—Original—

Sympathetic Excitation during Exercise as a Cause of Attenuated Heart Rate Recovery in Patients with Myocardial Infarction

Akiko Ushijima, Nagaharu Fukuma, Yuko Kato,
Noriko Aisu and Kyoichi Mizuno

Division of Cardiology, Hepatology, Geriatrics, and Integrated Medicine, Department of Internal Medicine,
Graduate School of Medicine, Nippon Medical School

Abstract

Background: Heart rate recovery (HRR) after exercise is known as a predictor of cardiac death in patients with heart disease. The mechanism is not fully understood, although a parasympathetic mechanism has been reported. To elucidate the factors that influence HRR, we evaluated the relationship of HRR with exercise performance and plasma norepinephrine (NE), lactic acid and B-type natriuretic peptide (BNP) responses to exercise testing.

Methods: The study population consisted of 52 male patients (age 58 ± 9.6 years) who had experienced myocardial infarction without residual ischemia, uncompensated heart failure or atrial fibrillation. All subjects underwent a symptom-limited cardiopulmonary exercise test without a cool-down period and echocardiography. NE, lactic acid and BNP were measured at rest and at peak exercise.

Results: HRR did not correlate with the left ventricular ejection fraction, peak VO_2, lactic acid and BNP. HRR significantly correlated with the increment in heart rate (HR) from rest to peak exercise (ΔHR) ($r=0.30$, $p<0.05$). When we divided ΔHR into two phases at the anaerobic threshold (AT), HRR significantly correlated with ΔHR (peak-AT) ($r=0.409$, $p<0.01$), but not with ΔHR (AT-rest). There was a significant negative correlation between HRR and NE both at rest and at peak exercise ($r=-0.286$, $p<0.05$, $r=-0.310$, $p<0.05$). HRR was also correlated significantly with ΔHR/logΔNE as an index of sensitivity to NE ($r=0.421$, $p<0.01$). Based on multiple regression analysis, ΔHR and logΔNE predicted HRR ($R^2=0.467$, $p=0.0027$).

Conclusions: Present findings suggest that enhanced sympathetic excitation at maximum exercise suppresses parasympathetic reactivation and results in attenuation of HRR.
(J Nippon Med Sch 2009; 76: 76–83)

Key words: heart rate recovery, exercise test, mechanism, sympathetic nervous system

Introduction

Many reports have indicated that various parameters identified through exercise testing can accurately predict the prognosis in patients with heart disease compared with factors such as the left ventricular ejection fraction (LVEF)[1–4]. These exercise-related indexes mainly consist of indicators of the heart rate (HR) response to exercise and

Correspondence to Akiko Ushijima, Department of Functional Pathophysiology for Human Organs, Graduate School of Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: ushijima@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

oxygen and carbon dioxide dynamics during cardiopulmonary exercise testing. In this report, we discuss HR recovery (HRR) within the first minute after exercise as one of the components of cardiac response to exercise, as HRR after exercise is known to be a powerful predictor of cardiac death even though its mechanism is not fully understood[1,5]. Information on HRR can be safely and easily acquired by routine exercise testing in comparison with data on other parameters.

It has been reported that an attenuated HRR is mainly caused by reduced parasympathetic reactivation and that parasympathetic impairment in patients with heart disease plays an important role in a poor prognosis[1,2,6,7]. A DNA sequence variation at the acetylcholine receptor subtype M2 (CHRAM2) locus was shown to be a potential modifier of HRR in healthy individuals[8]. However, these findings did not indicate that a parasympathetic mechanism is the sole regulator of HRR. On the other hand, an HR increase during exercise is considered to be due to many mechanisms, such as sympathetic activation, parasympathetic withdrawal, metabolic error in skeletal muscle with metabolite storage, central command mechanisms, etc.[2,9]. Therefore, it is considered that various factors influence HRR and chronotropic response and that not only parasympathetic impairment but other mechanisms could possibly be involved in HRR.

The present study aimed to clarify factors involved in HRR in patients who have had myocardial infarction. We particularly focused on expected HRR-related parameters consisting of intensity of exercise stress, left ventricular wall stress, sympathetic activity during exercise and metabolite production. The correlation of HRR with parameters of cardiopulmonary exercise testing, B-type natriuretic peptide (BNP), plasma norepinephrine (NE) and lactic acid was examined using univariate and multivariate statistical analysis.

