Impaired Chronotropic Response to Exercise in Acute Myocardial Infarction Patients with Type 2 Diabetes Mellitus

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SUMMARY

This study was undertaken in acute myocardial infarction (AMI) patients with non-insulin-dependent diabetes mellitus (type 2 DM) to investigate their impaired chronotropic response to exercise. Seventy-one AMI subjects entered the study, 30 with type 2 DM and 41 age- and body mass index-matched non-DM (control) patients. One month after the onset of AMI, these patients underwent cardiopulmonary exercise testing on a treadmill under a ramp protocol. Anaerobic threshold (AT) and peak oxygen uptake (peak VO2) were determined as indicators of exercise capacity. Plasma norepinephrine (NE) concentration was measured in blood samples obtained at 2 time points: during pre-exercise rest and immediately after peak exercise. The change in NE concentration during exercise, as an index of sympathetic nervous activity, was calculated as a percentage: \[ \Delta NE = \frac{(NE \text{ during exercise}) - (resting value)}{(resting value)} \times 100. \] The change in heart rate (HR) during exercise was calculated as a simple difference: \[ \Delta HR = (\text{peak HR}) - (rest HR). \] Index of chronotropic response to exercise was then quantified as the \[ \frac{\Delta HR}{\Delta NE}. \] No significant intergroup differences in ejection fraction at rest or HR at peak exercise were observed. However, VO2 at AT, peak VO2, \( \Delta HR \), and \( \Delta HR/\Delta NE \) were significantly lower in the type 2 DM group than in the non-DM group. \( \Delta HR \) correlated with VO2 at AT \( (r = 0.49, P < 0.001) \) and with peak VO2 \( (r = 0.53, P < 0.001) \) in all subjects. Also, \( \Delta HR/\Delta NE \) correlated with VO2 at AT \( (r = 0.42, P < 0.001) \) and with peak VO2 \( (r = 0.44, P < 0.001) \) in all subjects. AMI patients with type 2 DM had impaired cardiopulmonary responses to maximal and submaximal exercise testing and impaired chronotropic response to exercise, even though their cardiac function at rest was similar to that of non-DM AMI patients. The data suggest that one mechanism of impaired cardiopulmo-
nary response to exercise in AMI patients with type 2 DM groups is an impaired chronotropic response. (Jpn Heart J 2003; 44: 187-199)

**Key words:** Diabetes mellitus, Myocardial infarction, Exercise capacity, Chronotropic response

**Non-insulin-dependent** diabetes mellitus (type 2 DM) is associated with increased morbidity and mortality due to atherosclerotic and microvascular diseases.1) Acute myocardial infarction (AMI) in patients with diabetes carries with it a high risk of mortality.2-3) Although the prevalence of diabetes is estimated to be lower in Japan than in Western countries,4) epidemiological surveys have shown that diabetes among Japanese has been increasing quite rapidly in recent years.4) This is probably due to increased fat intake in the Japanese diet and a lack of exercise, a conception supported by a concomitant increase in the prevalence of obesity and hyperlipidemia in Japan.5-6) In persons with diabetes, there are several pathological factors that can be involved in decreased exercise capacity. Regensteiner, et al 7) observed that both male and female type 2 DM patients, in the absence of known complications, have reduced exercise capacity compared with age- and activity-matched normal subjects. Other researchers have reported that reduced cardiac output during exercise is found in patients with type 2 DM.8) Less well understood are the abnormal cardiovascular responses to exercise that are caused by cardiac autonomic nervous system dysfunction in type 2 DM patients.8-9)

In a previous study, patients with type 2 DM who had had an AMI showed impaired cardiopulmonary responses to maximal and submaximal exercise testing, even when their cardiac function at rest was similar to that of non-diabetes mellitus (DM) patients with AMI.10) The mechanism for this difference was not clarified. It has been suggested that impaired myocardial function and impaired oxygen transport in persons with type 2 DM may play a critical role in the abnormal exercise performance observed in these individuals.7)

In patients with congestive heart failure (CHF), the chronotropic response to peak exercise is reduced, and this reduction may play some part in the impaired cardiac output response during exercise.11)

Another previous report suggested that the ratio between the incremental changes in heart rate (HR) and norepinephrine (NE) concentrations during exercise, an indirect index of sino-atrial node sympathetic responsiveness, is markedly reduced in CHF patients and that this ratio inversely correlates with the severity of exercise impairment.12)

We hypothesized that patients with type 2 DM who have had an AMI would
have reproducible impairment in peak exercise performance in comparison to that of age-matched non-DM AMI patients, and we investigated whether such impairment is associated with a chronotropic response. Therefore, in this study, we investigated the chronotropic response via assessment of NE concentration changes as an index of sympathetic nervous activity.

