Influence of Autonomic Nervous Dysfunction Characterizing Effect of Diabetes Mellitus on Heart Rate Response and Exercise Capacity in Patients Undergoing Cardiac Rehabilitation for Acute Myocardial Infarction

Yusuke Kasahara, MS*,††; Kazuhiro Izawa, PhD**; Kazuto Omiya, MD†; Naohiko Osada, MD†; Satoshi Watanabe, BS**; Masakazu Saitoh, MS††; Atsuhiko Matsunaga, PhD‡; Takashi Masuda, MD‡

Background The aim of this study was to clarify the influence of sympathetic and parasympathetic nerve (SN and PN) dysfunction on the heart rate (HR) response to exercise and the exercise capacity of patients with acute myocardial infarction (AMI) and diabetes mellitus (DM).

Methods and Results Fifty-two male patients who underwent cardiopulmonary exercise testing (CPX) 1 month after onset of AMI were divided into 2 groups: (DM+) group, n=20; (DM-) group, n=32). HR, peak oxygen uptake ($\dot{V}O_{2peak}$), and plasma norepinephrine (NE) levels were measured during CPX. The high-frequency power (HF) was analyzed by HR variability. The $\Delta HR/\log \Delta NE$ obtained from changes of HR and NE from rest to peak exercise and HR change from baseline to the minimum HF (ΔHR_{HF}) were calculated as parameters of HR response derived from SN and PN activities, respectively. ΔHR , $\dot{V}O_{2peak}$, $\Delta HR/\log \Delta NE$, and ΔHR_{HF} were significantly lower in the (DM+) group than in the (DM-) group, and both of them showed positive correlations with $\dot{V}O_{2peak}$.

Conclusion An inadequate HR response to exercise is a major factor causing a decline of exercise capacity, which is derived from both of SN and PN dysfunction, in AMI patients with DM. (Circ J 2006; 70: 1017–1025)

Key Words: Acute myocardial infarction; Autonomic nervous system; Diabetes mellitus; Exercise; Rehabilitation

Type 2 diabetes mellitus (DM) is not only an independent risk factor for the development of coronary artery disease, but also contributes to mortality through the induction of arrhythmias or sudden death after acute myocardial infarction (AMI)! Furthermore, recent epidemiological surveys have shown that the morbidity of DM has rapidly increased in Japan in the past decade and in consequence the incidence of AMI complicated by DM has also increased remarkably² Because exercise capacity is reduced after AMI in patients with DM in comparison with similar patients without DM, comprehensive cardiac rehabilitation (CR) should be instituted in these patients after the onset of AMI.^{3,4} It is important to clarify the mechanisms underlying the decline of exercise capacity after AMI in patients with DM, in order to offer the appropriate exercise training program to them.

Heart rate (HR) response to exercise is regulated by the

balance between sympathetic and parasympathetic nerve (SN and PN) activities in the human body.⁵ An insufficient HR response to exercise caused by autonomic nervous dysfunction seems to be an important mechanisms in patients with DM who show decreased exercise capacity.^{3,6} It is well known that norepinephrine (NE) secretion from the terminals of the SNs decreases during exercise in patients with DM, as compared with normal subjects.⁷ A previous study concerning the relationship between HR response and SN activity during exercise showed that the HR response corresponding to NE secretion is reduced in AMI patients with DM, resulting in a decline in exercise capacity.³ In addition, it has been reported that patients with DM have not only SN dysfunction but also PN dysfunction, which is shown by a decrease in the high-frequency power (HF) in HR variability (HRV).⁸ However, there are few reports evaluating the influence of PN activity separately from SN activity on the HR response to exercise and exercise capacity of patients with AMI, and moreover, the impact of DM in causing insufficient HR response to exercise. It is very important to clarify the mechanism of HR response to exercise regulated by SN and PN activities in order to prescribe appropriate CR that takes in to account the decreased exercise capacity in AMI patients with DM.

It is reported that an imbalance of autonomic nervous activities causes excessive elevation of blood pressure and HR during exercise training in patients with AMI⁹ and that the marked activation of SN induces ventricular arrhythmias in patients with coronary artery disease.¹⁰ Thus, it is

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*Department of Rehabilitation Medicine, St Marianna University School of Medicine Yokohama City Seibu Hospital, Yokohama, **Department of Rehabilitation Medicine, St Marianna University School of Medicine, †Division of Cardiology, St Marianna University School of Medicine, Kawasaki, ††Graduate School of Medical Science and ‡Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Sagami-hara, Japan

Mailing address: Takashi Masuda, MD, Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, 1-15-1 Kitasato, Sagami-hara 228-8555, Japan. E-mail: tak9999@med.kitasato-u.ac.jp

Fig 1. Protocol of cardiopulmonary exercise testing. MET, metabolic equivalent.

important to assess the HR response derived from the balance between SN and PN activities, so that exercise training can be performed at a safe and effective intensity, and to avoid the risk of sudden cardiac death during exercise. Generally, the anaerobic threshold (AT) is used to decide the appropriate intensity of exercise training in CR,¹¹ because neither elevation of the lactic acid level nor activation of the SN system occur at exercise intensities lower than the AT.^{12,13} It is also known that the increase in HR in healthy subjects is predominantly derived from the decreased PN activity that occurs at an exercise intensity below the AT.¹³ However, the relationship between HR response to exercise and PN activity at intensities below the AT in AMI patients with DM remains unclear.

