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Determinants of Heart Rate Recovery in Patients with Suspected Coronary Artery Disease

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***Background*: Heart rate recovery after exercise is an independent prognostic indicator for cardiovascular and all-cause mortality. The purpose of this study was to clarify the clinical determinants of heart rate recovery.**

***Methods and results*: We examined 114 consecutive male patients who underwent exercise myocardial perfusion single-photon emission computed tomography and echocardiography for the evaluation of suspected coronary artery disease. Heart rate recovery was obtained from the subtraction of heart rate in the first minute of recovery after exercise from maximal heart rate during exercise. Abnormal heart rate recovery was present in 50 patients (43.9%). Patients with abnormal heat rate recovery were more likely to have diabetes mellitus.**

Patients with abnormal heart rate recovery had a higher heart rate at rest than those with normal heart rate recovery (77.5 ± 13.6 vs. 72.3 ± 12.5 (bpm), $p<0.05$). However, no differences in left ventricular geometry investigated with echocardiography were observed between patients with normal and abnormal heart rate recovery. Furthermore, there was no difference in various scintigraphic variables between patients with normal and abnormal heart rate recovery. A stepwise multivariate analysis showed that heart rate at rest and diabetes mellitus were independent predictor of heart rate recovery ($p<0.05$).

***Conclusion*: Our results suggested that heart rate recovery is associated with clinical factors related to the cardiac autonomic function such as diabetes mellitus and heart rate at rest, but not with other ones such as left ventricular geometry and myocardial ischemia.**

Clinical and observational studies have shown that heart rate recovery (HRR) immediately after exercise is a strong predictor of cardiovascular and overall mortality, independently of cardiac risk factors, and exercise test results (3, 9, 11, 15).

Cardiac autonomic dysfunction is likely to play an important role in the reduced HRR immediately after exercise (1, 7, 13, 14). However, other clinical factors such as left ventricular geometry, left ventricular function and myocardial ischemia may contribute to the impaired HRR. Therefore, the purpose of this study was to clarify the clinical determinants of HRR.

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MATERIALS AND METHODS

Subjects

The population of the present study consisted of 114 consecutive male patients who underwent exercise myocardial perfusion single-photon emission computed tomography (SPECT) for the evaluation of suspected coronary artery disease.

Hypertension was defined by a history of blood pressure >140/90 mmHg and/or antihypertensive drug use. Diabetes mellitus (DM) was diagnosed by the World Health Organization criteria (17) to be fasting glucose greater than 140mg/dl, 2-hour postchallenge glucose was greater than 200mg/dl or patients who were receiving hypoglycemic medication. No patients on medication with β-adrenergic blockers or other drugs with a direct influence on the heart rate, such as digitalis, calcium channel blockers with chronotropic action, or other antiarrhythmic agents were included in this study. In this study, 31 patients were receiving antihypertensive medication with either angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, or combinations thereof. The purpose and risk of this study were explained to each patient before written informed consent was obtained.

Echocardiography

Subjects were examined in the left lateral decubitus position using a standard commercial ultrasound sonography (ACUSON Sequoia C256) with a 3.5 MHz phased array probe. The images were acquired from 2 standard views: the short-axis and the apical long-axis view of the left ventricle. In the short-axis view, images obtained at the level of the papillary muscles were used for analysis. Left ventricular diameters and wall thickness were measured from two-dimensional targeted M-mode echocardiography. In the apical long-axis view, transmitral flow velocity patterns were obtained by pulsed doppler images. We examined the following parameters and findings: left ventricular end-diastolic dimension (LVDd); left ventricular end-systolic dimension (LVDs); left ventricular percent fractional shortening (%FS); end-diastolic thickness of ventricular septum (IVS); end-diastolic thickness of left ventricular posterior wall (PW); peak early ventricular diastolic filling velocity (E); late ventricular diastolic filling velocity (A) and the deceleration time of early diastolic filling wave (E-DCT).