Materials and Methods

Study Population

Fifty-two male patients were studied more than one month (93.5 ± 61.1 days) after the onset of myocardial infarction. Those with residual ischemia after myocardial infarction had undergone successful percutaneous coronary intervention. Patients with angina pectoris, uncontrolled congestive heart failure, implanted pacemaker, atrial fibrillation or who were being administered digitalis were excluded. All subjects underwent transthoracic echocardiography to analyze LVEF. Medical therapy consisted of a beta-blocker (n=42) or a dihydropyridine Ca channel blocker (n=11), but not a non-dihydropyridine Ca channel blocker. Informed consent for participation in this study was obtained from all subjects in accordance with the ethics committee of our institution.

Exercise Tests

All subjects underwent symptom-limited cardiopulmonary exercise tests. Symptom-limited cardiopulmonary exercise testing was performed with a cycle ergometer (StrenghErgo.240, Mitsubishi Co., Tokyo, Japan) with the subject in a sitting position. After a 4-min rest period, exercise began with a 4-min warm-up at 0 W and 60 rpm, after which intensity was increased incrementally by 1 or 2 W every 6 s according to the ramp protocol. HR and 12-lead electrocardiogram were monitored continuously (ML-5000, Fukuda Denshi, Tokyo, Japan). During the testing, blood pressure was measured every minute by an automatic indirect cuff manometer (STBD-780B, Nihon Collin Co., Ltd., Aichi, Japan). Exercise was stopped upon symptoms of exhaustion without a cool-down period. No patient experienced angina, syncope, ischemic ST segment changes or serious arrhythmia during exercise. Oxygen consumption (VO_2), carbon dioxide production (VCO_2) and ventilatory equivalent (VE) were measured using a breath-by-breath gas analyzer (AE-300, Minato Medical Science, Osaka, Japan), and we determined the anaerobic threshold (AT) by the V-slope method[10]. The value of the HRR was defined as the reduction in the HR from the rate at peak exercise to the rate 1-min after the cessation of exercise. We defined the increment in HR from rest to peak exercise as ΔHR. Additionally, HR change from at rest to that at the AT level was defined as ΔHR (AT-rest), and the HR change from

Table 1 Baseline characteristics of study subjects

Variable	All (n=52)	HRR ≥ 28 (bpm) (n=23)	HRR<28 (bpm) (n=29)	P value
Age (years)	57.8 ± 9.64	54.8 ± 9.17	60.2 ± 9.48	0.014
Diabetes mellitus	22 (42.3%)	10 (43.4%)	12 (41.3%)	NS
Hypertension	47 (90.4%)	20 (86.9%)	27 (93.1%)	NS
LVEF (%)	60.3 ± 8.10	59.4 ± 6.3	60.9 ± 9.39	NS
Beta-blocker	42 (82.7%)	18 (78.2%)	24 (82.7%)	NS
Dihydropyridine CCB	11 (21.1%)	4 (17.4%)	7 (24.1%)	NS

Values are indicated as mean ± SD or percentage (%). P values are statistically calculated between two groups separated by the median value of HRR. LVEF, left ventricular ejection fraction; CCB, calcium channel blocker; bpm, beats per minute

at the AT level to that at peak exercise was defined as ΔHR (peak-AT).

Measurement of Norepinephrine, BNP and Lactic Acid Concentration

We collected blood samples from the antecubital vein into three tubes while the patient was at rest and at peak exercise. Two tubes contained ethylenediaminetetraacetic acid (EDTA) for measurement of NE and BNP. Blood samples in the tube containing EDTA were centrifuged at 3,000 rpm for 10 min and plasma was extracted. Plasma concentration of NE was analyzed by high-performance liquid chromatography, and the BNP level was measured using CLEIA (chemiluminescent enzyme immunoassay) kits (Shionogi & Co., Ltd., Osaka, Japan). The third tube contained lactate oxidase for measurement of lactic acid. The blood sample was centrifuged at 3,000 rpm for 5 min and analyzed by an enzymatic method.

Assessment of Sympathetic Function

We examined sympathetic function at rest and during exercise using the response of NE to exercise and the sinoatrial nodal responsiveness to increments of NE. The index of sympathetic responsiveness was evaluated by the ratio of the increment in HR to the increment in NE from rest to peak exercise (ΔHR/logΔNE)[11]. Since plasma NE increases exponentially during the ramp exercise protocol, we expressed this value using a logarithm.

