



Myocardial Flow Reserve Partially Recovered after Additional Intensive Anti-Hyperglycemic Therapy in Patients with Type 2 Diabetes

Ikuo Yokoyama^{1*}, Yusuke Inoue² and Toshiyuki Moritan³

Abstract

Background: Hyperglycemia has been suggested as a significant factor in coronary microangiopathy in patients with type 2 diabetes (T2DM), but whether it can be reversed through treatment of hyperglycemia is still unknown.

Aim: To clarify whether glycemic control can improve coronary microangiopathy in T2DM.

Methods: Subjects were 34 T2DM patients who underwent coronary angiography and 17 age-matched controls. Myocardial segments perfused by angiographically normal coronary arteries were studied. Baseline myocardial blood flow (MBF, ml/min/100 g) and MBF during dipyridamole administration (0.56 mg/kg/min) were measured using positron emission tomography (PET). Myocardial flow reserve (MFR) was calculated by the ratio of MBF during dipyridamole administration to the baseline MBF. After the first PET study, patients were subdivided into an additional intensive therapy group (ATG) and no-additional therapy (NATG) group. Second PET scan was performed 6 to 9 months later.

Results: Baseline MBF was comparable among the ATG (87.5 ± 24.1), NATG (87.2 ± 16.9) and controls (78.2 ± 33.3). However, MBF during dipyridamole administration was significantly lower in both the ATG (170 ± 52.0) and NATG (192 ± 52.6) than in controls (293 ± 159, p<0.01) as was the MFR (ATG, 1.96 ± 0.52; NATG, 2.27 ± 0.63; controls, 3.69 ± 1.09; p<0.01 respectively). MFR was significantly improved in the ATG (2.51 ± 0.77; p<0.05), but not in the NATG (2.14 ± 0.69; p=ns). There was a significant inverse relationship between percent change in MFR and percent change in glycemic control. However, no significant relationships were seen between the percent change in MFR and percent change in plasma lipid fractions.

Conclusion: Reduced myocardial flow reserve in patients with T2DM can be partially reversed by additional intensive therapy for hyperglycemia.

Keywords

Hyperglycemia; Type-2 diabetes mellitus; Flow reserve; Coronary microangiopathy; Positron emission tomography (PET); Glucose

Introduction

Impaired myocardial perfusion, such as coronary microangiopathy, is one of the important pathophysiological characteristics of diabetes [1,2] and a clinically important unresolved clinical question [3]. The importance of glycemic control in the development of atherosclerosis in patients with diabetes has been suggested [4-10]. We previously reported that myocardial flow reserve (MFR) was related to glycemic control rather than to the mode of therapy in patients with type 2 diabetes (T2DM) [11]. We also have revealed that hyperglycemia rather than insulin resistance is related to the reduced MFR in T2DM [12]. In addition, reduced MFR in angiographically normal coronary arteries in T2DM has been observed and such reduced MFR was shown to be related to glycemic control in those with T2DM [13]. Such results have indicated that glycemic control is an essential factor for diabetic coronary microangiopathy. In addition, it has also been reported that coronary flow reserve can be a good predictor for cardiac mortality in patients with known CAD or suspected CAD [14] and in patients with T2DM without CAD and patients with CAD without T2DM [15]. However, it remains controversial whether such diabetic coronary microangiopathy can be reversed. For instance, Miyazaki et al. demonstrated that optimal anti-hyperglycemic therapy is important to improve the coronary flow reserve (CFR) in poorly controlled diabetic patients [16]. Moreover, Ichiki et al. found that hyperglycemia was directly related to vascular resistance in the coronary artery tree in normal subjects [17]. On the other hand, Jarnert et al. found that strict glycemic control failed to improve CFR in T2DM [18]. We also showed that chronic use of troglitazone over 12 months with the aim of improving glycemic control through improving insulin resistance in both heart and skeletal muscle failed to improve MFR in patients with T2DM [19]. In addition, Schindler et al. demonstrated that an abnormal myocardial blood flow (MBF) in response to the cold pressure test can be significantly improved with euglycemic control in patients with T2DM, suggesting that myocardial vascular endothelial function in T2DM can be improved through euglycemic control [20]. Since impaired endothelial function is an important factor in abnormal coronary microvascular function, it is important to clarify whether intensive glycemic control could reverse an abnormal MFR in T2DM. Actually, Levy et al. noted in their review that endothelial dysfunction causes coronary microangiopathy and that coronary microangiopathy plays a common role in the development of a reduced MFR in subjects with conventional coronary risk factors including T2DM and essential hypertension [21]. Thus, in this study, we have aimed to examine whether the reduced MFR in segments that were perfused by angiographically normal coronary arteries in patients with T2DM can be improved by the control of hyperglycemia.

