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Impaired coronary microvascular function in diabetics

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Global and regional myocardial uptake was determined with technetium-99m tetrofosmin and a 4 hour exercise (370 MBq iv) and rest (740 MBq iv) protocol, in 24 patients with non-insulin dependent diabetes mellitus and in 22 control subjects. The purpose of this study was to evaluate impaired coronary microvascular function in diabetics by measurement of % uptake increase in myocardial counts. The parameter of % uptake increase (ΔMTU) was calculated as the ratio of exercise counts to rest myocardial counts with correction of myocardial uptake for dose administered and physical decay between the exercise study and the rest study. Global ΔMTU was significantly lower in the diabetics than in control subjects ($14.4 \pm 5.4\%$ vs. $21.7 \pm 8.5\%$, $p < 0.01$). Regional ΔMTU in each of 4 left ventricular regions (anterior, septal, inferior, posterolateral) was significantly lower in the diabetic group than in the control group ($p < 0.01$) respectively, but there were no significant differences between ΔMTU in the 4 left ventricular regions in the same group. ΔMTU was useful as a non-invasive means of evaluating impaired coronary microvascular function in diabetics.

Key words: diabetes mellitus, coronary flow reserve, tetrofosmin, coronary microcirculation, SPECT

INTRODUCTION

Microaneurysms,[1] hyalinization[2] or wall thickening of intramural arterioles,[2–4] and reduced density of capillary vessels[5] have been described as morphological changes in the heart of diabetics. Functionally, the maximum pharmacological reserve of coronary blood flow has been found to be depressed, and the mechanism of regulation of coronary vascular resistance during atrial tachypacing has been found to be impaired in diabetics compared with nondiabetic patients, suggesting impairment of coronary microcirculation.[6–14] Reduced coronary flow reserve has been reported not only in diabetes mellitus but in various other diseases such as coronary stenosis,[15] hypertrophied heart[16,17] and syndrome X.[18,19]

An index of ^{99m}Tc tetrofosmin (TF) or ^{99m}Tc methoxybutylisonitrile (MIBI) myocardial single-photon emission computed tomography (SPECT) calculated from the ratio of exercise counts to rest myocardial counts,[20–24] has shown promise as a tool to assess coronary flow reserve noninvasively. The index provides functional and quantitative information for use in combination with conventional inspection of myocardial SPECT images.

The purpose of this study was to evaluate impaired coronary microvascular function based on noninvasive measurement of coronary flow reserve in diabetics by a radioisotope technique.

MATERIALS AND METHODS

Patient Characteristics

Forty-six subjects without significant (> 75%) coronary artery stenosis on coronary angiography or left ventricular wall motion abnormality were studied. They were divided into a control group and a diabetic group.

The 22 control subjects did not have mellitus on the basis of their history and blood chemistry data.

The 24 diabetics had non-insulin dependent diabetes mellitus, and 3 of them (12.5%) were on insulin therapy. The average interval since diagnosis was 11.0 ± 10.9 years. The average serum HbA_{1C} was $7.4 \pm 2.0\%$, and their serum immuno-reactive insulin was 5.7 ± 4.3 μU/m*l*.

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Table 1 Patient characteristics

No. of subjects	Control group (N = 22)	Diabetic group (N = 24)
Age (years)	58.6 ± 10.6	56.8 ± 14.4
Sex (M : F)	13 : 9	17 : 7
HT	0%	29.1%*
FBS (mg/d*l*)	103.9 ± 23.8	155.0 ± 51.8*
T-cho (mg/d*l*)	214.1 ± 27.4	209.2 ± 30.5
TG (mg/d*l*)	155.5 ± 96.2	131.9 ± 78.9
BMI (kg/m^2)	23.4 ± 2.4	25.6 ± 4.5

HT: history of hypertension; FBS: fasting blood sugar; N: number of patients; T-cho: serum total cholesterol; TG: serum triglyceride; BMI: body mass index. Values are means ± SD. *$p < 0.05$