The purpose of the present study was to clarify the influence of the autonomic nervous dysfunction characterizing DM on exercise capacity in patients undergoing CR for AMI, focusing on separate SN and PN activities that affected HR response to exercise.

Methods

Patients

Male patients who were admitted to St Marianna University School of Medicine Hospital from November 1998 to March 2000 because of AMI were eligible for the present study, if they completed a routine 4-week CR program while hospitalized and performed cardiopulmonary exercise testing (CPX) 1 month after onset of AMI. Patients who were older than 70 years, had severe heart failure (New York Heart Association class 4), uncontrolled arrhythmia, atrial fibrillation, or left bundle branch block, or who underwent coronary artery bypass grafting surgery or treatment with β -blockers were excluded. Female patients were also excluded because it is well known that they have significantly lower exercise capacity than males.¹⁴ Consequently, 52 male patients were recruited for the study and were divided into 2 groups according to whether or not they had DM: there were 20 patients in the DM(+) group and 32 in the DM(−) group.

The diagnosis of AMI was confirmed by the existence of chest pain that lasted 30 min or more, ST-segment elevation of 0.1 mV or more in at least 2 contiguous leads of 12-lead electrocardiogram (ECG), and a significant increase of serum creatine kinase-myocardial band (CK-MB) levels 2-fold or more from the upper limit of the normal range. DM was diagnosed if patients were under treatment with oral hypoglycemic agents or insulin injection, or if an oral glucose tolerance test performed after admission was positive. In the DM(+) group, 18 patients were being treated

with oral hypoglycemic agents, and 7 by insulin injection.

Age, body weight, height, body mass index, location of AMI, maximum CK-MB (max CK-MB) and glycosylated hemoglobin (HbA_{1c}) were recorded as clinical characteristics in all patients. While the patients were hospitalized for AMI, they underwent coronary angiography (CAG) and left ventriculography (LVG). The number of significant stenoses of the coronary arteries ($\geq 75\%$; especially left main trunk, $\geq 50\%$) was evaluated based on the definition that coronary stenosis was measured as the luminal diameter loss in comparison with the nearest proximal normal segment. Left ventricular ejection fraction (LVEF) was calculated via biplane LVG. All patients underwent direct percutaneous transluminal coronary angioplasty for AMI on admission. The medications, including nitrates, calcium channel antagonists, and angiotensin-converting enzyme inhibitors were recorded, when CPX was performed.

The study was approved by the St Marianna University School of Medicine institutional committee on human research. Informed consent was given by each patient before entering the study 1 month after onset of AMI.

Exercise Testing

Symptom-limited CPX was performed with a treadmill (MAT-2500, Fukuda Denshi, Tokyo, Japan) according to a ramp protocol. After patients rested for 3 min on the treadmill, exercise was performed with the increment of load by 1 MET/min following a 3-min warm-up period (speed, 1.0 mile/h; slope, 0%) (Fig 1). HR and 12-lead ECG were continuously monitored by the Stress Test System (ML-5000, Fukuda Denshi), and systolic and diastolic blood pressure (SBP and DBP) were measured by the cuff method via an automatic blood pressure monitor (STBP-780, Colin, Aichi, Japan) at 1-min intervals throughout the CPX period. As expired gas was sampled using a breath-by-breath method, oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and tidal volume ($\dot{V}E$) were measured simultaneously with a respiromonitor (AE-280, Minato Ikagaku, Tokyo, Japan) and a gas analyzer (MG-360, Minato Ikagaku) during CPX. The endpoint of CPX was determined according to the criteria of the American College of Sports Medicine¹⁵ or by a leveling off of $\dot{V}O_2$ that showed no change despite increasing exercise intensity. None of the patients showed ischemic ECG changes during CPX.

