Abnormality of Myocardial Oxidative Metabolism in Noninsulin-Dependent Diabetes Mellitus

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The purpose of this study was to evaluate oxidative metabolism and its response by dobutamine in patients with noninsulin-dependent diabetes mellitus (NIDDM) using ^{11}C-acetate PET. **Methods:** We studied 16 patients with NIDDM (9 men, 7 women; mean age 53.7 ± 12.8 yr) and 6 healthy male control subjects (mean age 41.8 ± 17.2 yr). None of them had an abnormality on stress-perfusion SPECT. The ^{11}C-acetate clearances (Kmono) were compared regionally for five myocardial segments in all subjects at rest and during low-dose dobutamine stress in 13 patients (8 patients with NIDDM, age 51.9 ± 13.6 yr; 5 healthy male control subjects, age 45.6 ± 16.3 yr). Correlation between regional Kmono and rate-pressure product (RPP) was also studied. **Results:** At rest, the clearance of ^{11}C-acetate was slightly heterogeneous for both patients with NIDDM and healthy control subjects, with smaller values in the apex and inferior wall in both groups. The difference became significant during dobutamine stress in the patients. The RPP-to-Kmono (average for five segments) ratio at rest was slightly smaller in the patients (1042.7 ± 559.1 × 0.01) than in the healthy control subjects (1391.4 ± 209.6 × 0.01, not significant), and those during dobutamine stress were almost the same in the two groups (1457.3 ± 737.4 × 0.01 and 1486.0 ± 211.8 × 0.01, respectively). A significant correlation was seen between regional Kmono and RPP in every segment in the healthy control subjects (average; $r = 0.89$; $p < 0.01$), whereas more scattered correlation with greater regional variation was observed in the patients (average; $r = 0.31$; p value was not significant). **Conclusion:** Patients with NIDDM showed slight regional heterogeneity in myocardial oxidative metabolism. They also had more scattered correlation between myocardial oxidative metabolism and cardiac work (RPP) than healthy control subjects, with the smallest correlation coefficient observed in the inferior wall. These findings may help the understanding of dynamics in myocardial oxidative metabolism of NIDDM hearts.

Key Words: diabetes; myocardial oxidative metabolism

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It is well known that patients with poorly controlled diabetes frequently have a poor prognosis, with a high incidence of cardiac events (*1–3*). In humans, nuclear medicine approaches have revealed several abnormalities in the diabetic heart, including perfusion (*4*), glucose metabolism (*5–7*), cardiac function (*8,9*) and sympathetic neuronal supply (*10,11*) and have suggested that metabolic or neuronal abnormalities occur regionally rather than globally (*11*). Three-dimensional analysis of myocardial PET images enables the assessment of the regional oxidative metabolism. The assessment of the inferior cardiac wall, in particular, was not possible before the introduction of this method (*12,13*). The purposes of this study were to evaluate oxidative metabolism and its response to sympathetic stimulation in patients with noninsulin-dependent diabetes mellitus (NIDDM) without ischemic heart disease using ^{11}C-acetate PET and low-dose dobutamine test and to clarify the pathologic mechanism in the diabetic heart.

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MATERIALS AND METHODS

Patients

We recruited 18 patients with NIDDM without any history or symptoms of coronary artery disease. All patients underwent stress-perfusion SPECT in combination with first-pass radionuclide angiography (FPRNA) as routinely performed at our institute using ^{99m}Tc-tetrofosmin. To exclude the effect of ischemic heart disease, two patients with perfusion abnormality identified by the stress test were excluded from the study population. The final study population included 16 patients with NIDDM (9 men, 7 women; mean age 53.7 ± 12.8 yr) and 6 healthy male control subjects (mean age 41.8 ± 17.2 yr). Patient characteristics were as follows: duration of illness; 16.0 ± 7.5 yr; fasting blood sugar, 198.9 ± 93.9 mg/dl; hemoglobin A1c, 8.8% ± 2.0%; and ejection fraction, 62.9% ± 12.2%. Patients were selected from those who were recently hospitalized to control blood sugar levels, including insulin therapy. All had more or less severe diabetic retinopathy but not serious nephropathy (renal failure) except for 1 patient (Patient 7, Table 1). Although peripheral neuropathy was observed in all patients on the basis of vibratory sensation test and Achilles tendon reflex test, severe autonomic neuropathy (positive for orthostatic hypotension >20 mm Hg after 60° head-up tilt) was observed in only 3 patients. These 3 patients did not undergo the low-dose dobutamine test because they had high systolic blood pressure (>180 mm Hg) in the supine position. PET and low-dose dobutamine stress studies were performed after acquiring written informed consent. All procedures were approved by the Ethics Committee for Research on Human Subjects at Kyoto University Hospital.