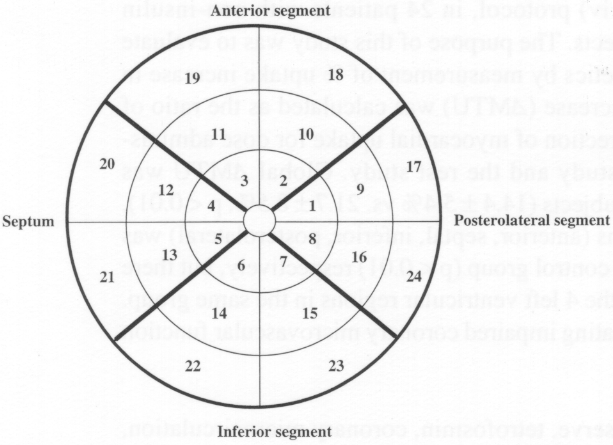

Fig. 1 The left ventricle was divided into 24 segments in a bull's-eye polar map. Mean radiotracer uptake and the ratio of myocardial tetrofosmin uptake during exercise to uptake at rest (ΔMTU) were calculated in each segment and in 4 left ventricular regions (anterior, septal, inferior, posterolateral segment).

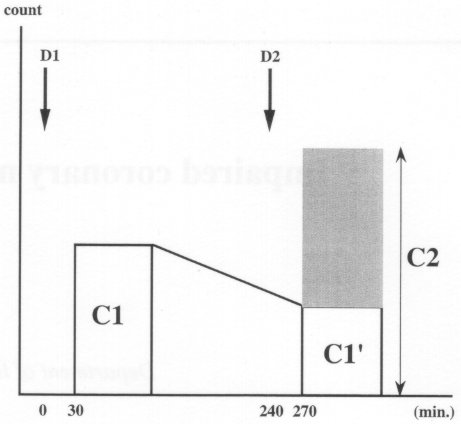

Fig. 2 Ratio of myocardial tetrofosmin uptake during exercise to uptake at rest. The myocardial tetrofosmin counts on exercise and rest images were calculated (C1 and C2). Decreased C1 counts on rest image are represented by C1′, and the counts of real rest image were abbreviated as C2 – C1′. ΔMTU was determined in the following manner. $\Delta MTU = \{[C1/(C2 - C1')] \times R - 1\} \times 100$ (%), where R = D2/D1, D1 = the first dosage of ^{99m}Tc tetrofosmin, D2 = the second dosage of ^{99m}Tc tetrofosmin.

Table 2 Hemodynamics

		HR	MBP	RPP
C	b	82.5 ± 12.7	104.2 ± 14.2	11631 ± 2719
	d	144.3 ± 17.0	139.0 ± 16.8	30336 ± 5468
DM	b	82.3 ± 14.0	104.8 ± 12.1	11625 ± 2201
	d	136.8 ± 15.9	136.4 ± 14.9	28641 ± 3781

C: control group, DM: diabetic group, HR: heart rate (beat/min), MBP: mean blood pressure (mmHg), RPP: rate pressure product. b: before exercise, d: during exercise. Values are means ± SD.

Eighteen of them (75%) had a history of proteinuria, and 3 (12.5%) had a history of diabetic retinopathy. No patients had a history of diabetic neuropathy. The diagnosis of diabetes mellitus was made on the basis of presentation with classic symptoms and a random blood glucose test value of 200 mg per deciliter or greater. If diabetes was suspected but not confirmed by the random glucose determination, the diagnosis of diabetes mellitus was established by a blood glucose value after an overnight fasting of 140 mg or more per deciliter on at least two separate occasions.

No significant difference was found between the two groups with regard to sex distribution or average age. The incidence of a history of hypertension was significantly higher in the diabetic patients (29.1%) than in the control patients (0%) ($p < 0.05$). Fasting blood sugar was significantly higher in the diabetic patients than in the control patients ($p < 0.05$), but there were no significant differences in the serum total cholesterol or serum triglyceride values. The body mass index was similar in both groups (Table 1).

Exercise and Rest TF Myocardial SPECT

We performed exercise stress testing with a bicycle ergometer in a symptom-limited manner. Exercise was started at 25 watts, and the load was increased by 25 watts every 3 minutes until the exercise endpoint was reached. In each group we selected only patients who reached a rate pressure product greater than 20000 at the exercise endpoint.