The HR at rest (HR_{rest}), warm-up (HR_{wu}), and peak exercise (HR_{peak}) were determined from the HR recorded throughout the CPX period, and the increase from HR_{rest} to HR_{peak} (Δ HR) was calculated. The duration from the beginning of exercise to peak exercise (exercise time) was mea-

Fig 2. Time course in heart rate (HR) and high-frequency power (HF) of heart rate variability during cardiopulmonary exercise testing. HF_{baseline}, average of high-frequency power at warm-up period; HR_{HF}, the HR when HF reached the minimum level; ΔHR_{HF}, HR change from HR_{wu} to HR_{HF}; HR_{peak}, heart rate at peak exercise.

sured, and HR slope indicating an increase of HR per min was also calculated throughout the CPX period. In addition, the time constant of HR decay for the first 30 s of recovery period (T₃₀) was calculated by the method described by Imai et al.¹⁶ HR reserve (HRR) estimated according to patient's age and HR_{rest}, and the %HRR were calculated:¹⁷

$$\text{HRR} = 220 - \text{age} - \text{HR}_{\text{rest}}$$

$$\% \text{HRR} = (\text{HR}_{\text{peak}} - \text{HR}_{\text{rest}}) / (220 - \text{age} - \text{HR}_{\text{rest}}) \times 100\%$$

The gas exchange ratio ($\dot{V}\text{CO}_2/\dot{V}\text{O}_2$: GER) was calculated, and the $\dot{V}\text{O}_2$ slope was assessed as an increase of $\dot{V}\text{O}_2$ per min. The oxygen pulse (O₂ pulse) indicating stroke volume was calculated:¹⁸

$$\text{O}_2 \text{ pulse} = \dot{V}\text{O}_2 / \text{HR}$$

We measured SBP, $\dot{V}\text{O}_2$, GER and O₂ pulse at rest (SBP_{rest}, $\dot{V}\text{O}_{2\text{rest}}$, GRE_{rest} and O₂ pulse_{rest}, respectively), and SBP, $\dot{V}\text{O}_2$, GER and O₂ pulse at peak exercise (SBP_{peak}, $\dot{V}\text{O}_{2\text{peak}}$, GRE_{peak} and O₂ pulse_{peak}, respectively), and calculated the change from O₂ pulse_{rest} to O₂ pulse_{peak} (ΔO₂ pulse). After determining the AT by the V-slope method,¹¹ we measured HR, SBP, $\dot{V}\text{O}_2$, GER and O₂ pulse at the AT (HR_{AT}, SBP_{AT}, $\dot{V}\text{O}_{2\text{AT}}$, GRE_{AT} and O₂ pulse_{AT}, respectively). Then, we calculated the ratio of HR_{AT} to HR_{peak} (HR_{AT}/HR_{peak} × 100), to assess the workload at HR_{AT} relative to that at peak exercise.

Blood Sampling

Blood samples for measurement of NE were obtained from a catheter inserted into an antecubital vein before warm-up and at peak exercise, and were immediately ice-cooled. After centrifugation at 3,000rpm at 4°C for 10 min, separated plasma was stored at -80°C until analyzed. The plasma concentration of NE was determined by using high performance liquid chromatography.

The change from NE at rest (NE_{baseline}) to NE at peak exercise (NE_{peak}) was converted to a logarithmic value (logΔNE), because NE increases exponentially during incremental exercise.¹⁹ Consequently, sympathetic nervous activity was assessed as the ratio of ΔHR to logΔNE (ΔHR/logΔNE).

HRV

R-R intervals obtained from ECG monitoring throughout CPX were converted to digital data by 250Hz sampling rate for HRV analysis. The HRV of the R-R intervals was analyzed by the MemCalc method²⁰ and the frequency domain power spectra were calculated for the low (0.04–

Table 1 Parameters Indicating Autonomic Nervous Activity

Sympathetic nervous activity

NE_{baseline}: NE at resting state

NE_{peak}: NE at peak exercise

ΔNE: NE change from NE at rest to NE at peak exercise

ΔHR: HR change from HR at rest to HR at peak exercise

ΔHR/log ΔNE: the ratio of ΔHR to log ΔNE

LF/HF_{baseline}: the ratio of LF to HF at warm-up period

LF/HF_{peak}: the ratio of LF to HF at peak exercise

Parasympathetic nervous activity

HF_{baseline}: HF at warm-up period

HF_{peak}: HF at peak exercise

HR_{HF}: the HR when HF reached the minimum level

ΔHR_{HF}: HR change from HR at warm-up to HR at HR_{HF}

NE, norepinephrine; ΔNE, change of NE concentration from rest to peak exercise; ΔHR, change of heart rate (HR) from rest to peak exercise; LF, low-frequency power in heart rate variability; HF, high-frequency power in heart rate variability; ΔHR_{HF}, HR change from HR at warm-up to HR at the minimum level during cardiopulmonary exercise testing.