**SUBJECTS AND METHODS**

The study subjects were selected from among 49 consecutive DM patients who were admitted to St. Marianna University School of Medicine Hospital for evaluation of AMI between November 1998 and March 2000. The study subjects were scheduled for cardiopulmonary exercise testing at 1 month after the onset of AMI. The diagnosis of AMI was made on the basis of chest pain persisting for at least 30 minutes, ST-segment elevation of at least 0.1 mV in at least 2 contiguous leads, and serum creatine kinase-myocardial band (CK-MB) elevation to more than twice the upper limit of normal. Patients were considered to have type 2 DM if they were already receiving oral hypoglycemic therapy or dietary treatment for type 2 DM or if, after admission, an oral glucose tolerance test was positive for the disease according to the World Health Organization criteria. Patients with type 2 DM that was controlled with insulin were included in this study.13-14)

Of the 49 type 2 DM patients, 30 who completed the exercise testing and a routine 4-week AMI cardiac rehabilitation program were included in this study. The remaining 19 patients failed to complete the test because of cerebrovascular disease, an orthopedic disorder, ST segment changes, or chest pain during exercise and were therefore excluded from the study. The patients with type 2 DM had been first diagnosed with the disease an average of 8.54 ± 8.24 years earlier. Forty-one non-DM patients with AMI who matched the 30 study patients with respect to age, height, and CK-MB level and who had completed the same exercise test during the same period were selected retrospectively as control subjects from among 71 potential control subjects.

All 71 subjects completed the routine 4-week AMI cardiac rehabilitation program while hospitalized. Patients with severe heart failure, angina pectoris, ischemic ST segment changes, uncontrolled arrhythmia, atrial fibrillation, valvular heart disease, treatment with beta-blockers, or left bundle branch block were excluded. Those having had coronary artery bypass surgery or who were above 75 years of age were also excluded. Prescribed cardiac medications were continued on the day of the exercise test.

**Ethical considerations:** The study was approved by the St. Marianna University School of Medicine institutional committee on human research. Informed consent was obtained from each patient at 1 month after the onset of AMI.
Study protocol: Subjects underwent cardiopulmonary exercise testing under a ramp treadmill protocol\(^{15}\) 1 month after the onset of AMI. Anaerobic threshold (AT), peak oxygen uptake (\(\dot{V}O_2\)), and peak exercise time were measured. Expired gas analysis was used as an index of cardiovascular dynamics during exercise.

Exercise test: Symptom-limited exercise testing was undertaken with a MAT-2500 treadmill (Fukuda Denshi Co., Tokyo). Patients rested for 3 minutes on the treadmill. Exercise began with a 3-minute warm-up (speed, 1.0 mph; grade, 0%) which was followed by an increase (speed or grade) in the load every 60 seconds. Throughout the test, a 12-lead electrocardiogram (ECG) was continuously monitored, and heart rate (HR) was measured from the R-R interval of the ECG (ML-5000, Fukuda Denshi Co.,). Systolic blood pressure was measured by the cuff method via an automatic blood pressure monitor (stress test system, STBP-780, Colin Co., Aichi, Japan) at 1-minute intervals. \(\dot{V}O_2\), carbon dioxide production (\(\dot{V}CO_2\)), minute ventilation (\(\dot{V}E\)), tidal volume (TV), end tidal CO\(_2\) (ETCO\(_2\)), and the ventilatory equivalent for CO\(_2\) (\(\dot{V}E/\dot{V}CO_2\)) were measured throughout the exercise period with an RM-300 respirometer and a MG-360 gas analyzer (Minato Ikagaku Co., Tokyo). The measurement system for cardiopulmonary exercise testing was carefully calibrated before the start of each individual test. Expired gas was sampled using a breath-by-breath method. The endpoint of exercise testing was determined.\(^{16}\) The appearance of a leveling-off of \(\dot{V}O_2\) (\(\dot{V}O_2\) plateau despite increasing exercise intensity) assisted in determination of the exercise endpoint.