SPECT Data Acquisition and Processing

A 370 MBq dose of TF was injected during peak exercise, and a 740 MBq dose of TF was re-injected 4 hours after the completion of exercise. After each injection, we flushed the TF remaining in the vein with 5 m*l* of normal saline. The images were acquired at 30 minutes after the first and the second injection, by means of a rotating large-field-of-view gamma camera (SNC5100R, Shimadzu, Kyoto, Japan) equipped with a low-energy high-resolution parallel-hole collimator centered on the 140 keV photopeak for Tc-99m, with a 20% window. Thirty-two views were collected with a 64 × 64 acquisition matrix for

30 seconds per projection over 180 degrees. A series of transmural slices were reconstructed from the raw scintigraphic data by a backprojection technique with a Ramp filter. Short-axis and vertical and horizontal long axis tomograms were reconstructed with a data processor (Scintipac 7000, Shimadzu, Kyoto, Japan).

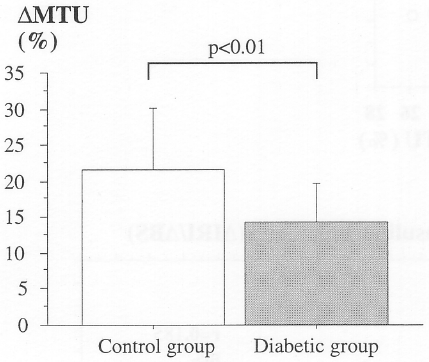

Fig. 3 Bar graph showing difference in ΔMTU of the entire left ventricle in the control group and diabetic group. Open bar, control group (n = 22); Closed bar, diabetic group (n = 24). Values are means ± SD.

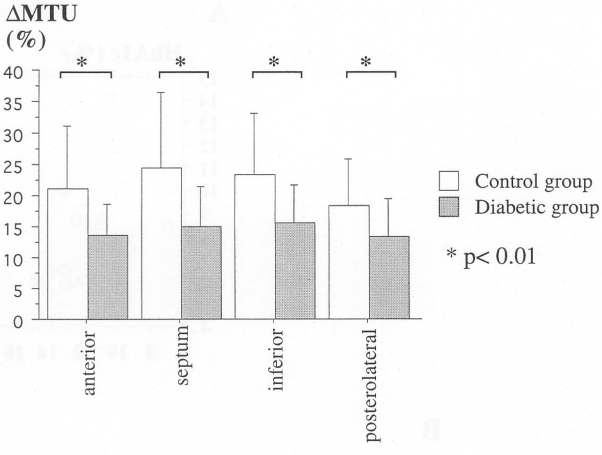

Fig. 4 Bar graph showing regional difference in ΔMTU in the control group and the diabetic group. The left ventricle was divided into 4 segments (anterior, septal, inferior, posterolateral segments). Open bar, control group (n = 22); Closed bar, diabetic group (n = 24). Values are means ± SD.

