/100 g)	SBP (mm Hg)	DBP (mm Hg)	TC (mmol/L)	LDL (mmol/L)	HDL (mmol/L)	TG (mmol/L)	Age (y)
Well controlled	7.19 ± 0.65	8.17 ± 1.09	27.3 ± 6.04	72.5 ± 15.2	133 ± 14.3	77.3 ± 10.8	4.64 ± 0.648	2.84 ± 0.581	1.18 ± 0.231	1.30 ± 1.06	63.3 ± 5.80
Poorly controlled	9.35 ± 1.07*	11.2 ± 2.37*	29.4 ± 14.1	86.5 ± 23.2	148 ± 27.8	72.3 ± 11.8	4.82 ± 0.748	3.12 ± 0.738	1.08 ± 0.626	1.61 ± 0.909	59.6 ± 6.41

*$P < 0.05$ versus well controlled.
TC = total cholesterol; TG = triglycerides.

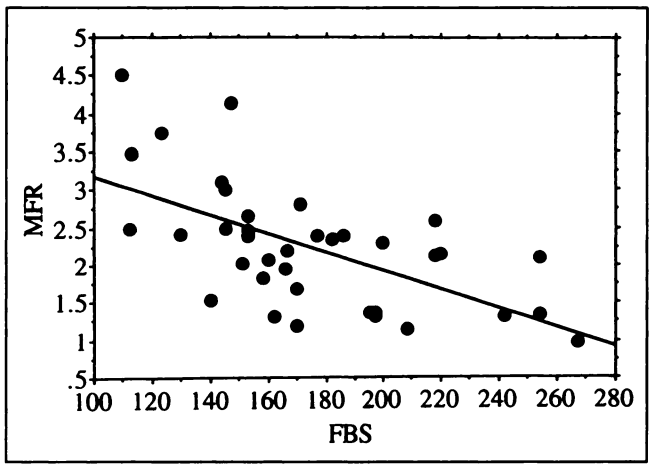

FIGURE 1. Significant inverse relationship between MFR in segments perfused by normal coronary arteries and average FBS concentration (mg/dL) in NIDDM ($r = -0.61$; $P < 0.01$).

in microvascular angina is caused by a microvascular abnormality (with a small possibility of the coexistence of angiographically undetectable balanced macrovascular diffuse atherosclerosis) (*34*). The percentage of male patients with microvascular angina was relatively higher than that in NIDDM patients with CAD. However, when male patients were analyzed separately, the MFR was also significantly lower in patients with NIDDM with microvascular angina than that in those with CAD. Therefore, the higher percentage of male patients in the microvascular angina group cannot account for the difference in the MFR between the 2 patient subgroups. The presence of significant coronary stenosis in 1 myocardial segment did not influence the MFR in the anatomically normal coronary arteries in NIDDM patients because the MFR was significantly lower in patients with NIDDM with microvascular angina than that in those with CAD. The reason for the difference in the MFR between the 2 groups is speculative. In this study, there were more patients with LVH among those with microvascular

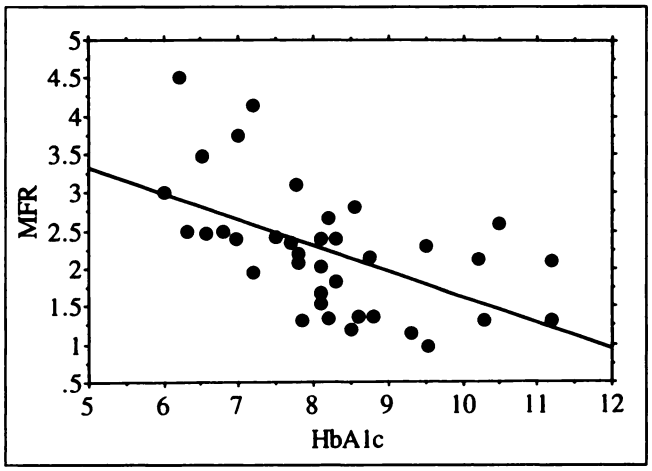

FIGURE 2. Significant inverse relationship between MFR in segments perfused by normal coronary arteries and average HbA_{1c} (%) in NIDDM ($r = -0.54$; $P < 0.01$).

angina (8/19) than among those with CAD (2/18). This is another possible explanation for our findings because the MFR was significantly lower in patients with LVH. Because multivariate regression analysis showed that glycemic control was an independent factor for the reduced MFR in patients with NIDDM, some unknown mechanisms for the reduced MFR in microvascular angina might exist. In this study, severity scores of major complications—that is, retinopathy, neuropathy, and nephropathy—were significantly higher in patients with microvascular angina than those in patients with CAD. These results suggest that the increased susceptibility to hyperglycemia of vascular cells in several organs as well as neural cells or retinal cells in NIDDM patients with microvascular angina could be a possible mechanism for the reduced MFR.

Glycemic Control and Coronary Microangiopathy

In this study, the reduced MFR in angiographically normal coronary arteries was related to glycemic control but not to insulin resistance or lipid fractions, suggesting that coronary microangiopathy is most likely related to glycemic control. These results are consistent with previous reports that showed a relationship between chronic glycemic control and the MFR in NIDDM patients without evidence of ischemia (*17,18*). A relationship between hyperglycemia and macrovascular complications has been suggested in diabetic animals (*37*) and diabetic patients (*7,8,10,12,13*). Glycemic control and its relationship to microvascular complications also has been suggested in insulin-dependent diabetics (*11*), but the influence of hyperglycemia on coronary microangiopathy in NIDDM has remained uncertain. Whether the reduced MFR can be attributed to coronary microangiopathy, coronary macroangiopathy, or both is uncertain (*17,18*). However, the results of this study indicate a relationship between glycemic control and microangiopathy in these patients. Furthermore, this relationship is more prominent in NIDDM patients with microvascular angina than that in NIDDM patients with CAD.

CONCLUSION

Coronary angiopathy is seen more prominently in patients with NIDDM and microvascular angina than in those with NIDDM and CAD. Glycemic control appears to play a central role in coronary microangiopathy in patients with NIDDM.

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