Parameters evaluated: Ventilatory equivalents were calculated for O\(_2\) (\(\dot{V}E/\dot{V}O_2\)), and CO\(_2\) (\(\dot{V}E/\dot{V}CO_2\)), and the gas exchange ratio (GER) (\(\dot{V}CO_2/\dot{V}O_2\)) on a personal computer (Model PC-9801, NEC Co., Tokyo). AT was determined by the original V-slope method\(^{17}\) as well as conventionally by determining when \(\dot{V}E/\dot{V}O_2\) increases after holding constant or decreases while \(\dot{V}E/\dot{V}CO_2\) remains constant or decreases, and by determining the period at which GER starts to increase steeply.\(^{18}\)

Cardiac catheterization: At 1 month after the onset of AMI, left ventriculography and selective coronary angiography were performed in all subjects according to the Judkins technique. Ejection fraction was calculated via biplane left ventriculography. The luminal diameter of the coronary artery was measured by comparing the average diameter loss with the nearest proximal normal segment.

Blood sampling: Blood samples for measurement of NE were obtained from a catheter inserted into an antecubital vein at 2 time points: during pre-exercise resting and immediately after peak exercise. The sampled blood was immediately ice-cooled and centrifuged for 10 minutes at 4°C and 3000 rpm, thereby separating the plasma, which was maintained in frozen storage at -70°C until the day of analysis. NE was extracted by absorption on an activated alumina microcolumn.
and then quantitated by high pressure liquid chromatography. The change in NE concentration during exercise was calculated as a percentage: \[ \Delta \text{NE} = \frac{\text{(NE during exercise)} - \text{(resting value)}}{\text{resting value}} \times 100. \]

**Sympathetic nervous activity:** Sympathetic nervous activity was then quantified as a ratio representing the relation between HR and NE during exercise. The change in HR during exercise was calculated as: \[ \Delta \text{HR} = |\text{(peak HR)} - \text{(rest HR)}|. \]

The change in the HR to NE ratio during exercise was calculated as: \[ \Delta \text{HR/}\Delta \text{NE} \times 10^2. \]

**Statistical analysis:** All data are expressed as the mean ± SD. The patient characteristics and results were compared using an unpaired t-test for parametric factors and \( \chi^2 \) test for nonparametric factors. Regression analysis (least-squares linear estimation) was used to determine the correlations between \( \Delta \text{HR} \) and \( \dot{\text{VO}}_2 \) at AT, peak \( \dot{\text{VO}}_2 \), and between \( \Delta \text{HR/}\Delta \text{NE} \) and \( \dot{\text{VO}}_2 \) at AT, peak \( \dot{\text{VO}}_2 \). Statistical analyses were performed with an SPSS 9.0J statistical software program (SPSS Japan, Inc.), and a \( P \) value of < 0.05 was considered significant.

**RESULTS**

**Clinical characteristics of the two groups:** We evaluated several patient characteristics, including age, height, weight, treatment in the acute phase of AMI, number of diseased coronary arterial vessels, CK-MB, and dosages of medications (Table I). The mean age, height, weight, and body mass index (BMI) of the subjects were almost identical between the two groups. During the acute phase of AMI, direct percutaneous transluminal coronary angioplasty (PTCA) was performed in 61 patients, and intracoronary thrombolysis (ICT) was performed in 10. Other patients were treated conservatively during the acute phase of AMI. The oral dosages of drugs did not differ statistically between the two groups. The ejection fraction 1 month after the onset of AMI did not differ significantly in the type 2 DM group (47.7 ± 10.2%) and the non-DM group (48.6 ± 8.3%). The difference between left ventricular end-diastolic volume index between the groups 1 month after onset of AMI was also insignificant: 81.9 ± 20.7 mL/m\(^2\) in the type 2 DM group and 82.6 ± 19.8 mL/m\(^2\) in the non-DM group. The percentages of patients treated with various drugs did not differ significantly between the two groups. Before PTCA or ICT, triple-vessel coronary artery stenosis was found significantly more often (\( P < 0.05 \)) in the DM patients than in the non-DM patients, whereas single-vessel disease was found significantly more often in the non-DM patients than in the DM patients (\( P < 0.05 \)). After PTCA or ICT, all differences between the groups were insignificant.

**Exercise tolerance and HR response during exercise:** The endpoint of the exercise test for both groups was leg fatigue, shortness of breath, and GER ≥ 1.20. No
patient showed ischemic ST changes or experienced chest pain during exercise testing. The change in VO\textsubscript{2} at AT and at the peak exercise differed between the two groups: VO\textsubscript{2} at AT was significantly lower in the type 2 DM group than in the non-DM group (14.6 ± 2.7 vs 16.8 ± 2.1 mL/min/kg, \(P < 0.01\), Table II). VO\textsubscript{2} at peak exercise was also significantly lower in the DM group than in the non-DM group (22.6 ± 4.5 vs 26.1 ± 3.4 mL/min/kg, \(P < 0.01\)). HR at rest tended to be