Materials and Methods

Study population

General characteristics of study subjects: Thirty-four patients with T2DM with indications for coronary angiography (CAG), such as symptoms or signs of myocardial ischemia or coronary artery disease (CAD) (typical or atypical chest pain, chest oppression, chest

*Corresponding author: Ikuo Yokoyama, MD, Department of Cardiovascular Medicine, Clinical Research Center, Sanno Hospital, International University of Health and Welfare 8-10-16 Akasaka, Minato-ku, Tokyo 107-0052, Japan, Tel: +81-3-3402-3151; Fax: +81-3-3402-3652; E-mail: yokochan-ty@umin.ac.jp

Received: November 11, 2012 Accepted: February 18, 2013 Published: February 22, 2013

tightness etc.), were entered into the study. Patients with plasma total cholesterol (TC) more than 6.00 mmol/L and those with left ventricular hypertrophy (wall thickness ≥ 13 mm) were excluded. Patients who had undergone coronary artery bypass operation or percutaneous coronary angioplasty were excluded. Patients with well-controlled essential hypertension using long-acting calcium antagonists (CILNIDIPINE 5-10 mg; AMLODIPINE, 2.5-5 mg/day), diuretics, any angiotensin converting enzyme inhibitor (ENALAPRIL, 5-10 mg/day; LISINOPRIL, 10-20 mg/day) and any angiotensin II receptor blocker (LOSARTAN, 25-50 mg/day; CANDESARTAN CILEXETIL, 4-8 mg/day; VALSARTAN, 40-80 mg/day) or both were included. Seventeen (13 males, 4 females) normo-lipidemic, normo-glycemic asymptomatic age-matched individuals without a history of heart disease or chronic disease were selected as control subjects. Details of coronary angiographic findings of study patients are shown in [table 1](#). General characteristics of the study subjects are summarized in [table 2](#). There were no significant differences among the two groups in age, gender, body weight, height, body mass index, blood pressure at rest and during dipyridamole administration, heart rate at rest and during dipyridamole administration, and levels of TC, low density lipoprotein bound cholesterol (LDL), high density lipoprotein bound cholesterol (HDL) and triglycerides (TG). Fasting plasma glucose concentrations (FBS) and hemoglobin A1c values averaged for the previous 6 months from data gathered at regular clinic visits for diabetes were significantly higher in the T2DM patients than in control subjects. Data for control subjects were reviewed from records at local health service centers. Hemoglobin A1c was assayed by the latex aggregation method (normal range 4.3%-5.8%). Plasma fasting glucose concentration was measured after an overnight fast of greater than 12 hours. Plasma insulin concentrations were measured by radioimmunoassay (normal range under fasting was 3-18 U/ml). Participants were informed of the nature of the study before agreeing to take part in the study protocol, which was approved by the local Ethics Committee.

Subjects with T2DM: T2DM was diagnosed according to the following criteria: FBS greater than 7.0 mmol/L and hemoglobin A1c level greater than 6.5% before the initiation of therapy. All of these patients had undergone coronary angiography (CAG) due to symptoms of angina such as chest pain, chest oppression and/or chest

Table 1: Coronary angiographic findings in study patients.

Coronary angiographic findings	T2DM
Zero vessel disease	20
normal coronary arteries	20
One vessel disease	8
LAD	4
LCX	2
RCA	2
Two vessel disease	6
LAD+LCX	0
LAD+RCA	3
LCX+RCA	3
Number of patients with old myocardial infarction	3

T2DM: Type 2 Diabetes Mellitus; LAD: Left Descending Coronary Artery; LCX: Left Circumflex Coronary Artery; RCA: Right Coronary Artery

Table 2: General characteristics of study subjects.