Exclusion of Silent Myocardial Ischemia

All diabetic patients underwent stress–rest perfusion SPECT (2-day protocol) 1 wk before PET scan acquisition. For exercise stress, the standard Bruce or Modified Bruce protocol was used, depending on the patient's exercise capacity. Approximately 300 MBq ^{99m}Tc-tetrofosmin was injected at peak exercise, and the stress was discontinued 1 min after tracer injection. At the time of the injection, anterior view FPRNA was performed using a high-sensitivity, multicrystal gamma camera (SIM-400; Scinticor, Milwaukee, WI) as previously described (*14*). Perfusion SPECT was started 1 hr after tracer injection to allow for clearance of hepatobiliary activity. During the intervening hour, the patients were encouraged to have a light meal to accelerate tracer clearance. Sixty projection (20 × 3) SPECT images were acquired with a triple-head gamma camera (PRISM-3000; Picker International, Cleveland, OH) at 25 sec per image (total acquisition time approximately 12 min). All patients underwent another perfusion scan at rest on a different day in the same fashion to confirm the presence of reversible perfusion abnormality. Perfusion SPECT

TABLE 1
Subjects Undergoing Low-Dose Dobutamine Test

Patient no.	Age (yr)	Sex	Group	Characteristics				Dobutamine	Rest				Dobutamine			
				Duration (yr)	FBS (mg/dl)	HbA1c (%)	EF (%)	Dose (μg/kg/min)	sys-BP (mm Hg)	dia-BP (mm Hg)	HR (beats/min)	RPP	sys-BP (mm Hg)	dia-BP (mm Hg)	HR (beats/min)	RPP
1	26	M	Control					10	120	80	62	7440	158	80	78	12324
2	71	M	Control					8	120	94	70	8400	166	60	106	17596
3	42	M	Control					10	136	92	68	9248	162	84	72	11664
4	42	M	Control					10	122	71	82	10004	176	63	88	15488
5	47	M	Control					13	110	76	63	6930	136	72	99	13464
6	45	M	NIDDM	>5	258	7.1	55	10	127	84	66	8382	178	54	83	14774
7	61	M	NIDDM	10	205	6.5	72	9	113	65	49	5537	144	74	68	9792
8	61	M	NIDDM	5	103	7.6	48	12	126	87	77	9702	133	73	101	13433
9	61	F	NIDDM	7	181	10.1	53	10	84	50	54	4536	150	59	56	8400
10	27	F	NIDDM	12	218	12.5	70	10	135	89	65	8775	169	89	127	21463
11	46	M	NIDDM	10	226	12.6	69	10	135	78	63	8505	143	66	72	10296
12	69	M	NIDDM	30	325	9	78	7	147	86	64	9408	206	102	70	14420
13	45	M	NIDDM	>2	131	6.8	55	8	138	91	96	13248	172	89	141	24252

FBS = fasting blood sugar; HbA1c = hemoglobin A1c; EF = ejection fraction; Sys-BP = systolic blood pressure; Dia-BP = diastolic blood pressure; HR = heart rate; RPP = rate-pressure product; NIDDM = noninsulin-dependent diabetes mellitus.

images and FPRNA data were interpreted by nuclear medical specialists, with reference to other clinical information.

PET Acquisition

Only the patients without an abnormality on perfusion SPECT (n = 16) and the 6 control subjects underwent PET studies. Among them, 8 patients and 5 control subjects underwent ^{11}C-acetate PET both at rest and under low-dose dobutamine stress (Table 1). The other 9 control subjects underwent PET only at rest because of mechanical trouble (n = 3), hypoglycemic attack (n = 1), denial to receive dobutamine (n = 2) and high systolic blood pressure of >180 mm Hg (n = 3). Although myocardial acetate clearance was not influenced by substrate level, PET was performed during the fasting condition, in principle (*15*). Patients with NIDDM were encouraged to have some sweets or juice to prevent hypoglycemia. Insulin was not given until PET acquisition was completed. After transmission scanning (20 min), approximately 370 MBq ^{11}C-acetate was intravenously injected as a slow bolus over 30 sec. At the time of injection, dynamic PET acquisition (1 min per frame for 20 frames) was started and continued for 20 min using an 8-ring PET camera (PCT-3600W; Hitachi Medico, Tokyo, Japan), providing 15 slices with FWHM of 12 mm. For 13 of these subjects, another dynamic PET study was performed during the low-dose dobutamine stress test 120 min later.