0.15Hz) and high (0.15–0.4Hz) frequency components of the power spectrum (low-frequency power (LF) and HF, respectively). The power spectrum of the HF component is known to reflect cardiac PN activity, and the ratio of LF to HF (LF/HF) indicates the predominance of cardiac SN activity. LF, HF, and LF/HF in the time series were analyzed at 10-s intervals during CPX. The averages of LF, HF and LF/HF were calculated as baseline values using all of the 18 data during warm-up period (LF_{baseline}, HF_{baseline} and LF/HF_{baseline}, respectively). They were calculated as the moving average using consecutive data of LF, HF and LF/HF, respectively, during ramp exercise. Furthermore, the averages of LF, HF and LF/HF at HR_{peak} were calculated from 2 data before the end of ramp exercise (LF_{peak}, HF_{peak} and LF/HF_{peak}, respectively), to avoid the interference of data from a recovery period. After ΔHR was divided into 5 stages by the 20% of ΔHR in the ramp exercise, LF, HF and LF/HF at HR of each stage (HR_{rest} + 20%ΔHR, HR_{rest} + 40%ΔHR, HR_{rest} + 60%ΔHR, HR_{rest} + 80%ΔHR and HR_{peak}) were assessed in the 2 groups to compare the changes of SN and PN activities to the relative exercise intensity during exercise. Because arrhythmias such as premature ventricular contraction (PVC) and premature atrial contraction (PAC) affect HRV analysis, we excluded patients who had more than 4 PVCs or PACs per min during exercise. The number of arrhythmia episodes was automatically counted by a diagnosis program during the 12-lead ECG study.

Table 2 Patients' Characteristics

	DM (–) group	DM (+) group	p value
Number	32	20	
Age (years)	57.0±1.5	58.2±1.7	NS
Body weight (kg)	62.5±1.3	61.4±1.8	NS
Height (cm)	163.5±1.0	164.3±1.4	NS
BMI (kg/m ²)	23.4±0.5	22.8±0.6	NS
Max CK-MB (IU/L)	233.7±44.2	248.2±44.2	NS
HbA _{1c} (%)	5.3±0.2	7.2±0.2	<0.001
LVEF (%)	50.7±1.7	50.4±4.3	NS
LVEF <40%	7 (22%)	5 (25%)	NS
Location of AMI			
Anterior wall	9 (28.1%)	4 (20.0%)	NS
Inferior wall	16 (50.0%)	13 (65.0%)	NS
Lateral or posterior wall	7 (21.9%)	3 (20.0%)	NS
Medication			
Nitrates	26 (81.3%)	15 (75%)	NS
Ca antagonist	7 (21.9%)	5 (25%)	NS
ACE inhibitor	23 (72.9%)	13 (65.0%)	NS
Oral hypoglycemic agent	–	18 (90.0%)	–
Insulin	–	7 (35.0%)	–
Significant stenosis of coronary artery before PCI			
1 vessel disease	17 (53.1%)	10 (50.0%)	NS
2 vessel disease	13 (40.6%)	8 (40.0%)	NS
3 vessel disease	2 (6.3%)	2 (10.0%)	NS

Data are mean±SE.

DM, diabetes mellitus; BMI, body mass index; Max CK-MB, maximum creatine kinase-myocardial band; HbA_{1c}, glycosylated hemoglobin; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme; PCI, percutaneous coronary intervention.

Fig2 shows the changes in HR and HF during CPX. HF decreased at the beginning of exercise and HR increased linearly with the incremental workload. HF converged on a lower value and then fixed without showing any change during exercise. When the HF reached the minimum level, the HR was defined as HR_{HF}, indicating that PN activity had nearly disappeared during exercise.^{21,22} The HR change from HR_{WU} to HR_{HF} was defined as ΔHR_{HF} , indicating the suppression of PN activity. In the present study, HR_{HF} was clearly shown in all patients. To assess the workload at HR_{HF} relative to that at peak exercise, we calculated the ratio of HR_{HF} to HR_{peak} (HR_{HF}/HR_{peak}×100). The parameters used in the present study, indicating the changes in SN and PN activities, are summarized in Table 1.

Statistical Analysis

All data are expressed as the mean±SE. An unpaired t-test or Mann-Whitney U-test was used to compare the DM (+) and DM (–) groups, and a paired t-test was used to compare HR_{AT} and HR_{HF} in each group. Pearson's correlation coefficient was used in a regression analysis to determine the correlations between parameters of cardiac function or autonomic nervous activities (LVEF, max CK-MB, NE_{baseline}, HF_{baseline}, $\Delta HR/\log \Delta NE$ or ΔHR_{HF}) and peak $\dot{V}O_2$, and between $\Delta HR/\log \Delta NE$ and ΔHR_{HF} . A two-way analysis of variance for repeated-measures (2 groups vs 6 stages: HR_{WU}, HR_{rest}+20% ΔHR , HR_{rest}+40% ΔHR , HR_{rest}+60% ΔHR , HR_{rest}+80% ΔHR and HR_{peak}) was used to analyze the differences in LF, HF and LF/HF among the 6 stages and between the DM (–) and DM (+) groups during CPX. If the F ratio was significant, Tukey's multiple range test was applied to find the significant differences between the adjacent 2 stages and between the DM (–) and DM (+) groups. Statistical analyses were performed with SPSS 12.0J statis-