Statistical Analysis

Results are presented by the mean ± standard deviation (SD). Correlations were performed using Pearson's correlation coefficient. Results are presented as the coefficient of correlation. P value <0.05 was considered statistically significant. Multiple regression analysis was used for studying multivariable models.

Results

Clinical characteristics are shown in **Table 1**. The mean age of the subject population was 57.8 ± 9.6 years (range 33 to 72 years) and the mean LVEF was 60.3 ± 8.1%. Almost half had diabetes mellitus, and most were taking a β-adrenergic blocking agent. To investigate the influence of clinical background on HRR, we classified patients into two groups according to the median value of HRR: low HRR (<28 beats per minute [bpm]) group and high HRR (≥28 bpm) group. Subjects in the high HRR group were younger than those in the low HRR group (54.8 ± 9.17 years vs. 60.2 ± 9.48 years, p<0.05), but other parameters did not differ significantly between groups.

Table 2 summarizes exercise test results. Exercise tolerance was preserved. Mean peak VO_2 was 22.6 ± 3.65 mL/kg/min and peak watt was 124.1 ± 27.1. Lactic acid at peak exercise increased beyond the normal range in both groups. Both HR and systolic blood pressure (SBP) before exercise testing did not differ between groups.

HRR did not correlate with LVEF and peak VO_2 (**Fig. 1**), nor with lactic acid and log-transformed BNP both at rest and at peak exercise (**Fig. 2**). There was a significant correlation between ΔHR

Table 2 Exercise test results

	All (n=52)	HRR ≥ 28 (bpm) (n=23)	HRR<28 (bpm) (n=29)	P value
Peak VO_2 (mL/kg/min)	22.6 ± 3.65	23.0 ± 3.53	22.3 ± 3.78	NS
Peak watt	124.1 ± 27.1	128.8 ± 24.5	120.6 ± 28.9	NS
Lactic acid at rest (mg/dL)	12.4 ± 3.68	11.2 ± 3.34	13.4 ± 3.69	0.02
Lactic acid at peak exercise (mg/dL)	44.8 ± 13.4	45.0 ± 15.0	45.0 ± 12.3	NS
HR at rest (beat/min)	68.3 ± 9.93	68.4 ± 9.01	68.3 ± 10.7	NS
SBP at rest (mmHg)	122.1 ± 20.8	116.6 ± 16.0	126.6 ± 23.3	NS

Values are indicated as mean ± SD. P values are statistically calculated between two groups separated by the median value of HRR. HRR indicates heart rate recovery; VO_2, oxygen consumption; HR, heart rate; SBP, systolic blood pressure; bpm, beats per minute.

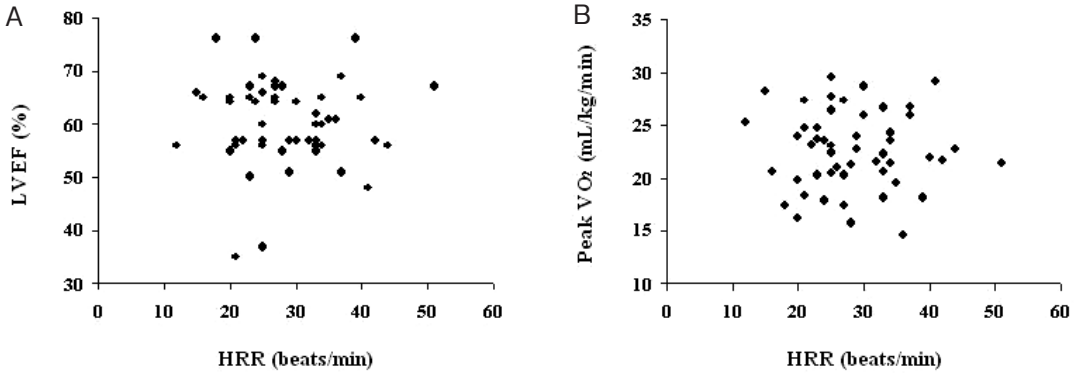

Fig. 1 Relationship of HRR with LVEF and peak VO_2.
A. HRR did not correlate with LVEF. **B**. HRR did not correlate with peak VO_2. HRR, heart rate recovery 1 min after exercise; LVEF, left ventricular ejection fraction; peak VO_2, peak oxygen consumption.