Exercise myocardial perfusion SPECT

After 5 minutes of supine rest, a 3-lead electrocardiogram was obtained at baseline for 1 minute. Exercise stress testing by bicycle ergometer was performed with continuous in all subjects. At peak exercise, thallium-201 111 MBq was injected intravenously and the patient continued to exercise at the same workload for an additional 1 minute. Blood pressure and cardiac status were monitored using 3 electrocardiographic leads and recorded during the exercise and at 1-minute intervals for 5 minutes after exercise. Exercise was terminated if there was increasing chest pain, a decrease in blood pressure >20 mmHg, limiting dyspnea or fatigue or sustained arrhythmia.

HRR was obtained by subtracting heart rate at the first minute of recovery from peak heart rate obtained during exercise. Abnormal HRR was defined as HRR$\leqq$18 beats per minute (16).

Within 5 min of thallium injection, SPECT images were acquired using a dual-head camera (Picker, PRIZM 2000) with a high-resolution collimator rotated in a 180^{o} orbit. Three hours later, delayed images were obtained. Images were interpreted by 2 experienced observers. Semi-quantitative visual interpretation of myocardial perfusion SPECT was performed with short-axis and vertical long-axis tomograms, which were divided 20 segments according to a method reported elsewhere (6). Each segment was scored by consensus of 2 expert observers who used 5-point grading system (0=normal to 4=absent).

The summed stress and the summed rest scores were obtained respectively. The difference between the summed stress score and the summed rest score was defined as the summed difference score (a marker of inducible ischemia). A summed difference score >2 indicated a presence of ischemia.

Statistical analysis

Continuous variables were expressed as mean ± SD and compared with Mann-Whitney test and categorical variables were compared using the chi-square test. A linear regression model with stepwise addition of clinical, exercise, echocardiographic and scintigraphic variables was created to determine those that were independently associated with HRR. A p value<0.05 defined statistical significant.

RESULTS

Clinical characteristics are summarized in Table 1. Abnormal HRR was present in 50 patients (43.9%). Patients with abnormal HRR were more likely to have DM. HRR was significantly lower in the diabetic patients than in non-diabetic patients (17.8 ± 7.7 vs. 21.6 ± 8.4 (bpm), p<0.05).

Table 2 shows echocardiographic characteristics. Patients with abnormal HRR had a lower % fractional shortening.

Exercise-related and scintigraphic characteristics are presented in Table 3. Patients with abnormal HRR had a higher heart rate at rest. However, there was no difference in various scintigraphic variables, such as summed stress score, summed rest score and summed difference score between patients with normal and abnormal HRR. In addition, there was no difference in HRR between patients with exercise induced ischemia or not.

In the multivariate analysis including all study subjects, the independent predictors of HRR were DM ($\beta = -0.27$, p=0.003) and heart rate at rest ($\beta = -0.19$, p=0.04).

Table 1. Clinical characteristics according to heart rate recovery

	Heart rate recovery		
	Normal (n=64)	Abnormal (n=50)	p value
Age (years)	70.4 ± 7.7	69.9 ± 6.2	0.45
Height (cm)	163.6 ± 7.6	163.6 ± 5.6	0.82
Weight (kg)	60.5 ± 8.4	61.7 ± 8.1	0.31
Body mass index (kg/m^2)	22.6 ± 2.8	23.1 ± 2.7	0.39
Hypertension	39 (61%)	40 (80%)	0.40
Diabetes mellitus	17 (27%)	25 (50%)	0.009
Previous myocardial infarction	11 (17%)	13 (26%)	0.18

Table 2. Comparison of echocardiographic characteristics in patients with normal and abnormal heart rate recovery

	Heart rate recovery		
	Normal (n=64)	Abnormal (n=50)	p value
LVDd (mm)	44.7 ± 5.1	44.5 ± 5.8	0.58
LVDs (mm)	27.7 ± 5.3	29.0 ± 6.9	0.53
%FS (%)	38.5 ± 7.0	35.2 ± 9.3	0.04
IVS (mm)	11.8 ± 2.3	11.6 ± 2.9	0.40
PW (mm)	10.0 ± 1.8	9.5 ± 1.9	0.13
IVS+PW (mm)	21.9 ± 3.6	21.2 ± 4.1	0.24
E (m/s)	0.47 ± 0.13	0.48 ± 0.14	0.73
A (m/s)	0.65 ± 0.12	0.70 ± 0.15	0.17
E/A ratio	0.74 ± 0.25	0.70 ± 0.17	0.60
E-DCT (ms)	211.4 ± 57.4	205.5 ± 48.6	0.76

LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; %FS, left ventricular percent fractional shortening; IVS, end-diastolic thickness of ventricular septum;PW, end-diastolic thickness of left ventricular posterior wall; E, peak early ventricular diastolic filling velocity; A, late ventricular diastolic filling velocity; E-DCT, deceleration time of early diastolic filling wave

Table 3. Comparison of exercise and single-photon emission computed tomographic variables in patients with normal and abnormal heart rate recovery

	Heart rate recovery		
	Normal (n=64)	Abnormal (n=50)	p value
Heart rate at rest (bpm)	72.3 ± 12.5	77.5 ± 13.6	0.046
Peak heart rate (bpm)	116.0 ± 12.5	109.9 ± 17.3	0.08
Exercise duration (sec)	331.4 ± 54.0	319.0 ± 69.0	0.36
Summed stress score	3.7 ± 7.1	4.7 ± 8.4	0.41
Summed rest score	2.2 ± 4.8	2.9 ± 5.7	0.31
Summed difference score	1.5 ± 3.9	1.8 ± 4.5	0.56
Presence of ischemia	14 (22%)	13 (26%)	0.38

DISCUSSION

In the present study, we demonstrated that DM and heart rate at rest are associated with HRR in patients with suspected coronary artery disease. Exercise results in prompt withdrawal of parasympathetic tone and subsequent sympathetic activation, while recovery is associated with parasympathetic activation followed by sympathetic withdrawal. HRR is

likely associated with parasympathetic activity. In the present study, we demonstrated that HRR was lower in diabetic patients than in non-diabetic patients.

Previous studies have shown that reduced HRR is associated with fasting plasma glucose (12). In our previous study, the development of abnormal HRR is associated with the extent of the autonomic dysfunction in diabetic patients (8). Therefore, our present study confirmed and extended the relation between HRR and DM to ordinary patients with suspected coronary artery disease. Moreover, a significant association was found between HRR and heart rate at rest. This finding is consistent with other studies (2). Heart rate at rest might be a global marker of cardiac autonomic function and patients with high parasympathetic activation usually showed low resting heart rate and baseline oxygen consumption. Thus, it is possible that resting heart rate was the prime independent predictor of HRR. Considering these factors, HRR might be associated with clinical factors related to cardiac autonomic function such as DM and resting heart rate.

In contrast, no significant association was found for left ventricular geometry, or left ventricular function with HRR. The lack of correlation between HRR and left ventricular geometry, left ventricular function in this study also confirmed previous studies showing a poor correlation of HRR with indexes of left ventricular geometry in diabetic patients (4). Thus, HRR is not likely to be influenced by left ventricular geometry and left ventricular function. In the present study, various myocardial SPECT markers such as summed stress score, summed rest score and summed difference score were not associated HRR. Moreover, a presence of myocardial ischemia judging from myocardial SPECT was not associated with HRR. As for myocardial ischemia, Georgouslias et al (5) have shown myocardial ischemia detected by myocardial SPECT to be related to HRR, which is inconsistent with the results of our study. In this study, there was no exclusion of patients on medication with β-adrenergic blockers or other drugs with a direct influence on heart rate such as digitalis and calcium channel blockers with a chronotropic action. Moreover, patients with previous myocardial infarction or heart failure were not involved in their study.

On the contrary, another study has shown that HRR was not associated with SPECT markers of myocardial ischemia (10). Therefore, the difference in study population may explain the disparity in results between the present and other studies. In addition, previous studies showed that abnormal HRR and exercise induced myocardial ischemia were independent predictors of all-cause mortality (15). These findings suggest that the mechanism of increased mortality associated with HRR might be more related to autonomic dysfunction than to the presence or extent of myocardial ischemia. Thus, HRR is not likely to be associated with myocardial ischemia. However, further research is needed to elucidate the role of ischemia on HRR.

In conclusion, HRR was associated with clinical factors related to the cardiac autonomic function, but not with other ones such as left ventricular geometry, left ventricular function and myocardial ischemia.

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