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<th>Table I. Clinical Factors in the Two Study Groups</th>
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DM = diabetes mellitus; BMI = body mass index; CK-MB = creatine kinase-MB; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; ACE = angiotensin converting enzyme inhibitors; OHA = oral hypoglycemic agent; VD = vessel disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; ICT = intracoronary thrombolysis; LVEF was measured in 30 patients with DM and in 40 patients with non-DM. *\(P < 0.05\).
higher in the DM group than in the non-DM group, but the difference was not significant (75.3 ± 13.2 vs 70.9 ± 11.1 beats/min, NS). HR at peak did not differ significantly between the type 2 DM group and the non-DM group (135.6 ± 16.7 vs 143.0 ± 16.2 beats/min, NS). Intergroup differences in systolic blood pressure at rest and during exercise were insignificant.

$\Delta$HR was significantly lower in the DM group than in the non-DM group (58.5 ± 14.1 vs 73.5 ± 13.7 beats, $P < 0.01$, Figure 1). $\Delta$HR/$\Delta$NE was also significantly lower in the DM group than in the non-DM group (10.2 ± 4.9 vs 13.1 ± 4.2 beats/%, $P < 0.01$, Figure 2). When the values of $\Delta$HR in relation to $\dot{V}O_2$ at AT and to peak $\dot{V}O_2$ for all subjects were plotted (Figure 3), significant positive correlations between $\Delta$HR and AT ($r = 0.49$, $P < 0.001$) and peak $\dot{V}O_2$ ($r = 0.53$, $P < 0.001$) were observed. When the values of $\Delta$HR/$\Delta$NE in relation to $\dot{V}O_2$ at AT and to peak $\dot{V}O_2$ for all subjects were plotted (Figure 4), significant positive correlations between $\Delta$HR/$\Delta$NE and AT ($r = 0.42$, $P < 0.001$) and peak $\dot{V}O_2$ ($r = 0.44$, $P < 0.001$) were also observed.
Figure 1. ∆HR values (mean±SD) 1 month after the onset of AMI. ∆HR was significantly lower in the type 2 DM group than in the non-DM group. AMI = acute myocardial infarction; HR = heart rate.

Figure 2. ∆HR/∆NE values (mean±SD) 1 month after the onset of AMI. ∆HR/∆NE was significantly lower in the type 2 DM group than in the non-DM group. AMI = acute myocardial infarction; HR = heart rate; NE = norepinephrine.

Figure 3. Correlations between ∆HR and VO₂ at AT and ∆HR and peak VO₂ in all patients combined. A positive correlation was observed between ∆HR and VO₂ at AT, and at peak VO₂. VO₂ = oxygen uptake; HR = heart rate; NE = norepinephrine; AT = anaerobic threshold.
DISCUSSION

Since the number of AMI patients with DM has increased remarkably in Japan over the past decade,5) we undertook an exercise physiology study to determine an appropriate cardiac rehabilitation protocol for such patients. The immediate goal of the study was to examine the relationship between the autonomic nervous system and HR responses during exercise in AMI patients with type 2 DM. We found that peak VO$_2$ and AT in patients with type 2 DM were lower than those of non-DM patients, even though they had similar indices of cardiac function during the resting state (Table II). There are potential causes for the reduced exercise capacity among diabetics with sensorineural and autonomic dysfunction.19) In the present study, $\Delta$HR were significantly lower in our type 2 DM group than in our non-DM group. Also, when both groups were considered together, we found a significant positive correlation between $\Delta$HR and AT and between $\Delta$HR and peak VO$_2$. Impaired HR response to exercise has been regarded as chronotropic incompetence.20) Chronotropic incompetence, defined as an inadequate HR increase to a given level of exercise, has been considered as a marker for the presence of coronary artery disease.21) It seems likely that an impaired HR response is closely related to the impaired cardiac performance even in the type 2 DM patients.