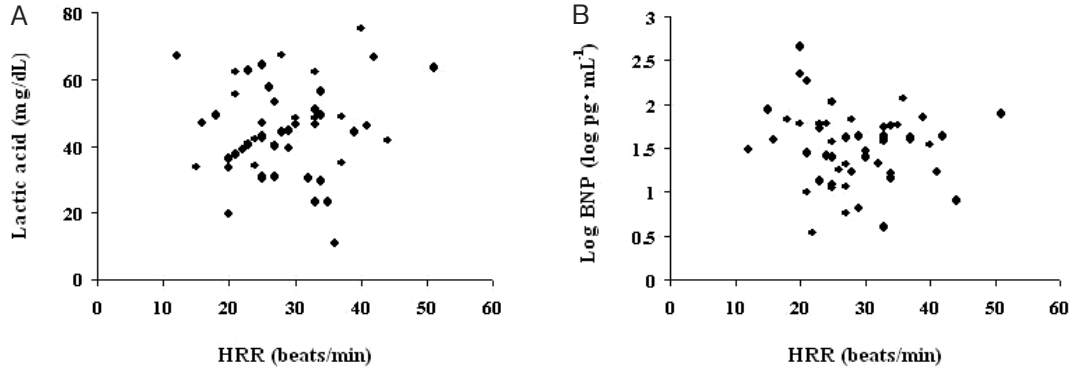

Fig. 2 Relationship between HRR and response of lactic acid and BNP at peak exercise.
A. Relationship with lactic acid. **B**. Relationship with BNP. HRR had no significant correlation with either lactate or log-transformed BNP at peak exercise.

and HRR ($r=0.30$, $p<0.05$). In addition, HRR did not correlate with ΔHR (AT-rest), but HRR significantly correlated with ΔHR (peak-AT) ($r=0.409$, $p<0.01$) **(Fig. 3)**. There was a significant negative correlation between HRR and NE concentration both at rest and at peak exercise ($r=-0.286$, $p<0.05$, $r=-0.310$, $p<0.05$) **(Fig. 4)**. HRR was significantly correlated with ΔHR/logΔNE ($r=0.421$, $p<0.01$) **(Fig. 5)**. NE concentration both at rest and at peak exercise did not correlate with LVEF, peak VO_2 and log-transformed BNP at rest and at peak exercise, respectively. There was no correlation of ΔHR/logΔNE with LVEF, peak VO_2 and log-transformed BNP at peak exercise.

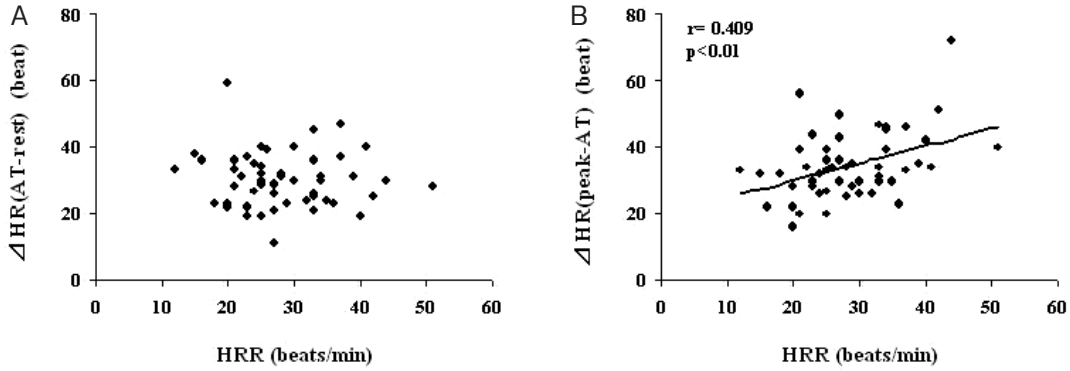

Fig. 3 Relationship of HRR with ΔHR (AT-rest) and ΔHR (peak-AT).
A. HRR did not correlate with ΔHR (AT-rest). **B**. HRR significantly correlated with ΔHR (peak-AT). ΔHR (AT-rest), increase in heart rate from rest to AT; ΔHR (peak-AT), increase in heart rate from AT to peak exercise; AT, anaerobic threshold.