	Controls	T2DM (all)
N (M/F)	17 (13/4)	34 (27/7)
Age (year)	54.9 \pm 10.4	62.1 \pm 6.1
BW (kg)	60.7 \pm 7.81	65.2 \pm 9.22
HT (cm)	164 \pm 11.3	163 \pm 8.60
BMI	23.4 \pm 4.10	24.5 \pm 2.76
SBP (Rest)	129 \pm 12.3	139 \pm 20.2
DBP (Rest)	76.8 \pm 7.34	79.0 \pm 10.5
HR (Rest)	67.1 \pm 13.9	65.2 \pm 10.8
RPP (Rest)	8892 \pm 1692	9067 \pm 1856
SBP (DP)	123 \pm 11.7	134 \pm 20.6
DBP (DP)	76.4 \pm 7.40	71.2 \pm 13.2
RPP (DP)	9564 \pm 1012	9673 \pm 1578
FBS (mmol/L)	4.82 \pm 0.49	9.11 \pm 2.22 **
HbA1c (%)	5.51 \pm 0.23	8.30 \pm 1.40 **
TC (mmol/L)	5.01 \pm 0.56	4.77 \pm 0.694
HDL (mmol/L)	1.46 \pm 0.66	1.10 \pm 0.27
TG (mmol/L)	1.28 \pm 0.45	1.42 \pm 0.97
LDL (mmol/L)	2.99 \pm 0.50	2.89 \pm 0.89
FI (μ U/L)	-	7.29 \pm 6.32
Duration of diabetes (M)	-	132 \pm 88.5

** p<0.01 vs controls

N: Number of study patients; M: Male; F: Female; T2DM: Type 2 Diabetes Mellitus; BW: Body Weight; HT: Height; DP: Dipyridamole; RPP: Rate Pressure Products; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: Hemoglobin A1c (%); FBS: Fasting Plasma Glucose Concentration; TC: Total Cholesterol; HDL: High Density Lipoprotein cholesterol; TG: Triglycerides; LDL: Low Density Lipoprotein cholesterol; FI: Plasma Fasting Insulin Concentration; M: Months

tightness or abnormalities on an electrocardiogram (ECG) at rest or abnormal findings during rest in stress ECG testing that suggested the existence of CAD, or abnormal findings in static images from rest-dipyridamole stress perfusion positron emission tomography (PET) scans, and were proven to have one, two or three normal coronary arteries within the three major branches as diagnosed by three independent specialists (0% stenosis). Cardiac angiography data were shown in [table 1](#). Among the 34 patients with T2DM were 8 with well-controlled essential hypertension. These study subjects were not common to those used in our other publications [[11-13,19,22-25](#)].

The 34 patients were subdivided into two groups. One group was treated with additional intensive treatment of hyperglycemia including insulin (NOVOLIN 30R or NOVOLIN R), ACARBOSE, POGLYBOSE and TROGLITAZONE and the other T2DM patients were not treated with additional therapy. Patient profiles and therapies for T2DM are shown in [table 3](#).

Control subjects: In all 17 control subjects, the resting ECG was normal. All potential control subjects underwent a symptom-limited treadmill test and those with typical chest pain or abnormal ECG indicating myocardial ischemia were excluded. Cardiac normality was not confirmed by CAG; however, since these subjects were selected among those with a low probability of cardiac disease they

Table 3: Data on MFR, glycemic control, and therapy in patients with T2DM who underwent PET perfusion studies.

S.No.	Age	Sex	CAG	Therapies (pre / post)
1.	71	M	0VD	D&E/D&E
2.	52	F	1VD	D&E/A300 mg
3.	60	M	2VD	D&E/P 0.6 g
4.	58	M	0VD	D&E/SU (GLIBENCRAMIDE 5 mg/day)
5.	60	M	0VD	D&E/A 300 g
6.	68	M	1VD	SU (GLICRARISIDE 80 mg/day)/In (NOVOLIN 30R (10-0-10))
7.	55	M	0VD	D&E/D&E
8.	56	M	0VD	SU (GLIBENCRAMIDE 5mg/day)/In (NOVOLIN R (8-6-6))
9.	64	F	2VD	D&E/A 300 mg
10.	62	F	1VD	D&E/D&E
11.	68	M	0VD	SU (GLIBENCRAMIDE 2.5 mg/day)/SU (GLIBENCRAMIDE 2.5 mg/day)
12.	56	M	0VD	SU (GLIMEPIRID 3 mg/day)/In (NOVOLIN R (10-10-10))
13.	69	M	1VD	In (NOVOLIN 30R (14-0-14))/In (NOVOLIN 30R (14-0-14))
14.	57	M	0VD	In (NOVORAPID 30R (18-0-12))/In (NOVORAPID 30R (18-0-12))
15.	66	F	2VD	A 300 mg/A300 mg
16.	64	F	2VD	In (NOVOLIN 30R (14-0-14))/In (NOVOLIN 30R (14-0-14)) +TRO 200 mg
17.	64	M	0VD	D&E/D&E
18.	51	M	0VD	D&E/D&E+P 0.6 g
19.	69	M	1VD	In (NOVOLIN 30R (8-0-8))/In (NOVOLIN 30R (8-0-8)) + D&E
20.	65	M	0VD	D&E/TRO 200 mg
21.	59	M	1VD	D&E/D&E
22.	64	M	2VD	D&E/D&E+SU (GLIMEPIRID mg/day)
23.	63	M	0VD	D&E/D&E
24.	68	F	0VD	SU (GLICRARISIDE 80 mg/day)/SU (GLICRARISIDE 80 mg/day +TRO 200 mg)
25.	55	M	2VD	SU (GLIMEPIRID 2 mg/day)/SU (GLIMEPIRID 2 mg/day)
26.	65	M	0VD	D&E/D&E
27.	56	M	0VD	SU (GLIMEPIRID 2 mg/day)/SU (GLIMEPIRID 2 mg/day)
28.	66	M	1VD	SU (GLIBENCRAMIDE 2.5 mg/day)/SU (GLIBENCRAMIDE2.5 mg/day)+TRO 200 mg
29.	64	M	0VD	D&E/TRO 200 mg
30.	48	F	0VD	D&E/D&E
31.	64	M	1VD	D&E/TRO 200 mg
32.	72	F	0VD	D&E/D&E
33.	60	M	0VD	D&E/D&E
34.	66	M	0VD	D&E/In (NOVOLIN R (8-6-6))