Table 3 Parameters for Cardiopulmonary Exercise Testing

	DM (–) group	DM (+) group	p value
HR _{rest} (beats/min)	71.2±1.7	77.0±2.6	NS
SBP _{rest} (mmHg)	122.3±3.5	125.3±3.5	NS
$\dot{V}O_{2rest}$ (ml·min ^{–1} ·kg ^{–1})	4.0±0.1	4.2±0.2	NS
GER _{rest}	0.83±0.1	0.83±0.1	NS
O ₂ pulse _{rest} (ml·min ^{–1} ·beat ^{–1})	3.6±0.1	3.3±0.1	NS
HR _{AT} (beats/min)	106.6±2.3	104.2±2.4	NS
SBP _{AT} (mmHg)	147.3±3.7	143.2±4.5	NS
$\dot{V}O_{2AT}$ (ml·min ^{–1} ·kg ^{–1})	16.4±0.4	15.2±0.6	NS
GER _{AT}	0.9±0.0	0.9±0.0	NS
O ₂ pulse _{AT} (ml·min ^{–1} ·beat ^{–1})	9.8±0.3	9.0±0.4	NS
Exercise time (s)	533.4±15.3	519.0±33.1	NS
HR _{peak} (beats/min)	148.0±2.5	135.8±3.1	0.004
SBP _{peak} (mmHg)	173.8±4.3	167.0±5.8	NS
$\dot{V}O_{2peak}$ (ml·min ^{–1} ·kg ^{–1})	20.6±0.6	22.5±0.6	0.002
GER _{peak}	1.17±0.01	1.17±0.01	NS
O ₂ pulse _{peak} (ml·min ^{–1} ·beat ^{–1})	10.9±0.3	10.2±0.4	NS
ΔHR (beats/min)	76.8±2.5	58.8±2.3	<0.001
ΔO_2 pulse (ml·min ^{–1} ·beat ^{–1})	7.4±0.3	6.9±0.4	NS
%HRR (%)	84.5±2.9	70.5±3.1	0.002
HR slope (beats/min ²)	8.7±0.3	7.5±0.4	0.016
$\dot{V}O_2$ slope (ml/min ²)	145.7±5.0	126.4±6.8	0.025
T ₃₀	33.9±4.2	74.2±2.7	0.028

Data are mean±SE.

DM, diabetes mellitus; HR, heart rate; SBP, systolic blood pressure; $\dot{V}O_2$, oxygen consumption; GER, gas exchange ratio; ΔHR , change of HR from rest to peak exercise; ΔO_2 pulse, change of O₂ pulse from rest to peak exercise; %HRR, ratio of ΔHR to heart rate reserve estimated according to age and HR_{rest}; T₃₀, time constant of heart rate decay for the first 30 s of recovery period.

tical software program (SPSS Japan), and a p-value <0.05 was considered statistically significant.

Results

The patients' characteristics including age, body weight, height, body mass index, max CK-MB, HbA_{1c}, LVEF, and location of AMI are shown in Table 2. There were no significant differences between the DM (+) and DM (–) groups in these parameters, except HbA_{1c}, and medication for AMI. No significant difference was shown between the DM (+) and DM (–) groups in the proportion of multivessel disease evaluated by CAG performed on admission.

Table 3 shows the results obtained from CPX. No significant differences were shown between the DM (+) and DM (–) groups in HR_{AT}, SBP_{AT}, $\dot{V}O_{2AT}$, GER_{AT} and O₂ pulse_{AT}. There were also no significant differences between the 2 groups in exercise time, SBP_{peak}, GER_{peak}, O₂ pulse_{peak} and ΔO_2 pulse. However, HR_{peak}, $\dot{V}O_{2peak}$, ΔHR , %HRR, HR slope, and $\dot{V}O_2$ slope were significantly lower in the DM (+) group than in the DM (–) group (p=0.004, p=0.002, p<0.001, p=0.002, p=0.016 and p=0.025, respectively). T₃₀ was significantly higher in the DM (+) group than in the DM (–) group (p=0.028).

Fig 3 shows the changes in LF, HF and LF/HF during CPX. Although there was no significant difference between the 2 groups in LF/HF_{baseline}, LF_{baseline} and HF_{baseline} were significantly lower in the DM (+) group than in the DM (–) group (p<0.01 and p<0.01, respectively). LF was significantly lower at HR_{rest}+20% ΔHR in the DM (+) group than in the DM (–) group (p<0.01), and HF was also significantly lower at HR_{rest}+20% ΔHR and HR_{rest}+40% ΔHR in the DM (+) group (p<0.01 and p<0.01, respectively). There was no significant difference between the 2 groups in

Fig 3. Changes in LF, HF and LF/HF during cardiopulmonary exercise testing. LF, low-frequency power in heart rate variability; HF, high-frequency power in heart rate variability; LF/HF, the ratio of LF to HF in heart rate variability; ΔHR, heart rate (HR) change from HR at rest to HR at peak exercise; %ΔHR, ratio to ΔHR. (○) Diabetes mellitus (DM)(+) group, (●) DM(-) group. *Significant differences between the 2 groups ($p < 0.01$). #significant difference between adjacent 2 stages ($p < 0.01$).