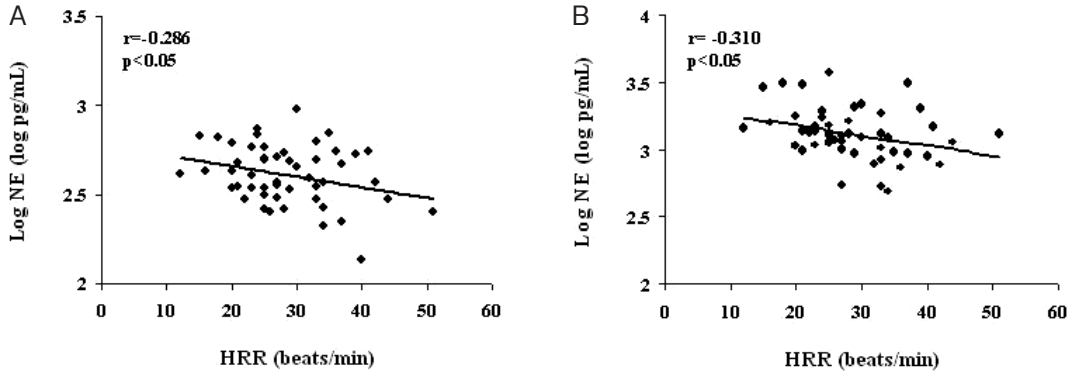

Fig. 4 Relationship between HRR and plasma NE concentration at rest and at peak exercise.
A. HRR had a significant negative correlation with log-transformed NE at rest. **B**. HRR had a significant negative correlation with log-transformed NE at peak exercise. NE, norepinephrine.

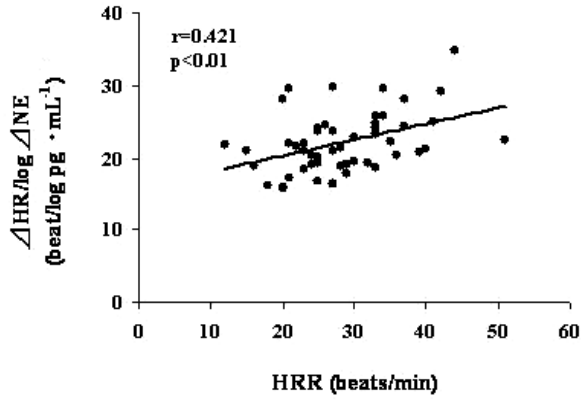

Fig. 5 HRR and the ability of HR to respond to NE.
HRR significantly correlated with ΔHR/logΔNE. ΔHR/logΔNE, ratio of increase in HR from rest to peak exercise to NE response to peak exercise. NE was assessed after log transformation. NE, norepinephrine.

We evaluated factors regulating HRR using stepwise multiple regression analysis. We set the explanatory variables as follows: clinical background, LVEF, peak VO_2, plasma concentrations of lactate and BNP at rest and at peak exercise, change in HR and NE from rest to peak, and ΔHR/logΔNE. When there was a significant correlation with an explanatory variable, these parameters were analyzed separately. Results of these analyses showed that ΔHR ($t=2.937$, $p=0.0050$) and logΔNE ($t=-2.782$, $p=0.0077$) independently correlated with HRR ($R^2=0.467$, $p=0.0027$).

Discussion

Although reduced parasympathetic reactivation was reported to play an important role in attenuated HRR after exercise[6], other factors related to attenuated HRR have not been sufficiently examined. Therefore, to reveal other mechanisms for the alteration of HRR, we investigated possible

mechanisms based on examination of each factor that influenced HR dynamics after exercise. The results shown in this report indicated that HRR significantly correlated with ΔHR (peak-AT), NE concentration and ΔHR/logΔNE, but not with the clinical background, LVEF and exercise intensity in our population. These findings indicated that not only parasympathetic impairment but also enhanced sympathetic activity during exercise influenced HRR. This is thought to be the first clinical report on the role of sympathetic function during exercise in HRR.

HRR and Exercise Intensity

It is not fully understood whether insufficient exercise intensity results in attenuated HRR. Therefore, we investigated exercise-intensity related parameters that included lactate production and peak VO_2. In patients with enhanced lactate production at peak exercise, it is expected that HRR would be delayed by the clearance of the metabolite. However, HRR was not related to the plasma lactate concentration at peak exercise. As shown in **Table 2**, we classified patients into two groups according to the median value of HRR, and the value for lactic acid at rest was the only statistically significant difference between the two groups. But those values in each group were within normal range, so we considered that this finding had no clinical significance. Similarly, HRR did not correlate with peak VO_2, although we assumed that intense exercise attenuates HRR. These results mean that HRR within 1 min after exercise is not easily affected by these two parameters of exercise intensity. We also investigated BNP as a parameter of left ventricular wall stress[12], but found no correlation between HRR and BNP at rest and at peak exercise. This means that HRR was not affected by stimulation such as pressure and volume overload of the left ventricle, that is, causing ventricular stretch.