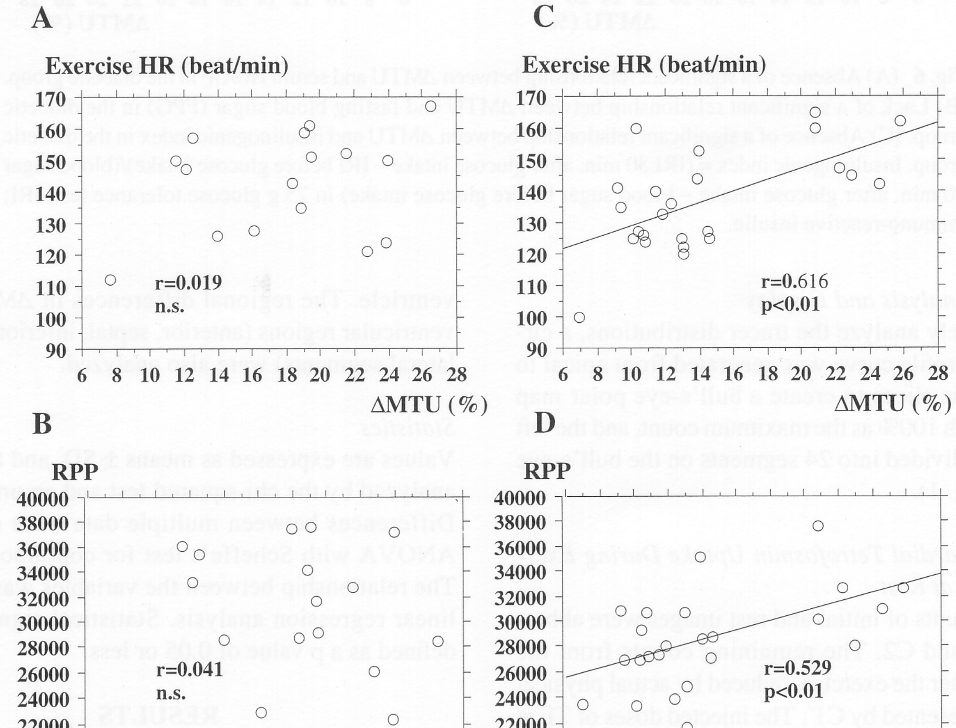

Fig. 5 (A) Absence of a significant relationship between ΔMTU and heart rate during exercise (Exercise HR) in the control group. (B) Absence of a significant relationship between ΔMTU and rate pressure product during exercise (RPP) in the control group. (C) Relationship between ΔMTU and Exercise HR in the diabetic group. ΔMTU was positively correlated with exercise HR (r = 0.616, p < 0.01). (D) Relationship between ΔMTU and RPP in the diabetic group. ΔMTU was positively correlated with RPP (r = 0.529, p < 0.01).

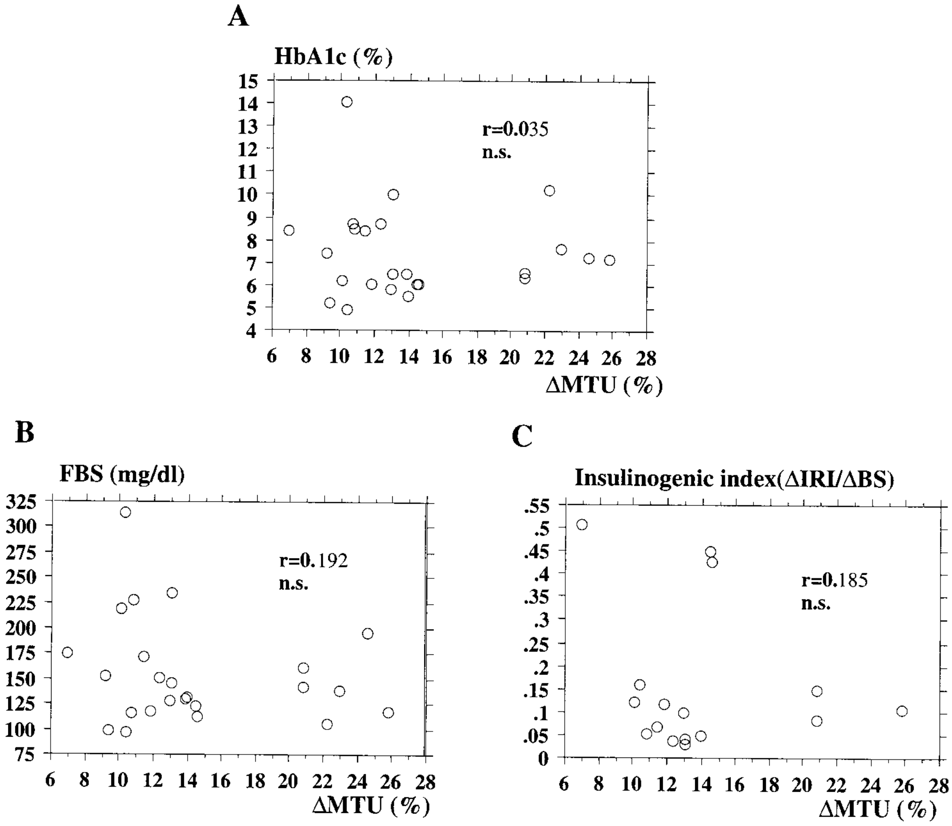

Fig. 6 (A) Absence of a significant relationship between ΔMTU and serum HbA$_{1C}$ in the diabetic group. (B) Lack of a significant relationship between ΔMTU and fasting blood sugar (FPG) in the diabetic group. (C) Absence of a significant relationship between ΔMTU and insulinogenic index in the diabetic group. Insulinogenic index = (IRI 30 min. after glucose intake – IRI before glucose intake)/(blood sugar 30 min. after glucose intake – blood sugar before glucose intake) in 75 g glucose tolerance test. IRI; immuno-reactive insulin.