MFR: Myocardial Flow Reserve; CAG: Coronary Angiography Findings; 0VD: 0 Vessel Disease; 1VD: 1 Vessel Disease; 2VD: 2 Vessel Disease; D: Diet Therapy; E: Exercise Therapy; SU: Sulfonylurea Drugs; A: Acarbose; P: Poglybose; TRO: Troglitazone; In: Insulin

can be considered to be appropriate as normal control subjects as reported by Rozanski et al. [25]. Due to the difficulty of recruiting normal control subjects for studies using PET, all but two of these control subjects were those used for our other studies [11-13,22-24].

Positron Emission Tomography (PET)

Regional baseline MBF and that during dipyridamole administration were measured using PET and ¹³N-ammonia. Twenty-four hours before PET, we stopped all medications and caffeine intake. For all patients, follow-up PET study was performed 6 to 9 months after the first study.

Myocardial flow images were obtained using a Headtome IV scanner (Shimadzu Corp., Kyoto, Japan). This scanner has seven imaging planes; in-plane resolution is 4.5 mm at full width at half maximum and the z-axial resolution is 9.5 mm at full width at half maximum. Effective in-plane resolution is 7 mm after using a smoothing filter. The sensitivities of the Headtome IV scanners are 14 and 24 kilo counts per sec (μCi/ml) for direct and cross planes, respectively.

After acquiring transmission data to correct for photon attenuation prior to obtaining images, 15-20 mCi of ¹³N-ammonia was

injected and dynamic PET was performed for 2 min and static scan for 8 min. After waiting 45 min to allow for decay of the radioactivity of ^{13}N ammonia, dipyridamole (0.56 mg/kg) was administered intravenously. Five min after dipyridamole administration, 15-20 mCi of ^{13}N -ammonia was injected and, exactly at the same time, a second dynamic scan was performed for 2 min and a static scan for 8 min. The dynamic scan was performed every 15 sec (8 times) during the 2-min period and dynamic data were obtained for seven slices. Only one channel electrocardiographic monitoring in limb leads was made during the scan.

Determination of myocardial blood flow (MBF) and myocardial flow reserve (MFR)

Regional MBF was calculated basically according to the two-compartment ^{13}N -ammonia tracer kinetic model [26,27]. This model has been well validated [26,27] and has been used frequently in the clinical studies of MFR [11-13,19,22-25,28-30]. Metabolites of ^{13}N -ammonia can be negligible during the first 90 sec after infusion of ^{13}N -ammonia [31]. The time activity curve of the left ventricular cavity was used as an input function. Tracer spillover was corrected by least square nonlinear regression analysis on our program to calculate the MBF with the assumption that both myocardial and left ventricular radioactivity were influenced by each other. Details were given in our published paper [11].

All data were corrected for dead time effects to reduce error to less than 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, wall thickness was measured with two dimensional echocardiography by specialists in our hospital. The recovery coefficients were taken into consideration in our program to measure MBF.