LF/HF during CPX. Although LF and HF decreased significantly during CPX ($p < 0.01$), they reached the minimal levels at lower HR in the DM(+) group as compared with the DM(-) group.

Table 4 shows the NE levels and HR response to exercise during CPX. Although there were no significant differences between the 2 groups in NE_{baseline}, NE_{peak} and logΔNE, ΔHR/logΔNE and ΔHR_{HF} were significantly lower in the DM(+) group than in the DM(-) group ($p < 0.001$ and $p < 0.001$, respectively).

Fig 4 shows the correlation between ΔHR_{HF} and ΔHR/logΔNE in all 52 patients. There was a positive and significant correlation between ΔHR_{HF} and ΔHR/logΔNE ($r = 0.63$, $p < 0.001$).

Figs 5–7 show the correlations between ΔHR and $\dot{V}O_{2peak}$, and between ΔHR/logΔNE or ΔHR_{HF} and $\dot{V}O_{2peak}$ in all 52

Table 4 NE Levels and HR Response to Exercise

	DM (-) group	DM (+) group	<i>p</i> value
NE _{baseline} (pg/ml)	239.2±17.2	221.0±29.1	NS
NE _{peak} (pg/ml)	1,933.6±182.3	1,640.0±206.5	NS
logΔNE	7.3±0.1	7.1±0.1	NS
ΔHR/logΔNE	10.6±0.4	8.3±0.3	<0.001
ΔHR _{HF} (beats/min)	29.4±1.7	16.4±1.4	<0.001

Data are mean ± SE.

NE, norepinephrine; HR, heart rate; DM, diabetes mellitus; ΔNE, change of NE concentration from rest to peak exercise; ΔHR, change of HR from rest to peak exercise; ΔHR_{HF}, HR change from HR at warm-up to HR at the minimum level during cardiopulmonary exercise testing.

Fig4. Correlation between ΔHR_{HF} and $\Delta HR/\log \Delta NE$. ΔHR_{HF} , heart rate (HR) change from HR at warm-up to the HR when HF reached the minimum level; ΔHR , HR change from HR at rest to HR at peak exercise; ΔNE , norepinephrine (NE) change from NE at rest to NE at peak exercise. (○) Diabetes mellitus (DM)(+) group, (●) DM(-) group.

Fig5. Correlation between ΔHR and $\dot{V}O_{2peak}$. ΔHR , heart rate (HR) change from HR at rest to HR at peak exercise; $\dot{V}O_{2peak}$, oxygen consumption at peak exercise. (○) Diabetes mellitus (DM)(+) group, (●) DM(-) group.

patients. There were positive correlations between ΔHR and $\dot{V}O_{2peak}$ ($r=0.64$, $p<0.001$), between $\Delta HR/\log \Delta NE$ and $\dot{V}O_{2peak}$, ($r=0.63$, $p<0.001$), and between ΔHR_{HF} and $\dot{V}O_{2peak}$ ($r=0.51$, $p<0.001$). However, there were no significant correlations between LVEF, max CK-MB, $NE_{baseline}$ or $HF_{baseline}$, and $\dot{V}O_{2peak}$ ($p=0.476$, $p=0.421$, $p=0.089$, and $p=0.060$, respectively).

Fig8 shows the comparison between HR_{HF} and HR_{AT} in each group. There was no significant difference between HR_{AT} and HR_{HF} in the DM(-) group ($p=0.254$), but, in contrast, HR_{HF} was significantly lower than HR_{AT} in the DM(+) group ($p=0.005$).

Fig9 shows the ratio of HR_{AT} or HR_{HF} to HR_{peak} in the 2 groups. The ratio of HR_{AT} to HR_{peak} was significantly higher in the DM(+) group than in the DM(-) group ($p=0.004$), whereas there was no significant difference in the ratio of HR_{HF} to HR_{peak} between the 2 groups.

Discussion

In the present study, we focused on the HR response to exercise, which is derived from the balance between SN

Fig6. Correlation between $\Delta HR/\log \Delta NE$ and $\dot{V}O_{2peak}$. ΔHR , heart rate (HR) change from HR at rest to HR at peak exercise; ΔNE , norepinephrine (NE) change from NE at rest to NE at peak exercise; $\dot{V}O_{2peak}$, oxygen consumption at peak exercise. (○) Diabetes mellitus (DM)(+) group, (●) DM(-) group.