Low-Dose Dobutamine Stress Test

To assess myocardial response to beta-adrenergic stimulation, a low-dose dobutamine stress test was performed (*16*). Table 1 lists the subjects who completed the test during second PET acquisition. They included 8 patients with NIDDM (5 men, 3 women; mean age 51.9 ± 13.6 yr) and 5 healthy male control subjects (mean age 45.6 ± 16.3 yr). Incremental doses of dobutamine were intravenously infused by an electrical infusion pump (STC-525; Terumo, Tokyo, Japan) under electrocardiogram monitoring by cardiologists. The initial dobutamine dose was 5 μg/kg/min, and the dose was gradually increased to a maximum of 20 μg/kg/min until one of the following endpoints had been reached: heart rate increase by 20% or to >80% of maximum predicted heart rate for age, systolic blood pressure increase by 20% or >200 mm Hg, occurrence of chest pain, ST sequence of electrocardiogram segment depression ≥2 mm or ST segment elevation ≥1 mm or occurrence of significant atrial or ventricular arrhythmia. All of the subjects reached one of the endpoints before the administration of the maximum dose. None of them showed severe signs of ischemia including chest pain or significant ST depression. The mean infused dose was 10.2 ± 1.8 μg/kg/min for the control subjects and 9.5 ± 1.5 μg/kg/min for the patients. Dynamic PET scanning was started at least 3 min after the final dose of dobutamine. A bolus of ^{11}C-acetate was injected slowly through another intravenous catheter. Dobutamine infusion was discontinued 17 min after PET acquisition began.

PET Data Analysis

Reconstructed PET data were analyzed three-dimensionally, as previously reported (*12,13*). Briefly, PET data for each frame were reoriented into a series of short-axis images and displayed on a polar map with nine myocardial segments (apex, midanterior, midseptal, midinferior, midlateral, bas-anterior, bas-septal, bas-inferior and basal-lateral). The mean regional counts of each segment were calculated in every frame to generate time-activity curves. Washout elements of the time-activity curves were fitted using monoexponential least-squares curve fitting technique to derive the clearance rate constant (Kmono), which is reported to be an index of myocardial oxidative metabolism (*17*). Curve fitting was performed for the data of 10–12 min in the first component of washout elements that were considered within 20 min postinjection (*16*). The starting point for curve fitting was altered according to the peak of the time-activity curve (Fig. 1), but it was at least 6 min after tracer injection because a previous study reported blood-pool activity was low and unchanged 6 min after injection (*18*). Because the clearance of blood-pool activity was rapid, the spillover activity from the blood pool to the myocardium was considered minimal and was not corrected in this study. Regional Kmono values were computed in the apical and four midventricular segments (midanterior, midlateral, midinferior and midseptal walls), because the data for the basal segments might contain errors caused by extra myocardial activities.

Statistical Analysis

All data are expressed as mean ± s.d. Intra- and intergroup comparisons were made with the paired and unpaired Student's t-test, respectively. The difference was considered to be significant when $p < 0.05$.

RESULTS

Regional Heterogeneity of Clearance Rate Constant

Regional differences of ^{11}C-acetate clearance (Kmono) for five segments were compared in 22 subjects (16 patients, 6

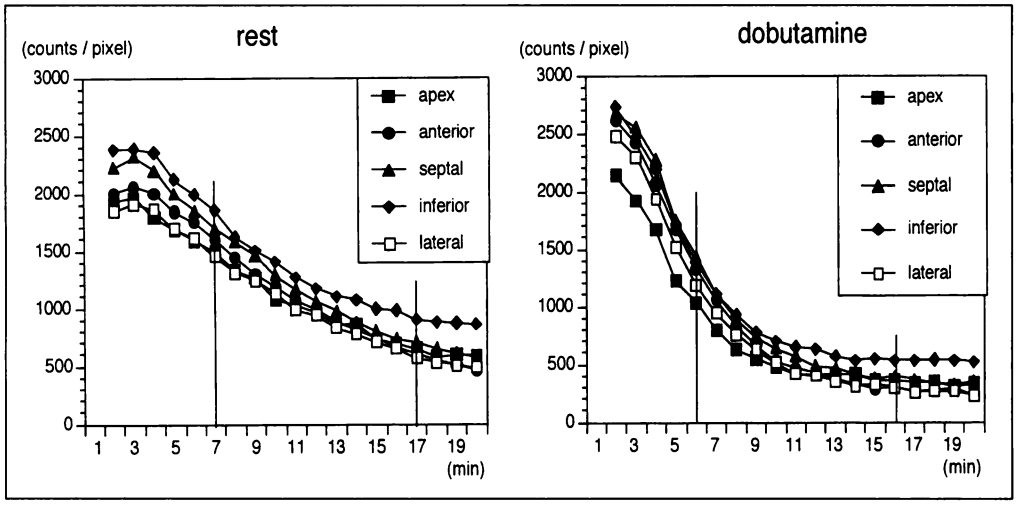

FIGURE 1. Representative time-activity curve of patient with noninsulin-dependent diabetes mellitus. Because peaktune of curve was different in each study, monoexponential curve fitting was performed for different periods of data accordingly (between 6 and 18 min). In this patient, curve fitting was performed for data between 7 and 17 min at rest and between 6 and 16 min during dobutamine stress.

controls) at rest and in 13 subjects (8 patients, 5 controls) during dobutamine stress. Table 2 lists the regional Kmono values. At rest, the clearance of ^{11}C-acetate was more homogeneous for the controls, as indicated by the smaller coefficient of variation (COV). Regionally, both groups showed slightly smaller values in the apex and inferior wall, but there was no significant difference. During dobutamine stress, although overall acetate clearance became slightly more homogeneous in the patients with smaller COV, regional differences became clearer between the inferior and anterior walls. The Kmono value of the inferior wall became significantly smaller than that of the anterior wall in the patients with NIDDM ($p < 0.05$).