To determine MBF, regions of interest were placed on the transaxial images manually. Only myocardial segments which were perfused by anatomically normal coronary arteries were selected in this study. Those segments which were perfused by coronary arteries after percutaneous transluminal angioplasty or coronary artery bypass grafting were excluded. As has been reported previously [23], each transaxial image was divided into 8 segments. Segments for the mid to mid-lower septum, upper septum, anterior wall on the mid-ventricular transaxial slice and mid to mid-lower septum, upper septum, and anterior wall on the lower slice were defined as the left descending coronary artery region. Segments for the lateral wall (mid-upper, mid-lower) on the middle slice and lateral wall on the lower slice were defined as the left circumflex coronary artery region. Segments for the lower septum and lower lateral wall on the middle slice and lower septum and lower lateral wall on the lower slice were defined as the right coronary artery region. When there was not enough space to place a region of interest on the right coronary arterial region visually, those segments were excluded. To obtain input function, small regions of interest were placed on the left ventricular cavity of each slice. Averages of the regional MBF corresponding to the same target coronary artery were used for this study. We then determined the MFR as follows:

MFR = regional MBF during dipyridamole administration/
regional baseline MBF

Statistics

Baseline MBF, MBF during dipyridamole loading, MFR, body weight, systolic blood pressure, diastolic blood pressure, height, body mass index and lipid parameters in the two groups were compared using analysis of variance, and then individual data were analyzed by the two-tailed unpaired *t*-test. Wilcoxon signed-rank test was used to determine whether each therapy was effective for the improvement in MFR. Spearman rank order correlation coefficient analysis was used to determine the relationship between percent change in FBS and percent change in MFR. Values are expressed as the mean \pm standard deviation.

Results

Hemodynamic and electrocardiographic responses to dipyridamole administration

There were no significant differences in systolic blood pressure at rest and during dipyridamole administration and rate pressure product between T2DM and control subjects (Table 2). During dipyridamole administration, typical chest pain or chest oppression accompanied by electrocardiographic changes were observed in 17 study patients. Due to difficulty in recording the radiolucent electrocardiogram in the precordial leads during PET, a detailed description of electrocardiographic response to dipyridamole was not possible.

Baseline MBF and MBF during dipyridamole administration

Baseline MBF (ml/min/100 g weight heart) was comparable among T2DM (86.8 ± 22.3 ml/min/100 g weight heart) and control subjects (78.2 ± 33.3 ml/min/100 g weight heart). However, MBF during dipyridamole administration was significantly lower in those with T2DM (188 ± 60.4 ml/min/100 g weight heart) than in control subjects (293 ± 159 ml/min/100 g weight heart, $p < 0.01$).

MFR

MFR was significantly lower in all 34 patients with T2DM (2.12 ± 0.58) than in control subjects (3.69 ± 1.09 , unpaired *t* test: $p < 0.01$).

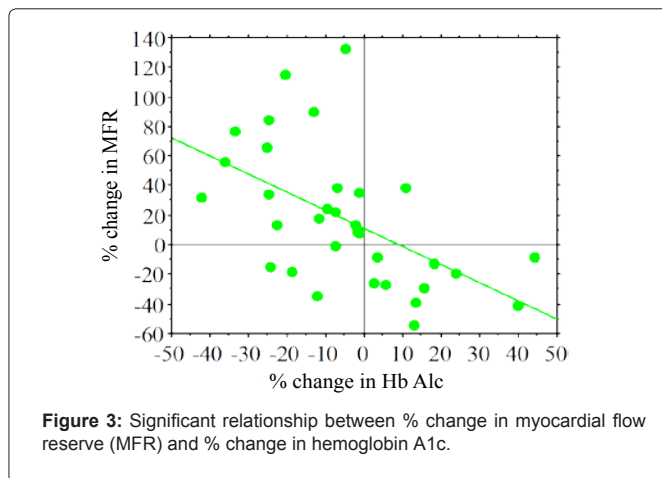
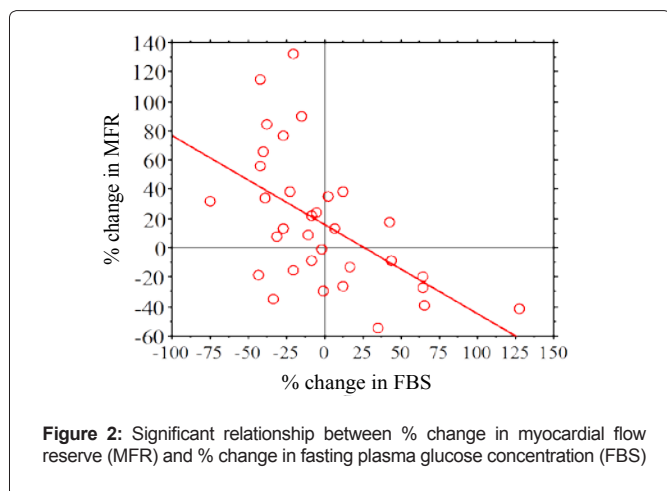
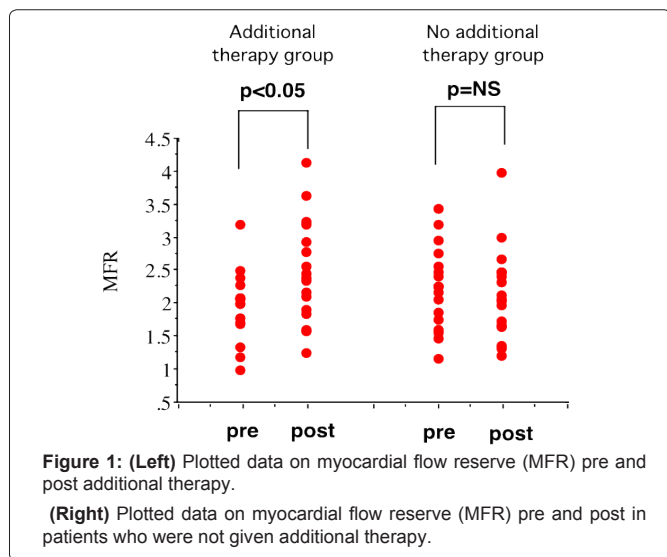
Effect of anti-hyperglycemic therapy on MBF and MFR