HRR and Chronotropic Response

The present results showed that HRR correlated with the HR response to peak exercise. Additionally, to confirm the details of this finding, we divided HR response to exercise into two responses, which were the early and late exercise phases; the early phase was from rest to the AT level and the late phase was from the AT level to peak exercise. The HR response mainly reflects rapid parasympathetic attenuation in the early phase and sympathetic activation in the late phase[7]. For this report, we evaluated the relationship of HRR and HR response in both the early and late phrases of exercise and found that HRR had a significant relationship with HR response in the later but not in the early phase of exercise. This phenomenon means that the impaired sympathetic HR response to exercise is accompanied by a reduced HRR although the parasympathetic mechanism is not.

We have the following thoughts about this phenomenon. This study population was examined a relatively short time (93.5 ± 61.1 days) after the onset of myocardial infarction, which suggests that most of these subjects had an autonomic imbalance such as parasympathetic dysfunction [13]. Parasympathetic dysfunction caused by a clinical condition such as the post-myocardial infarction state may be one reason why HR response in the early phase did not correlate with HRR. It is supposed that impaired sympathetic HR response is related to an attenuated HRR.

HRR and Sympathetic Function

Our results indicated the possibility that HRR is affected by both NE concentration and ΔHR/logΔNE as an index of sympathetic responsiveness. Concerning an increase in NE concentration at rest and at peak exercise, sympathetic hyperactivity both at rest and at peak exercise is associated with an attenuated HRR. It is suggested that persistent sympathetic hyperactivity is accompanied by a reduced HRR. Previous studies reported on an autonomic imbalance after myocardial infarction[13,14]. Sympathetic hyperactivity occurs after acute myocardial infarction and remains for months, despite an absence of complications[14], and infarct localization had no effect on autonomic function[13]. It is supposed that the clinical condition in this study subjects is one of the causes of sympathetic hyperactivity and enhanced released NE leads to

attenuated HRR.

We also showed a relationship of HRR with sensitivity to NE. As Colucci WS noted[11], ΔHR/logΔNE indicates sensitivity of the β-adrenergic pathway through postsynaptic sensitization. In this population, both sympathetic hyperactivity and hyposensitivity are associated with an attenuated HRR; therefore, it can be speculated that the desensitization to NE via chronically sympathetic stimulation restricts HR response to intense exercise and results in attenuated HRR. As a possible cause of hyposensitivity to catecholamine, the down regulation of the β-adrenergic receptor, including an abnormality of the intracellular transmission pathway, is supposed[15]. Also, factors related to a sympathetic abnormality such as cytokinemia possibly have a harmful pathological effect in heart disease. In a population similar to that in the present paper, we reported previously that a sympathetic abnormality appeared through excess oxidative stress after myocardial infarction[16].

This present report indicates that prompt HRR is necessary to avoid excess sympathetic activation at peak exercise. Sympathetic desensitization is speculated to influence indirectly HRR and lead to attenuated HRR with exposure to sympathetic excitation. Therefore, we consider that sympathetic hyperactivity at peak exercise directly suppresses parasympathetic reactivation after exercise and results in attenuation of the return of the HR in the recovery phase.

Multivariate Analysis

It is thought that HRR is regulated by various factors and is weakly correlated with each factor. In the present investigation, HRR was actually significantly associated with several factors but the relationship was not close. Therefore, we evaluated the relationship of HRR with several independent parameters using multivariate analysis. As a result of multiple regression analysis, clinical features such as age, findings of cardiopulmonary exercise testing and BNP as the index of mechanical stress[12,17] had no obvious influence on HRR. The significant variables by univariate analysis independently participated in the alteration of HRR and formed a significant multiple correlation coefficient with HRR as the explanatory variable. The parameters that independently correlated with HRR in multiple regression analysis can suggest the essential condition of the disease. In other words, they reveal more closely the pathophysiological circumstances in comparison with ambiguous factors such as exercise intensity. Therefore, HRR is thought accurately predict the prognosis in patients with heart disease.