Fig7. Correlation between ΔHR_{HF} and $\dot{V}O_{2peak}$. ΔHR_{HF} , heart rate (HR) change from HR at warm-up to the HR when high-frequency power (HF) reached the minimum level; $\dot{V}O_{2peak}$, oxygen consumption at peak exercise. (○) Diabetes mellitus (DM)(+) group, (●) DM(-) group.

and PN activities, during incremental exercise in patients with DM who were regaining health after AMI. Previous studies report that AMI patients with DM have a lower exercise capacity than those without DM, which possibly results from inappropriate secretion of catecholamines in the heart.^{3,7} In addition, studies using myocardial scintigraphy have shown a positive correlation between ^{123}I -metaiodobenzylguanidine uptake and peak HR during incremental exercise in patients with congestive heart failure, indicating that decreased secretion of NE in the sinus node affected the HR response to exercise.²³ Bottini et al reported that the elevation of serum catecholamine during incremental exercise was lower in patients with DM suffering from autonomic nervous neuropathy than in normal subjects,⁷ and noted that SN dysfunction caused an inadequate HR response to exercise in DM patients, inducing an insecure cardiocirculatory condition.²⁴

As the HR response corresponding to the increase of serum NE is less sufficient in patients with congestive heart failure than in normal subjects, it is also suggested that the sensitivity of the sinus node to NE has deteriorated in these patients.²⁵ The present study showed that severe SN dys-

Fig8. Comparison of between HR_{HF} and HR_{AT} in each group. Diabetes mellitus (DM)(-), patients without diabetes mellitus; DM(+), patients with diabetes mellitus; HR, heart rate. Open bars indicate the HR when the high-frequency power reached the minimum level (HR_{HF}). Closed bars indicate the HR at the anaerobic threshold.

Fig9. Comparisons in the ratio of HR_{AT} or HR_{HF} to HR_{peak} between the 2 groups. HR_{HF}, heart rate (HR) when the high-frequency power reached the minimum level; HR_{AT}, HR at the anaerobic threshold. Open bars indicate the Diabetes mellitus (DM)(-)group, Closed bars indicate the DM(+) group.

function was not observed, even in the DM(+) group, because there were no significant differences between the DM(+) and DM(-) groups in NE_{baseline}, LF/HF_{baseline}, LF/HF_{peak} and NE_{peak} as indicators of SN activity. Furthermore, the study showed a close and positive correlation between $\Delta\text{HR}/\log\Delta\text{NE}$ and $\dot{V}\text{O}_{2\text{peak}}$ and a significantly lower value of $\Delta\text{HR}/\log\Delta\text{NE}$ in the DM(+) group as compared with the DM(-) group, indicating that the sensitivity of the sinus node to NE plays a more important role in the elevation of HR than does the amount of NE secreted from the SN terminal. Therefore, it seems that an inadequate HR response to exercise is a major factor in the decline in exercise capacity of patients with AMI and DM, and that $\Delta\text{HR}/\log\Delta\text{NE}$, reflecting the HR response derived from SN activity, may be a useful indicator in the assessment of the exercise capacity of AMI patients.

It was previously reported that PN activity at rest assessed by HRV shows a positive correlation with maximal $\dot{V}\text{O}_2$ in healthy subjects, leading to the conclusion that the decrease in PN activity associated with aging is related to the decline in exercise capacity that is also associated with aging.²⁶ However, there are few reports of the relationship between the HR response derived from PN activity and the exercise capacity of AMI patients with DM, although DM patients are known to show lower PN activity compared with normal subjects.⁸ The HF in HRV is commonly used to estimate the change in PN activity, because it decreases in response to increasing exercise intensity or inhibition of cholinergic receptors during exercise.²⁷ In the present study, we assessed HRV using the MemCalc method, which can analyze the power spectral densities of a time series.²⁰ We found that HF was significantly lower during exercise and reached the minimum level at a lower HR in the DM(+) group as compared with the DM(-) group, indicating that PN dysfunction shown by a significant decrease of $\Delta\text{HR}_{\text{HF}}$

caused an inadequate HR response to exercise. In addition, it seemed that the decline in exercise capacity resulted from an inadequate HR response to exercise in AMI patients with DM, because there was a positive correlation between $\Delta\text{HR}_{\text{HF}}$ and $\dot{V}\text{O}_{2\text{peak}}$.

It is well known that cardiopulmonary function, blood flow to skeletal muscles, and muscle oxygen usage are important factors, together with age and sex, in regulating exercise capacity. An inadequate increase in stroke volume is one reason for the decline in exercise capacity of patients with AMI and DM, particularly those who have diabetic cardiomyopathy or lower LVEF because of severe AMI.²⁸ The present study, however, showed no significant differences in LVEF, O_2 pulse_{peak} and ΔO_2 pulse between the 2 groups. Because the DM(+) group consisted of patients with AMI who had mild to moderate cardiac dysfunction and could perform the exercise training using a treadmill or cycle ergometer, the present study failed to show that left ventricular function was one of the main factors causing the decline in exercise capacity. However, we assessed the O_2 pulse to estimate the stroke volume during exercise. A previous study reported that the O_2 pulse was equivalent to the stroke volume calculated echocardiographically at the maximal HR during ramp exercise.⁸ Therefore, we believe that the O_2 pulse substantially reflects the stroke volume and is a parameter of cardiac function during exercise. It is generally known that HR is 2- to 3-fold higher at maximum exercise than at rest, despite only 1.5- to 2-fold increase in stroke volume.²⁹ Although the present study showed a positive correlation between ΔHR and $\dot{V}\text{O}_{2\text{peak}}$ in all patients, both ΔHR and HR slope were significantly lower in the DM(+) group as compared with those in the DM(-) group. Therefore, it seems that the inadequate increase in cardiac output during exercise is caused by poorer elevation of HR than of stroke volume in AMI patients with DM, if they

have the same resting cardiac function as patients without DM.