After randomization, additional medications were introduced. In these patients, the MFR significantly improved (pre 1.96 ± 0.52 vs. post 2.51 ± 0.77 , $p < 0.05$, Figure 1 on the left) as did the MBF during dipyridamole administration (pre 170 ± 52.0 ml/min/100 g vs. post 224 ± 56.5 ml/min/100 g, $p < 0.05$). However, baseline MBF did not change significantly (pre 87.5 ± 24.1 vs. post 94.7 ± 32.3). In these 17 patients, the hemoglobin A1c value was significantly reduced, ($8.06 \pm 1.38\%$ vs. $7.08 \pm 1.03\%$ $p < 0.01$) as were the FBS (10.4 ± 2.49 mmol/L vs. 8.38 ± 1.83 mmol/L) and TC (4.86 ± 0.936 mmol/L vs. 4.40 ± 0.781 mmol/L, $p < 0.05$). LDL tended to be reduced (3.08 ± 0.672 mmol/L vs. 2.64 ± 0.696 mmol/L, $p < 0.1$). On the contrary, HDL (1.01 ± 0.266 mmol/L vs. 1.08 ± 0.297 mmol/L), TG (1.71 ± 0.891 mmol/L vs. 1.50 ± 0.619 mmol/L) and blood pressures (systolic pressure, 132 ± 30.6 mmHg vs. 130 ± 28.9 mmHg; diastolic pressure, 79.9 ± 7.18 vs. 78.3 ± 7.01 mmHg) did not significantly change.

In 17 patients for whom additional therapy was not given, MFR did not significantly change (pre 2.27 ± 0.63 vs. post 2.14 ± 0.69 , $p = \text{ns}$) (Figure 1 on the right) nor did baseline MBF (pre 87.2 ± 16.9 ml/min/100 g weight heart vs. post 89.5 ± 32.0 ml/min/100 g weight

heart). MBF during dipyridamole administration tended to be reduced (pre 192 ± 52.6 ml/min/100 g weight heart vs. post 164 ± 43.7 ml/min/100 g weight heart). Values for hemoglobin A1c, (pre $7.7 \pm 1.2\%$ vs. post $7.6 \pm 1.0\%$), FBS (pre 9.77 ± 4.52 mmol/L vs. post 9.38 ± 2.71 mmol/L) and plasma lipid fractions (TC, pre 4.87 ± 0.822 mmol/L vs. post 4.84 ± 0.97 mmol/L; HDL, pre 1.20 ± 0.245 mmol/L vs. post 1.19 ± 0.341 mmol/L; TG, pre 1.95 ± 1.51 mmol/L vs. post 1.53 ± 0.68 mmol/L; LDL, pre 2.77 ± 0.585 mmol/L vs. post 2.97 ± 0.74 mmol/L) and blood pressures (systolic pressure, pre 129 ± 29.0 mmHg vs. post 131 ± 25.1 mmHg; diastolic pressure, pre 78.6 ± 7.03 mmHg vs. post 77.6 ± 6.87 mmHg) were comparable between the first and second PET study.