Comparison Between Patients and Control Subjects

The values of rate-pressure product (RPP) were almost the same for the two groups at rest, at 9816 ± 4182 in the patients and 8935 ± 1722 in the control subjects (Fig. 2A). The Kmono values were significantly greater for the patients in all five segments ($p < 0.05$) (Table 2). During dobutamine stress, the Kmono value was further elevated in all segments, showing the same trend, although the RPP values were similar for patients (14604 ± 5629) and control subjects (14107 ± 2431, not significant). The RPP-to-Kmono (average for five segments) ratio at rest was slightly smaller in the patients (1292.6 ± 494.8 × 0.01) than in the control subjects (1578.1 ± 494.1 × 0.01, not significant), and those during dobutamine stress were almost the same in the two groups (1457.3 ± 737.4 × 0.01 and 1486.0 ± 211.8 × 0.01, respectively) (Fig. 2B).

For those subjects who underwent low-dose dobutamine testing (8 patients, 5 controls), the correlation between RPP and regional Kmono values was studied in each myocardial segment. A significant positive linear correlation was found in every segment in the control subjects (average Kmono versus RPP: $r = 0.89$, $p < 0.0001$). On the other hand, correlation was scattered in the patients with NIDDM (average Kmono versus RPP: $r = 0.31$, not significant), and there was regional variation of the correlation coefficients, with the smallest value ($r = 0.17$) observed in the inferior wall (Fig. 3).

DISCUSSION

The results revealed regional variation of oxidative metabolism in patients with NIDDM who had apparently healthy hearts. This study also discovered differences in the relationship between regional oxidative metabolism and global cardiac work (RPP) between patients with NIDDM and healthy control subjects.

Regional Variation of Oxidative Metabolism

There is fairly good agreement that even normal human hearts can show regional variations in substrate metabolism. In this study, the inferior wall and apex in control subjects showed slightly (approximately 10%) smaller Kmono values compared with the anterior wall. The difference, by 10%–15%, may be within the range of normal variation, because several previous studies demonstrated variations within the same range; however, slow ^{11}C-acetate clearance was consistently found in the inferior wall and apex in previous studies with three-dimensional analysis, although they did not always reach a significant level (*5,12,19,20*).

The proposed mechanisms for this variation include hetero-

TABLE 2
Clearance Rate Constant

	Patients with NIDDM		Healthy control subjects	
	Rest (n = 16)	Dobutamine (n = 8)	Rest (n = 6)	Dobutamine (n = 5)
Apex	7.17 ± 1.72	10.79 ± 1.83	5.48 ± 1.24	9.61 ± 1.28
Anterior	7.92 ± 1.56	11.26 ± 1.67*	6.00 ± 0.88	9.93 ± 1.20
Septal	7.57 ± 1.49	10.72 ± 1.77	6.11 ± 0.79	9.75 ± 1.15
Inferior	7.01 ± 1.39	9.38 ± 2.04*	5.52 ± 0.77	8.78 ± 1.11
Lateral	7.89 ± 1.60	10.85 ± 1.86	6.01 ± 0.81	9.49 ± 1.20
Mean	7.60 ± 1.39	10.60 ± 1.75	5.82 ± 0.84	9.51 ± 1.04
COV	0.09 ± 0.08	0.08 ± 0.04	0.08 ± 0.04	0.07 ± 0.04

*$p < 0.05$ compared with the anterior segment.
NIDDM = noninsulin-dependent diabetes mellitus; COV = coefficient of variation.
Data are expressed as mean ± s.d. × 0.01.

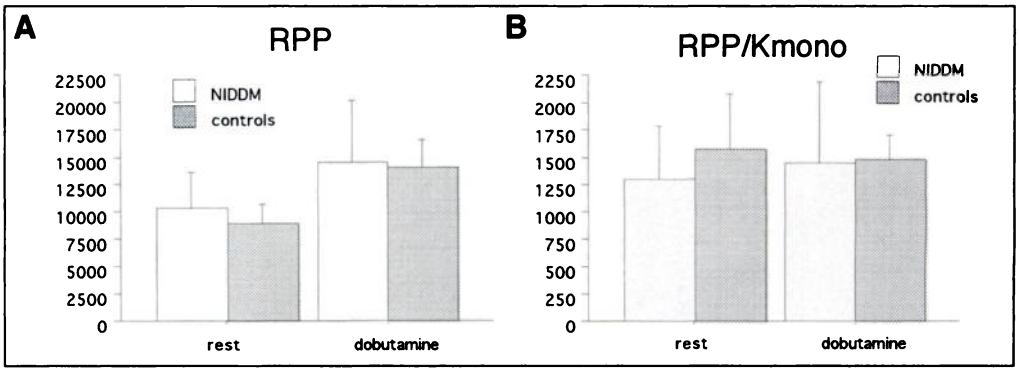

FIGURE 2. (A) Values for rate-pressure product (RPP) were similar for patients with noninsulin-dependent diabetes mellitus and control subjects both at rest (left) and during dobutamine stress (right). (B) RPP-to-Kmono (average for five segments) ratio for control subjects decreased during dobutamine stress, whereas that for patients increased. Ratio for patients was slightly smaller than that for controls at rest, although difference was not significant. The two groups showed similar ratios under dobutamine stress.