This study has several limitations. One is the problem concerning parasympathetic activity markers. We did not directly measure parasympathetic activity in our study population. If parasympathetic function had been examined, its influence might have been confirmed. However, HRR may have only weakly correlated with parasympathic activity, as parasympathic dysfunction may be present in our study population because parasympathetic dysfunction commonly appears after myocardial infarction[13]. Another limitation is that all subjects had experienced myocardial infarction and most were being administered a β-blocker unless contraindicated. However, in those subjects who were not taking a β-blocker, the principal results were not altered in comparison with those receiving this medication.

Even if evaluated based on these limitations, this present article includes some original findings. The most important is that sympathetic excitation during exercise was found to be responsible for the mechanism of attenuated HRR. This result is supported by previous reports, which suggested that an attenuated HRR leads to worsening of mortality and morbidity through the mechanisms relating to sympathetic excitation[18]. In the future, we intend to clarify the universality of our results in other subjects such as those with cardiomyopathy and further investigate the clinical implications.

In conclusion, sympathetic excitation during exercise leads to attenuated HRR in patients with myocardial infarction. It is considered that sympathetic excitation during exercise suppresses parasympathetic reactivation after exercise. Sympathetic down regulation under continuous sympathetic excitation is a possible cause for desensitization to NE.

References

1. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS: Heart-rate recovery immediately after exercise as a predictor of mortality. N Eng J Med 1999; 341: 1351–1357.
2. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetire P: Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352: 1951–1958.
3. Myers J, Prakash M, Froelicher V, Do D, Partingtin S, Atwood JE: Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002; 346: 793–801.
4. Frolkins JP, Pothier CE, Blackstone EH, Lauer MS: Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 2003; 348: 781–790.
5. Watanabe J, Thamiarasan M, Blackstone EH, Thomas JD, Lauer MS: Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: The case of stress echocardiography. Circulation 2001; 104: 1911–1916.
6. Imai K, Sato H, Hori M, et al.: Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Col Cardiol 1994; 24: 1529–1535.
7. Arai Y, Saul JP, Albrecht P, et al.: Modulation of cardiac autonomic activity during and immediately after exercise. Am J Physiol 1989; 256: H132–H141.
8. Hautala AJ, Rankinen T, Kiveniemi AM, et al.: Heart rate recovery after maximal exercise is associated with acetylcholine receptor M2(CHRM2)gene polymorphism. Am J Physiol 2006; 291: H459–H466.
9. Falcone C, Buzzi MP, Klersy C, Schwartz PJ: Rapid heart rate increase at onset of exercise predicts adverse cardiac events in patients with coronary disease. Circulation 2005; 112: 1959–1964.
10. Beaver WL, Wasserman K, Whipp BJ: A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986; 60: 2020–2027.
11. Colucci WS, Ribeiro JP, Rocco MB, et al.: Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic β-adrenergic desensitization. Circulation 1989; 80: 314–323.
12. Matsumoto A, Hirata Y, Momomura S, et al.: Effects of exercise on plasma level of brain natiruretic peptide in congestive heart failure with and without left ventricular dysfunction. Am Heart J 1995; 129: 139–145.
13. Detollenaere MS, Duprez DA, De Buyzere ML, Vandekerckhove HJ, De Backer GG, Clement DL: Autonomic imbalance in the recovery period after myocardial infarction. Eur Heart J 1993; 14: 1189–1194.
14. Graham LN, Smith PA, Stoker JB, et al.: Time course of Sympathetic Neural Hyperactivity After Uncomplicated Acute Myocardial Infarction. Circulation 2002; 106: 793–797.
15. Bristow MR, Ginsburg R, Minobe W, et al.: Decreased catecholamine sensitivity and β-adrenergic-receptor dencity in failing human hearts. N Engl J Med 1982; 307: 205–211.
16. Kato K, Fukuma N, Kimura-Kato Y, et al.: Improvement of sympathetic response to exercise by oral administration of ascorbic acid in patients after myocardial infarction. Int Heart J 2006; 111: 240–246.
17. Win HK, Chang S-M, Raizner M, et al.: Percent change in B-type natriuretic peptide levels during treadmill exercise as a screening test for exercise-induced myocardial ischemia. Am Heart J 2005; 150: 695–700.
18. Cohn JN, Levine TB, Olivari MT, et al.: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311: 819–823.

(Received, December 3, 2008)
(Accepted, January 7, 2009)