Quantitative Analysis and Display

To quantitatively analyze the tracer distributions, a circumferential profile curve was generated from apical to basal short-axis slices to create a bull's-eye polar map normalized with 100% as the maximum count, and the left ventricle was divided into 24 segments on the bull's-eye polar map (Fig. 1).

Ratio of Myocardial Tetrofosmin Uptake During Exercise to Uptake at Rest

Myocardial counts of initial and rest images were abbreviated as C1 and C2. The remaining counts from the examination after the exercise, reduced by actual physical decay, are represented by C1′. The injected doses of TF at peak exercise and at rest are referred to as D1 and D2 (Fig. 2). The ratio of myocardial TF uptake (MTU) during exercise to uptake at rest was calculated by the formula.

$$\Delta\text{MTU} = \{[\text{C1}/(\text{C2} - \text{C1}')] \times \text{R} - 1\} \times 100\,(\%)$$
$$(\text{where R} = \text{D2}/\text{D1})$$

ΔMTU was calculated in each of the 24 left ventricular segments, and the mean value of all segments in the entire left ventricle is represented by ΔMTU in the whole left ventricle. The regional differences in ΔMTU in 4 left ventricular regions (anterior, septal, inferior and posterolateral segments) were also analyzed.

Statistics

Values are expressed as means ± SD, and the data were analyzed by the chi-squared test and an unpaired *t*-test. Differences between multiple data were evaluated by ANOVA with Scheffe's test for continuous variables. The relationship between the variables was assessed by linear regression analysis. Statistical significance was defined as a p value of 0.05 or less.

RESULTS

Visual Inspection of Exercise and Rest TF Myocardial SPECT Images: There were no perfusion abnormalities in any of the patients.

Hemodynamic Change Before and After Exercise: As shown in Table 2, the rate pressure product at the exercise endpoint and the maximum heart rate were similar in the two groups.

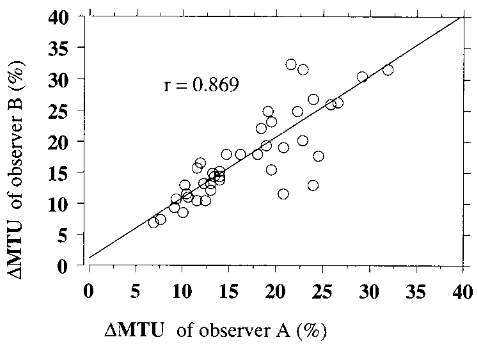

Fig. 7 Graph showing the correlation between two repeated measurements of ΔMTU by two different observers. A significant correlation was observed between values of ΔMTU calculated by observer A and observer B.

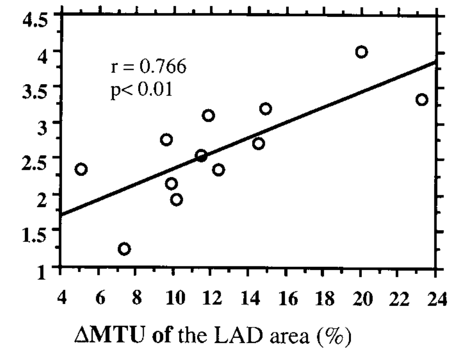

Fig. 8 Graph showing a correlation between ΔMTU of the left anterior descending artery (LAD) area and peak-to-resting coronary flow ratio determined with a Doppler flow wire inserted into the LAD of 12 subjects with normal coronary arteries. A significant positive correlation was observed between the ΔMTU of the LAD area and the peak-to-resting coronary flow ratio.

Ratio of Myocardial Tetrofosmin Uptake During Exercise to Uptake at Rest: ΔMTU in the entire left ventricle was 21.7 ± 8.5% in the control patients, and 14.4 ± 5.4% in the diabetic patients. The ΔMTU value of the diabetic group was significantly lower than that of the control group ($p < 0.01$) (Fig. 3).

Regional Differences in ΔMTU: We analyzed regional difference in ΔMTU in the control group and the diabetic group, and the ΔMTU in each of the left ventricular regions in the diabetic group was significantly lower than in the control group ($p < 0.01$), but no significant differences were found between the ΔMTU value for the 4 regions in the control group or the diabetic group (Fig. 4).