geneity in cardiac function, substrate availability and coronary blood flow. Regional heterogeneity in cardiac function was found in healthy human hearts using ultrafast CT or cine MRI, but the variation of the cardiac function was more marked for base-to-apex than for circumferential heterogeneity (*21–23*). Second, regional variation in substrate availability, reported by Hicks et al. (*20*), is considered to be another possible mechanism. They reported that free fatty acid infusion caused a small, but significant, increase in ^{11}C-acetate clearance and a decrease in myocardial glucose metabolism. As Schwaiger and Hicks (*24*) suggested, the lower oxidative consumption may be attributed to the relatively increased use of glucose, which is considered less efficient than using fatty acid as an energy source. This seems to be true particularly for the lateral wall, where oxidative metabolism was increased and glucose metabolism was decreased (*20*). However, they demonstrated that the inferior wall showed a slight decrease in both glucose and fatty acid metabolism. In this study, the reduction of oxidative metabolism in the inferior wall was more clearly observed (13% reduction) in the patients with NIDDM. As suggested in animal (*25*) and human studies (*7*), diabetic hearts may show an impairment of glucose metabolism. If the substrate availability is uniform, then regional reduction of glucose metabolism may result in a regional decrease of oxidative metabolism. Third, regional heterogeneity in coronary blood flow can change oxidative metabolism. Although we excluded diabetic patients with abnormal stress-perfusion studies, there is a possibility of slight regional ischemia that is undetectable with stress-perfusion SPECT. Because of the regional sympathetic denervation, the inferior wall may not permit sufficient increase of coronary blood flow when an increase in oxygen demand is required, which may lead to ischemic myocardial damage and less-active oxidative metabolism under the stress. The sympathetic regulation of coronary blood flow was reported in vivo by Di Carli et al. (*26*) in transplanted human hearts. As various groups, including ours, have reported, both diabetic patients and cardiac transplant recipients share a similar scintigraphic (^{123}I-metaiodobenzylguanidine or ^{11}C-HED) profile with significant regional denervation in the inferior cardiac wall and apex (*10,11,27,28*). In this study, the inferior wall had a small Kmono value that was more obvious during dobutamine stress. The less-marked increase in coronary blood flow in the inferior wall of diabetic patients during sympathetic stimulation may cause ischemic damage, resulting in less-active oxidative metabolism (Kmono) during dobutamine stress.

Several researchers have noted abnormal human cardiac metabolism in the patients with insulin-dependent diabetes mellitus (*5,6*). vom Dahl et al. (*5*) found increased oxidative metabolism in the inferior cardiac wall. Discordant regional heterogeneity is observed in the inferior wall in patients with insulin-dependent diabetes mellitus and in those with NIDDM. Currently, there is no clear explanation for the differences in oxidative metabolism between the two conditions. Further studies on the substrate metabolism of the heart in NIDDM patients should be done to clarify the metabolic differences in these two types of diabetes.

Increased Oxidative Metabolism in Patients with NIDDM

This study demonstrated significantly greater Kmono values at rest in all segments in patients with NIDDM as opposed to control subjects, suggesting global augmentation of the oxidative metabolism in these patients. A possible mechanism for this is the relatively higher free fatty acid (FFA) use in NIDDM hearts. Hall et al. (*29*) reported that pyruvate dehydrogenase activity was impaired in diabetic hearts. Reduction of this enzyme activity prevents decarboxylation of pyruvate to acetyl coenzyme A and may lead to an increase in the proportion of FFA metabolism by inhibiting the rate of glucose and lactate oxidation. Because oxidation of FFA produces adenosine triphosphate more efficiently than glucose, an apparent increase of oxidative metabolism may be observed. Considering that the values of RPP, an index of cardiac workload, were similar for the two groups, the greater oxygen consumption suggests lower cardiac efficiency in the patients with NIDDM. Because we did not perform echocardiography during the dobutamine stress test, we assessed cardiac efficiency by the simple ratio (RPP-to-Kmono) rather than using a work-metabolic index (*30*). The ratio we used did not incorporate the data for stroke volume, which may change during dobutamine stress testing; therefore, the increase or decrease of the ratio was considered to be less sensitive than that of work-metabolic index. Vanoverschelde et al. (*31*) reported that normal human hearts showed a decrease in cardiac efficiency of approximately 25% under dobutamine stress. Although the decrease in this study was smaller (5.8%), the data for the control subjects might support this finding.