Diabetes mellitus may be associated with the development of 1) macroscopic and microscopic coronary artery disease, 2) increased myocardial interstitial connective tissue accumulation, and 3) left ventricular contractile dysfunction.19,22) A lower ejection fraction in response to exercise concomitant with a normal resting ejection fraction has also been shown in other studies, and
this finding suggests that the contractile reserve is decreased in symptomatic patients. However, no patient revealed ischemic ST change or experienced chest pain during exercise testing in the present study as a cause of their reduced exercise capacity. Previous research has also shown that ejection fraction after myocardial infarction was lower in diabetic patients than in nondiabetic patients. However, our current data showed no difference between the DM and non-DM patients with regard to resting LVEF at 1 month after the onset of AMI, which suggests that cardiac function at rest is similar in DM and non-DM patients after AMI. According to an earlier report in patients with type 2 DM, substantial correction in the metabolic control of diabetes has been found to be associated with a significant improvement in left ventricular systolic function at rest. In another study that evaluated the effects of hyperglycemia on exercise performance, no association was found between hemoglobin A1c and exercise performance. With regard to the relation between DM control and exercise capacity, there is no agreement. The debate is related to differences in the degree of glycemic control. We also reported previously that impaired exercise performance in DM patients was not associated with the degree of glycemic control when it is not severe. Therefore, it seems likely that the blood glucose level is closely related to the reduced peak VO₂ and submaximal VO₂ in DM patients. Previously published findings support the observation that cardiac parasympathetic nervous activity may be related to the poor cardiac output response to exercise in patients with type 2 DM. Roy et al reported that poor cardiac response to exercise in diabetes patients resulted from a decrease in cardiac parasympathetic nervous activity and could be predicted by abnormal R-R variation. R-R variation data was not obtained in the present study. In another study and in the present study, HR at rest tended to be higher in the DM group than in the non-DM group. The relation between cardiac parasympathetic nervous activity and exercise performance needs further study. Kremser et al have suggested that the abnormalities in exercise performance observed in type 1 DM patients may be attributed to abnormalities of the cardiovascular autonomic nervous system. Diabetic neuropathy clearly affects the cardiovascular response to submaximal exercise, evidenced by an abnormal heart rate response.

Although there is ample evidence that resting sympathetic nervous activity is increased in patients with CHF, there is relatively little information available regarding the relation between systemic sympathetic nervous activity and HR response during exercise in patients with DM complicated AMI. Collucci et al reported that another possibility for the attenuated chronotropic response to exercise is end-organ desensitization of the β-adrenergic pathway in the sinoatrial node. HR response during exercise at any given NE level was found to be low in CHF patients; more importantly, the increase in HR for any given increase in NE
was markedly reduced.\textsuperscript{12} In the present study, $\Delta HR/\Delta NE$ as an index for chronotropic response was significantly lower in our type 2 DM group than in our non-DM group. In addition, we found a significant positive correlation between $\Delta HR/\Delta NE$ and AT and between $\Delta HR/\Delta NE$ and peak $\dot{VO}_2$. To the best of our knowledge, there are no publications describing the relation between $\Delta HR/\Delta NE$ and exercise tolerance. Our data are consistent with observations of an HR response relative to NE during exercise, and may support the hypothesis that the $\beta$-adrenergic pathway\textsuperscript{12} contributes to attenuated chronotropic responsiveness in AMI patients with type 2 DM.

During the acute phase of AMI, various pathophysiological changes increase the contractility of the myocardium at the noninfarcted zone.\textsuperscript{29} However, this response is impaired among diabetic patients and may be related to endothelial, microcirculation and diabetic cardiomyopathy, multivessel disease.\textsuperscript{29} These responses might be responsible for decreased exercise capacity in patients with AMI complicated by type 2 DM.

Recently, Yu, \textit{et al}\textsuperscript{30} reported that diabetic patients with coronary heart disease without previous MI had a mortality nearly 5 times higher than that of non-diabetic patients with MI. For patients with coronary artery disease able to perform exercise until exhaustion, the all-cause and cardiovascular mortality decreased with increasing peak $\dot{VO}_2$.\textsuperscript{31} Endo, \textit{et al}\textsuperscript{32} reported that chronotropic incompetence and the plasma catecholamine response to exercise are associated with a high risk of cardiac-cerebrovascular events in patients with type 2 diabetes. The influence of exercise training on the HR response relative to NE, or on the mortality in AMI patients with type 2 DM cannot be ascertained until further studies have been carried out. Exercise training for AMI patients with type 2 DM might improve not only exercise capacity, but also their health-related quality of life.

\textbf{Conclusion:} Patients with type 2 DM during recovery from AMI had impaired $\dot{VO}_2$ and cardiopulmonary responses to maximal and submaximal exercise tests compared with nondiabetic patients, even though cardiac function at rest was similar between the two groups. One mechanism of this impairment might be an impaired chronotropic response to exercise in AMI patients with type 2 DM.

\textbf{Study limitations:} The present study comprised a small sample and we examined changes in the HR response relative to sympathetic nervous activity during exercise. In the present study, indicators of parasympathetic nervous system activity such as the coefficient of variation of the R-R interval in the ECGs were not determined. Therefore, further studies are needed to investigate the interaction between the parasympathetic nervous system and HR response or exercise capacity in AMI patients with type 2 DM.
REFERENCES