Correlation between ΔMTU and Rate Pressure Product (RPP) in Each Group: There was a significant positive correlation between ΔMTU and RPP at the exercise endpoint in the diabetic patients, but not in the control group. In the diabetic group, ΔMTU was positively correlated with heart rate during exercise, but in the control group no significant correlation between the two was found (Fig. 5).

Correlation between ΔMTU and Parameters of Diabetic Control: There were no significant correlations between ΔMTU and serum HbA_{1C} levels, fasting blood sugar levels or insulinogenic index (ΔIRI/ΔBS) (Fig. 6).

In the diabetic patients, ΔMTU was the same in patients with hypertension and without hypertension (12.7 ± 4.5% vs. 15.1 ± 5.7%, n.s.).

Electrocardiographic changes during exercise
There were no patients with horizontal or downsloping ST-segment depression over 1 mm during exercise in any of the groups. ST segment deviation from the resting level in lead V_5 during exercise was −0.46 ± 0.50 mm in the control group and −0.48 ± 0.70 mm in the diabetic group (n.s.).

Reproducibility of the ΔMTU measurements
The measurements of the ΔMTU in each subject were made by two different observers. There was a significant correlation between the ΔMTU value measured by observer A and by observer B ($r = 0.869$) (Fig.7), and thus the ΔMTU measurement was found to be reproducible.

Validation of ΔMTU with a Doppler flow wire
We performed a preliminary study to determine if ΔMTU is a reliable parameter to detect change in myocardial blood flow during stress, a Doppler flow wire was inserted into the anterior descending artery (LAD) of 12 subjects with normal coronary arteries, and the peak-to-resting coronary flow ratio (coronary flow reserve) was measured during intravenous infusion of adenosine triphosphate (ATP). One day after the Doppler flow wire study, the ΔMTU of the area perfused by the LAD (LAD area) was detemined by ATP stress TF SPECT, and a significant positive correlation was found between the ΔMTU of the LAD area and the CFR ($r = 0.766$) (Fig. 8).

DISCUSSION

If the myocardial extraction rate of TF during exercise is assumed to be the same as that at rest in the present study, ΔMTU would seem to reflect the relative increase in the coronary blood flow/cardiac output ratio during exercise.[20–24] On the other hand, our preliminary study showed that the ΔMTU of the LAD area was correlated positively with peak-to-resting coronary flow ratio determined with a Doppler flow wire. ΔMTU may therefore reflect the changes in coronary blood flow during stress.

Since the rate pressure product during exercise and the maximum heart rate in the two groups were similar, exercise tolerance appears to have been similar in both groups. As the rate pressure product is positively correlated with myocardial oxygen consumption,[25] the workload in the diabetic group was similar to that in the control group. Our data showed that the ΔMTU in the diabetic group was significantly lower than in the control group. Global ΔMTU was $14.4 \pm 5.4\%$ in the diabetic group and $21.7 \pm 8.5\%$ in the control group. This lower ΔMTU value in diabetic patients may mean an attenuated coronary blood flow response to increased workload.

The ΔMTU of the diabetic patients was significantly lower than that of the control patients, not only in the entire left ventricle but in each of the left ventricular regions, and there were no significant regional differences between the ΔMTU values in any of the 4 left ventricular regions: anterior, septum, inferior or posterolateral. The low ΔMTU value in the diabetic group suggests diffuse impairment of myocardial blood flow, because there was no significant stenosis in any of the epicardial coronary arteries.

Some reports of animal experiments have suggested that coronary microcirculation is impaired in diabetes mellitus. The increase in coronary blood flow in isolated and perfused diabetic rat heart was found to be significantly lower than in the control rats during tachycardia elicited by electrical pacing.[26] The coronary dilator action of adenosine has been found to be lower in the heart of diabetic lambs than in the heart of control lambs.[27] A decrease in PGI_2 (a potent coronary vasodilator) synthesis in response to adrenergic stimulation has been reported in the coronary arteries of diabetic dogs.[28] This experimental evidence is consistent with our clinical findings. Three categories of factors influence coronary blood flow: physical factors, neural and neurohumoral factors, and metabolic factors.[29] Since aortic pressure, and workload during exercise of the two groups were similar, the physical and metabolic factors in the diabetic and control groups appear to have been similar, but the difference between the neural and neurohumoral factors of the two groups in our study remained to be determined.