These data also suggest an increase in cardiac efficiency under dobutamine stress for the patients with NIDDM. This increase in efficiency was also reported in a heterogeneous group of patients with ischemic and nonischemic cardiomyopathy (*32*) and in patients with dilated cardiomyopathy (*30*). There is no established explanation for the increase in efficiency under pathological conditions such as nonischemic cardiomyopathy and diabetes. However, several researchers proposed that the inotropic effects of dobutamine might lead to improvement of contractile function and reduction of wall stress, resulting in a decrease in oxygen consumption (*33*). Because the patients with NIDDM had normal cardiac function, their systolic function (ejection fraction) was already high. Therefore, the inotropic effects of dobutamine would be minimal, resulting in the mild increase (13%) of the RPP-to-Kmono ratio. The other explanation for this phenomenon is a change in substrate metabolism during dobutamine stress. According to

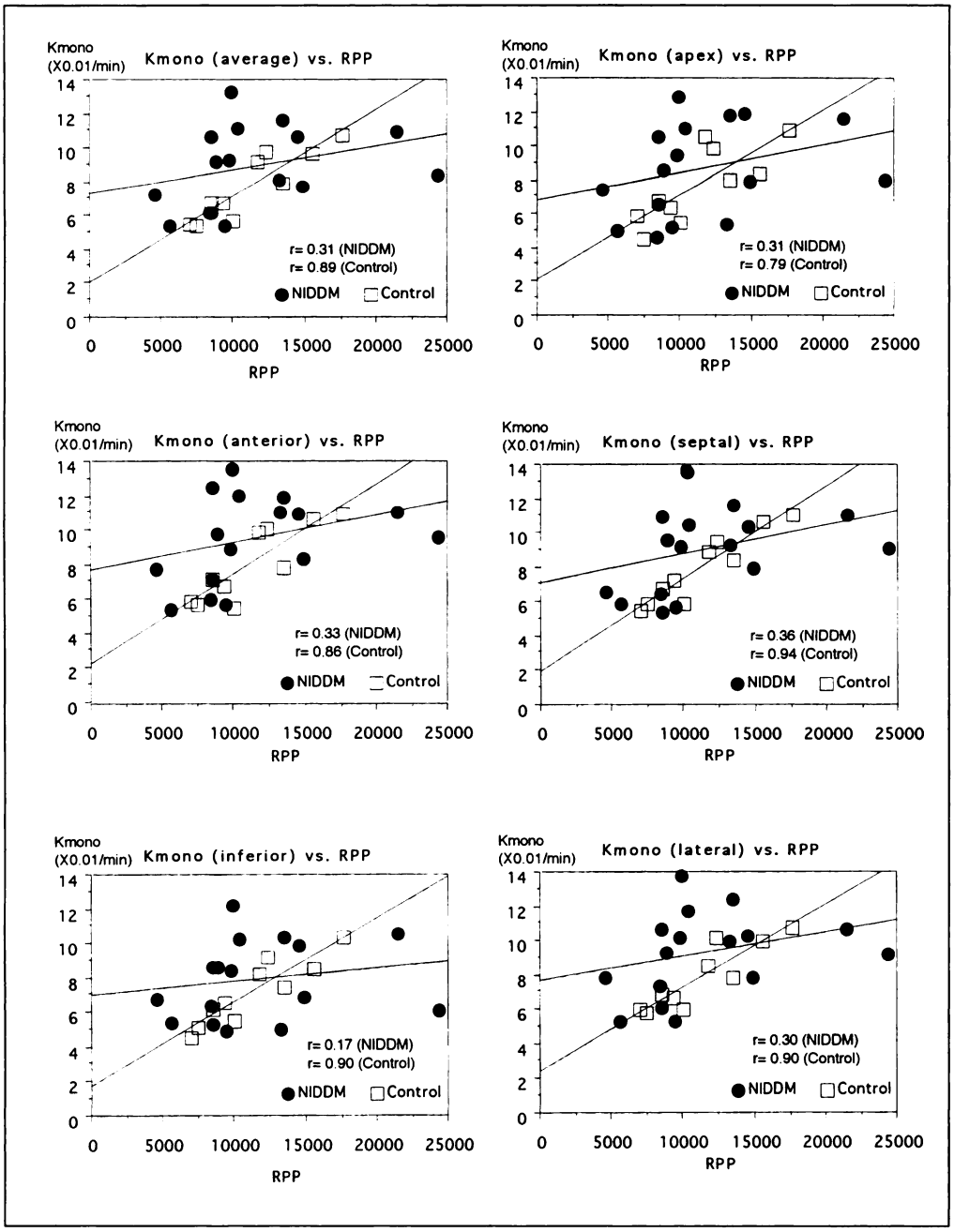

FIGURE 3. Rate-pressure product (RPP) is plotted against regional Kmono value. Data for control subjects showed significant positive linear correlation in each myocardial segment (average Kmono versus RPP: $r = 0.89$, $p < 0.0001$). Correlation was scattered in patients with noninsulin-dependent diabetes mellitus (average Kmono versus RPP: $r = 0.31$, not significant), and there was regional variation of correlation coefficients with smallest value, $r = 0.17$, observed in inferior wall.