There were significant inverse relationships between the percent change in MFR and the percent change in FBS ($r=-0.54$, $p<0.01$, Figure 2) as well as hemoglobin A1c. ($r=-0.54$, $p<0.01$, Figure 3) However, there was no significant relationship between the percent change in MFR and percent change in plasma lipid fractions. Spearman rank order correlation coefficient analysis also showed that there were significant inverse relationships between the percent change in MFR and percent change in FBS ($r=-0.56$, $p<0.01$) as well as hemoglobin A1c ($r=-0.61$, $p<0.01$).



Discussion

Reduced MFR in diabetes

It has been recognized that MFR is inversely correlated with the severity of coronary stenosis [32]. However, contrary to such a well-known general concept, it has been shown that MFR can be reduced without overt coronary stenosis [1,2,13,23,24] or without evidence of ischemia in the presence of a variety of coronary risk factors [11-13,22,28-30]. That such reduced MFR was more prominent in patients with familial hypercholesterolemia [22,23] or hyperlipidemia with familial CAD [30] was also implied. Improvements in MFR after therapy for coronary risk factors were seen in patients with hyperlipidemia who were treated with intensive low fat diet therapy (total daily cholesterol intake less than 50 mg) but without any medicines including statins [29], those treated with a combination of multiple anti-hyperlipidemic medicines including statins [23] and those treated only with statins [33,34]. In these reports, inconsistent effects of statins in improving the reduced MFR in patients with hypercholesterolemia have been shown. For instance, SIMVASTATIN but not PRAVASTATIN improved MFR in patients with hypercholesterolemia [34]. Another study using FLUVASTATIN revealed that improvement in MFR was delayed 4 months after the improvement in plasma lipid fractions in patients with hyperlipidemia with CAD [33]. Huggins et al. showed that the reduced MFR in patients with hypercholesterolemia was improved 2 months after the initiation of high doses of SIMVASTATIN (80 mg/day) [35]. Therefore, even when the same types of medicines, such as statins, were used, responses related to improvements in MFR could differ. Similarly, differences in responses to various medicines for diabetes for impaired MFR in patients with T2DM could occur. As the medications administered obviously varied in the additional intensive therapy group, differences in the effects of these antihyperglycemic medicines on myocardial perfusion should be considered. In addition, prior to our present study, it was still controversial whether the reduced MFR in diabetic individuals could be reversed by improvements in glycemia control. It still remains uncertain which kinds of medicines for diabetes are effective in improving the MFR in T2DM. For example, Miyazaki et al. showed that the CFR was improved by an optimal anti-hyperglycemic therapy [16], whereas Jarnert et al. found that strict glycemic control failed to improve CFR in patients T2DM as indicated by a placebo controlled study [18]. In addition, we recently also revealed that the MFR in patients with

T2DM was not improved after chronic therapy with troglitazone over a 12-month period [19]. Therefore, anti-insulin resistance therapy is not effective for the treatment of diabetic coronary microangiopathy whereas anti-hyperglycemic therapy is effective for the treatment of diabetic coronary microangiopathy. The present study, which addressed this issue, showed just such an effect. However, it is still uncertain whether kinds of medicine, types of therapy (medication, exercise, diet), and individual differences in response to those therapies could influence the results of intensive anti-hyperglycemic therapy. Therefore, more precise investigations are required on each medication and each type of therapy to determine whether any of those therapies could actually improve MFR.

Several factors could contribute to the reduced MFR in patients with T2DM, including coronary microangiopathy [1,2], endothelial dysfunction [2], an abnormal smooth muscle cellular mutation associated with atherosclerosis and angiographically undetectable balanced diffuse atherosclerosis [36]. Coronary microcirculation abnormality has been implicated as a possible mechanism for the reduced MFR in patients with essential hypertension [37]. Oxidative stress caused by an increase in reactive oxygen species can be a primary contributing factor to impaired endothelial function in the spontaneously hypertensive rat (SHR) [38]. Kubis et al. revealed that microvascular rarefaction because of lack of the endothelial nitric oxide synthase gene played an important role in the occurrence of arterial hypertension in a mouse experimental model [39]. Loss of microvessels due to apoptosis of endothelial cells that was caused by oxidative stress in the experiment using SHR was shown [40]. Levy et al. commented in their review that all of these experimental results could commonly be applied to explain mechanisms for the reduced MFR in patients with traditional coronary risk factors, including T2DM [21]. In patients with hypertension, an improvement of MFR by ENALAPRIL has been observed [41], and such improvement also was seen in those treated with NEBIVOLOL [42]. Usefulness of both CANDESARTAN and ENALAPRIL on the improvement of subcutaneous fat small arterial endothelial function in patients with T2DM and hypertension has been reported [43]. It has also been reported that myocardial capillary density and coronary flow reserve were improved with calcium antagonists (BENIDIPINE [44] and AMLODIPINE [45]) in a rat experimental model of hypertension. In this study, several kinds of anti-hypertensive drugs were used. Influences of different type of medicines for essential hypertension in T2DM should be considered for our results because effects of such drugs on MFR in patients with T2DM and hypertension were only partially understood clinically. Further investigations should be required.