There was significant positive correlation between ΔMTU and the hemodynamic parameters (RPP and maximum heart rate) in diabetic patients, but not in the control group, and this can be explained as follows. Because of the ample capacity for coronary dilation in control patients, high coronary blood flow was achieved during exercise. At high coronary blood flow, however, myocardial uptake of TF reaches a plateau,[30–32] so that there was no significant correlation between ΔMTU and the hemodynamic parameters in the control group. In the diabetic group, on the other hand, the capacity for coronary dilation is limited, and myocardial uptake of TF does not reach a plateau during exercise. As a result, there was a close correlation between ΔMTU and the hemodynamic parameters.

There was no significant correlation between ΔMTU in the diabetic group and the clinical indicators of diabetic control (fasting blood sugar, serum HbA_{1C} and the insulinogenic index) or the presence of diabetic complications. ΔMTU may therefore be an independent parameter that reflects impairment of coronary microcirculation in diabetic patients.

Nitenburg et al. reported, by using a Doppler guidewire in 11 diabetic patients, that maximum coronary flow reserve was reduced,[7] but 10 of the 11 patients had systemic hypertension, which affects coronary microcirculation, so that, they could not rule out the possibility of hypertensive modifications. Although the incidence of systemic hypertension was higher in the diabetic patients than in the control patients in our study, there was no significant difference in ΔMTU according to whether the diabetic patients had hypertension or not. Therefore, the low ΔMTU value in the diabetic group was not attributable to hypertension, but to the diabetes itself.

In addition, there were no significant differences between the diabetic group and the control group in the serum lipid levels, body mass index or the frequency of obesity.

There were no ischemic changes in the ECG of the diabetic group or in the control group either at rest or during exercise. Although there was no significant coronary stenosis in either group, this evidence does not rule out myocardial ischemia in the diabetic patients, because they may have had slight myocardial ischemia that was not detected by the ECG.[33]

The pathogenesis of the impaired microvascular function in diabetics remains uncertain. Nevertheless, there is evidence that suggests impaired coronary blood flow in diabetes mellitus because of both structural and functional changes in coronary microvessels,[1–7,13,14,26–28] and recent reports have suggested coronary endothelial dysfunction in diabetics.[7,34,35] In this study, visual and quantitative analysis of the RI examination non-invasively revealed changes in coronary microcirculation in diabetes mellitus.

A recent study by means of positron emission tomography showed that hyperglycemia is related to coronary flow reserve in non-insulin dependent diabetes mellitus.[13] It would therefore be important to control blood glucose levels to prevent deterioration in the function of coronary microcirculation in diabetic patients.

Limitations

When the presence of coronary epicardial stenosis is unknown, it is impossible to evaluate the coronary microvascular function in diabetic patients with ΔMTU, and the parameter may be influenced by the presence of coronary microvascular abnormalities due to other diseases such as hypertrophied heart and syndrome X.

ΔMTU values showed a substantial overlap between the normal group and the diabetic group, and this may be explained by the fact that the ΔMTU value is influenced by biological tracer washout, the extraction fraction of the tracer, gamma ray absorption by the body and cardiac output.

Clinical implications

With ΔMTU it was possible to evaluate impaired coronary microvascular function in diabetics. This parameter may allow assessment of impaired coronary microvascular function in other diseases such as hypertrophied heart and syndrome X.

In spite of the limitations as mentioned above, ΔMTU can be easily obtained without using invasive techniques. We selected exercise instead of pharmacologic stress in the present study because we think that it is clinically important to assess the response of the coronary microcirculation to exercise in diabetics. In this way, ΔMTU may facilitate early detection of a subset of patients with abnormalities in coronary microcirculation who are prone to myocardial ischemia and left ventricular dysfunction. ΔMTU will also make it possible to evaluate the effects of drugs on coronary microvascular function non-invasively.

CONCLUSIONS

The increase in myocardial tetrofosmin uptake during exercise was quantified to evaluate impaired coronary microvascular function in diabetics. With this parameter, it was possible to non-invasively assess impaired coronary microvascular function on exercise in diabetic patients.

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