the animal experiments conducted by Hall et al. (*29*), dobutamine stress induced a significant increase in glucose uptake and only a slight increase in FFA uptake for both diabetic and control groups. However, lactate uptake was significantly reduced in diabetic groups at rest, and the difference was much clearer during dobutamine stress because the stress increased lactate uptake in the control group but not in the diabetic group (*29*). We consider the reason of greater increase in RPP-to-Kmono ratio for diabetic hearts was the result of a smaller increase in Kmono during dobutamine stress, which was caused by the loss of ability to increase lactate metabolism during dobutamine stress.

The alteration of inotropic effects by dobutamine may be caused by up-regulation of postsynaptic beta-adrenoceptors. Using radiolabeled ligands of beta-receptor CGP-12177, Valette et al. (*34*) demonstrated postsynaptic up-regulation of adrenoceptors after chemical and mechanical denervation in a canine model. As reported previously (*11*), in NIDDM, regional sympathetic denervation occurs in the human heart. If up-regulation also occurs, the alteration of cardiac efficiency may appear in such hearts. The absence of a correlation between RPP and Kmono in this study suggests significant variation in the inotropic effects of dobutamine stress. In this study, we considered the patients with NIDDM as a group, but different stages of NIDDM may manifest different inotropic effects. Further studies should be done to clarify the relationship of the alteration of cardiac efficiency to the severity of sympathetic denervation.

Clinical Implications

This study has several clinical implications. Changes in cardiac oxidative metabolism and its response to dobutamine may be critical when the patient is in cardiac crisis. Dobutamine should be used carefully for patients with NIDDM, because it may cause unexpected inotropic effects. Second, the viability of infarcted myocardium should be carefully assessed by low-dose dobutamine test with ^{11}C-acetate for patients with NIDDM,

because apparent increase of Kmono may not always be accompanied by a real increase in oxidative metabolism (*35*).

CONCLUSION

Patients with NIDDM showed slight regional heterogeneity in myocardial oxidative metabolism. They also showed more scattered correlation between myocardial oxidative metabolism and cardiac work (RPP) than control subjects, with the smallest correlation coefficient observed in the inferior wall. These findings may help the understanding of dynamics in myocardial oxidative metabolism of NIDDM hearts.