As regards DM treatment, a previous study reported that insulin injection decreased HF and increased simultaneously LF/HF, as assessed by HRV in healthy subjects, resulting in an increment of HR at rest.³⁰ However, there is also a study reporting no significant changes of HF and LF/HF after an injection of insulin to patients with DM. The present study in which 7 patients in the DM(+) group had insulin therapy showed no significant differences between the 2 groups in NE at rest and peak exercise, and in HR at rest. Therefore, we consider that the difference in treatment regimens for DM had less influence on the study results in the comparison to the HR response. Furthermore, poor control of blood glucose is generally known to change the autonomic nervous activities regulating HR response to exercise in patients with DM. Larsen et al reported that the peak HR during incremental exercise was lower in the patients with poorly controlled DM ($HbA_{1c} > 8.4\%$) than in those who were well controlled.³¹ In the present study, the mean HbA_{1c} was $7.2 \pm 0.2\%$ in the DM(+) group and none had $HbA_{1c} > 8.0\%$, indicating poor control of DM.³² The patients with DM in the present study maintained a satisfactory level of blood glucose after admission to hospital. However, the DM(+) group showed significantly lower HR_{peak} and ΔHR than the DM(-) group, suggesting that AMI patients with DM had an insufficient HR response to exercise despite appropriate control of blood glucose, compared with those without DM.

The maximum $\dot{V}O_2$ or maximum HR obtained from CPX is often used as the target HR in the prescription of exercise therapy.³³ However, the value assessed by the maximum exercise should not be the target HR for patients in the acute phase of AMI, because it is difficult for them to perform at that level. Therefore, the AT obtained from the sub-maximum exercise is used for them to carry out exercise training at the target intensity. It is well known that the regular exercise training at the AT improves exercise capacity without a remarkable elevation of SN activity and serum lactic acid level.^{12,13,34} The present study showed no significant difference between HR_{HF} and HR_{AT} in the DM(-) group, supporting the previous report that PN activity reaches the lowest value at approximately 110% of AT in incremental exercise testing.¹³ However, HR_{AT} was significantly higher than HR_{HF} in the DM(+) group, and the ratio of HR_{AT} to HR_{peak} was also higher in the DM(+) group than in the DM(-) group. In addition, a positive correlation between ΔHR_{HF} and $\Delta HR/\log \Delta NE$ shown in the present study indicates that SN activity was elevated more excessively to obtain an adequate HR increase in AMI patients who showed an inadequate HR increase derived from PN dysfunction. These findings suggest that in the DM(+) group SN activity is more dominant in the regulation of HR at the intensity of the AT than is PN activity, and that the relative exercise intensity is stronger in the DM(+) group as compared with the DM(-) group. Therefore, the present study indicates that the more exercise intensity is loaded toward the AT, the more activation of SN is induced in the DM(+) group. Continuing the exercise at the intensity near AT may induce a hyperglycemic state during exercise in AMI patients with DM.³⁵ In addition, we should beware that the elevated SN activity causes excessive blood pressure elevation or exercise-induced arrhythmias in such patients, even at exercise training intensities lower than the AT.

Study Limitations

In the present study, we failed to evaluate the serial change of SN activity by using the LF/HF in HRV because of its dispersion, and we measured serum catecholamine levels at only 2 points (ie, rest and peak exercise). Blood samples need to be collected at various points during incremental exercise in future studies to detect the point of SN activation during exercise. Because the effects of regular exercise training on SN and PN activities is still unclear in the present study, further studies are needed to investigate the HR response to exercise derived from autonomic nervous function after regular exercise.

In the present study, various medical treatments were given to the patients with DM. Because there was an ethical difficulty in giving uniform therapy to them, we performed the study without modifying the treatments for DM. Therefore, in the future we should analyze the HR response to exercise among subgroups classified according to the DM treatment regimen.

Conclusions

The insufficient HR response to exercise derived from both of SN and PN dysfunction is a significant factor in the decreased exercise capacity of patients with AMI complicated with DM. The HR response to exercise is affected by SN activity, even at exercise intensities below the AT, in patients with AMI and DM, although it is commonly regulated by PN activity at intensities up to the AT in those without DM.

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