Since we studied reduced MFR in myocardial segments that were perfused by angiographically normal coronary arteries, coronary microangiopathy is an essential factor for the reduced MFR in our study subjects with T2DM. Thus, ineffective glycemic control, which would contribute to such microvascular damage, could be a major factor in the reduced MFR in T2DM. However, improvement in glycemic control would improve MFR and, in turn, be reflected by an additional improvement in other factors such as myocardial vasodilatation and diffuse macrovascular balanced atherosclerosis.

Lipid disorders have been shown to reduce MFR without evidence of CAD [22,23,30]. In the present study, plasma TC was significantly reduced and plasma LDL cholesterol values showed a tendency toward decreasing in patients who were provided with

intensive therapy for hyperglycemia. Reduced MFR and its negative relationship with plasma triglyceride concentrations in patients with hypertriglyceridemia in angiographically normal coronary arteries was reported [46]. Therefore, insignificant changes in plasma triglyceride concentrations after intensive therapy for hyperglycemia would also contribute to our results. Taken together, it may therefore be considered that a reduction in lipid fractions would be a factor in the improvement of MFR in T2DM patients undergoing additional therapy for glycemic control. However, there were no significant relationships between the percent change in the MFR and the percent change in plasma lipid fractions. Thus improvement in MFR can be ascribed to a more correct diet rather than to the secondary change in lipid parameters in response to the improvement in glycemic control.

Glycemic control and reduced MFR in myocardial segments that were perfused by anatomically normal coronary arteries in patients with T2DM

A relationship between hyperglycemia and diabetic vascular complications [4-10] has been shown as well as a relationship between glycemic control and MFR in T2DM [11-13]. Our current study showed an improvement in MFR in all 17 patients who received intensified treatment with additional medications, whereas a tendency toward the worsening of MFR was seen in patients who were not provided this additional treatment. There was a significant relationship between percent change in control of hyperglycemia and percent change in MFR. In support of our recent report that hyperglycemia rather than insulin resistance is related to the reduced MFR in T2DM [12], our current results confirm the concept that glycemic control is the most essential factor for diabetic microangiopathy in these patients. However, in the strict sense of the word, it remains uncertain whether improvement in MFR can be explained by the coronary microvascular vasodilatory function or coronary microvascular structural changes or both. Minor contribution of macrovascular vasodilatory dysfunction should also be considered. Although the MFR improved after successful anti-glycemic therapy, the MFR remained significantly lower than that of control subjects. In general, it can be supposed that damage to the myocardial vascular structure due to a reduction in the microvascular bed could not easily be reversed [2] and that a longer period of time and more stringent control of hyperglycemia may be required for such a reversal. Therefore, it is thought that the effect of anti-hyperglycemic therapy on the MFR should be examined in relation to the reduced MFR in T2DM over a much longer period of time.

Limitations of this study

In this study, we administered troglitazone to some of the study patients. However, due to serious side effects related to liver function, troglitazone was taken off the market. Therefore all studies using troglitazone ended, and this agent cannot be used in further studies. That is a limitation of this study. After March 2000, some of new anti-diabetic medicines has been emerged. Further studies should be required, however it is difficult to compare effects between troglitazone and new medicines. Moreover, the control subjects were normal individuals without CAD, but the study group was comprised of diabetic subjects with and without CAD. A group of nondiabetic subjects with CAD would be preferable for comparisons. However, it is difficult to obtain PET data on normo-lipidemic, normo-glycemic asymptomatic age-matched individuals with CAD.

Conclusion

Reduced MFR in angiographically normal coronary arteries in patients with T2DM can be partially reversed by an improvement in glycemic control.

Author Note

On March 2000, this study ended because troglitazone was prohibited for the treatment of diabetes mellitus and was withdrawn from the market due to serious side effects regarding liver function. Patients who were treated with troglitazone received no further treatment with troglitazone beginning in March 2000. Accordingly all data using troglitazone were accumulated before March 1.

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Author Affiliations


[Top](#)

¹Department of Cardiovascular Medicine, Sanno Hospital, International University of Health and Welfare, Japan

²Department of Radiology, Graduate School of Medicine, University of Tokyo, Japan

³Department of Clinical Engineering, Faculty of Medical Engineering, Suzuka University of Medical Science, Japan

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