REFERENCES

1. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication, and risk of cardiovascular events. The Framingham Study. *Diabetes* 1989;38:504–509.
2. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole thallium scintigraphy for evaluation of ischemic heart disease. *J Am Coll Cardiol* 1990;15: 109–116.
3. Orlander PR, Goff DC, Morrissey M, et al. The relation of diabetes to the severity of acute myocardial infarction and post-myocardial infarction survival in Mexican-Americans and non-Hispanic whites. The Corpus Christi Heart Project. *Diabetes* 1994;43:897–902.
4. Dayanikli F, Grambow D, Muzik O, Mosca L, Rubenfire M, Schwaiger M. Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography. *Circulation* 1994;90: 808–817.
5. vom Dahl J, Herman WH, Hicks RJ, et al. Myocardial glucose uptake in patients with insulin-dependent diabetes mellitus assessed quantitatively by dynamic positron emission tomography. *Circulation* 1993;88:395–404.
6. Monti LD, Lucignani G, Landoni C, et al. Myocardial glucose uptake evaluated by positron emission tomography and fluorodeoxyglucose during hyperglycemic clamp in IDDM patients. Role of free fatty acid and insulin levels. *Diabetes* 1995;44:537–542.
7. Ohtake T, Yokoyama I, Watanabe T, et al. Myocardial glucose metabolism in noninsulin-dependent diabetes mellitus patients evaluated by FDG-PET. *J Nucl Med* 1995;36:456–463.
8. Miller TR, Wallis JW, Landy BR, Gropler RJ, Sabharwal CL. Measurement of global and regional left ventricular function by cardiac PET. *J Nucl Med* 1994;35:999–1005.
9. Kreiner G, Wolzt M, Fasching P, et al. Myocardial m-[^{123}I]iodobenzylguanidine scintigraphy for the assessment of adrenergic cardiac innervation in patients with IDDM. Comparison with cardiovascular reflex tests and relationship to left ventricular function. *Diabetes* 1995;44:543–549.
10. Allman KC, Stevens MJ, Wieland DM, et al. Noninvasive assessment of cardiac diabetic neuropathy by carbon-11 hydroxyephedrine and positron emission tomography. *J Am Coll Cardiol* 1993;22:1425–1432.
11. Hattori N, Tamaki N, Hayashi T, et al. Regional abnormality of iodine-123-MIBG in diabetic hearts. *J Nucl Med* 1996;37:1985–1990.
12. Kotzerke J, Hicks RJ, Wolfe E, et al. Three-dimensional assessment of myocardial oxidative metabolism: a new approach for regional determination of PET-derived carbon-11-acetate kinetics. *J Nucl Med* 1990;31:1876–1883.
13. Miller TR, Wallis JW, Geltman EM, Bergmann SR. Three-dimensional functional images of myocardial oxygen consumption from positron tomography. *J Nucl Med* 1990;31:2064–2068.
14. Yano S, Tamaki N, Fujita T, et al. Motion correction in exercise first-pass radionuclide ventriculography without an external point source. *J Nucl Med* 1995;36:1941–1944.
15. Brown MA, Myears DW, Bergmann SR. Validity of estimates of myocardial oxidative metabolism with carbon-11 acetate and positron emission tomography despite altered patterns of substrate utilization. *J Nucl Med* 1989;30:187–193.
16. Henes CG, Bergmann SR, Walsh MN, Sobel BE, Geltman EM. Assessment of myocardial oxidative metabolic reserve with positron emission tomography and carbon-11 acetate. *J Nucl Med* 1989;30:1489–1499.
17. Walsh MN, Geltman EM, Brown MA, et al. Noninvasive estimation of regional myocardial oxygen consumption by positron emission tomography with carbon-11 acetate in patients with myocardial infarction. *J Nucl Med* 1989;30:1798–1808.
18. Tamaki N, Magata Y, Takahashi N, et al. Oxidative metabolism in the myocardium in normal subjects during dobutamine infusion. *Eur J Nucl Med* 1993;20:231–237.
19. Gropler RJ, Siegel BA, Lee KJ, et al. Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. *J Nucl Med* 1990;31:1749–1756.
20. Hicks RJ, Herman WH, Kalff V, et al. Quantitative evaluation of regional substrate metabolism in the human heart by positron emission tomography. *J Am Coll Cardiol* 1991;18:101–111.
21. Rumberger JA, Feiring AJ, Lipton MJ, Higgins CB, Ell SR, Marcus ML. Use of ultrafast computed tomography to quantitate regional myocardial perfusion: a preliminary report. *J Am Coll Cardiol* 1987;9:59–69.
22. Pflugfelder PW, Sechtem UP, White RD, Higgins CB. Quantification of regional myocardial function by rapid cine MR imaging. *AJR* 1988;150:523–529.
23. Feiring AJ, Rumberger JA, Reiter SJ, et al. Sectional and segmental variability of left ventricular function: experimental and clinical studies using ultrafast computed tomography. *J Am Coll Cardiol* 1988;12:415–425.
24. Schwaiger M, Hicks R. Regional heterogeneity of cardiac substrate metabolism? *J Nucl Med* 1990;31:1757–1760.
25. Almira EC, Garcia AR, Boshell BR. Insulin binding and glucose transport activity in cardiomyocytes of a diabetic rat. *Am J Physiol* 1986;250:E402–E406.
26. Di Carli MF, Tobes MC, Mangner T, et al. Effects of cardiac sympathetic innervation on coronary blood flow. *N Engl J Med* 1997;336:1208–1215.
27. Schwaiger M, Hutchins G, Kalff V, Rosenspire K, Haka M, Mallette S. Evidence for regional catecholamine uptake and storage sites in the transplanted human heart by positron emission tomography. *J Clin Invest* 1991;87:1681–1690.
28. De Marco T, Dae M, Yuen-Green MS, et al. Iodine-123 metaiodobenzylguanidine scintigraphic assessment of the transplanted human heart: evidence for late reinnervation. *J Am Coll Cardiol* 1995;25:927–931.
29. Hall JL, Stanley WC, Lopaschuk GD, et al. Impaired pyruvate oxidation but normal glucose uptake in diabetic pig heart during dobutamine-induced work. *Am J Physiol* 1996;271:H2320–H2329.
30. Beanlands RS, Bach DS, Raylman R, et al. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1993;22:1389–1398.
31. Vanoverschelde JL, Wijns W, Essamri B, et al. Hemodynamic and mechanical determinants of myocardial O_2 consumption in normal human heart: effects of dobutamine. *Am J Physiol* 1993;265:H1884–H1892.
32. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73:III168–III174.
33. Sundram P, Reddy HK, McElroy PA, Janicki JS, Weber KT. Myocardial energetics and efficiency in patients with idiopathic cardiomyopathy: response to dobutamine and amrinone. *Am Heart J* 1990;119:891–898.
34. Valette H, Deleuze P, Syrota A, et al. Canine myocardial beta-adrenergic, muscarinic receptor densities after denervation: a PET study. *J Nucl Med* 1995;36:140–146.
35. Hata T, Nohara R, Fujita M, et al. Noninvasive assessment of myocardial viability by positron emission tomography with ^{11}C acetate in patients with old myocardial infarction. Usefulness of low-dose dobutamine infusion. *Circulation* 1996;94:1834–1841.