Heart Rate Recovery After Exercise Is a Predictor of Silent Myocardial Ischemia in Patients With Type 2 Diabetes

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OBJECTIVE—Slow heart rate recovery (HRR) predicts all-cause mortality. This study investigated the relationship between silent myocardial ischemia (SMI) and HRR in type 2 diabetes.

RESEARCH DESIGN AND METHODS—The study enrolled 87 consecutive patients with type 2 diabetes and no chest symptoms. They underwent treadmill exercise testing and single-photon emission computed tomography imaging with thallium scintigraphy. Patients with abnormal myocardial perfusion images also underwent coronary angiography.

RESULTS—SMI was diagnosed in 41 patients (47%). The SMI group showed slower HRR than the non–SMI group (18 ± 6 vs. 30 ± 12 bpm; $P < 0.0001$). HRR was significantly associated with SMI (odds ratio 0.83 [95% CI 0.75–0.92]; $P = 0.0006$), even after adjustment for maximal exercise workload, resting heart rate, maximum heart rate, rate pressure product, HbA_{1c}, use of sulfonamides, and a history of cardiovascular disease.

CONCLUSIONS—HRR can predict SMI in patients with type 2 diabetes.

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Coronary artery disease (CAD) is the leading cause of death in patients with diabetes mellitus (1). Silent myocardial ischemia (SMI) is defined as myocardial ischemia without chest pain (2). It has been reported to occur in more than 20% of asymptomatic patients with type 2 diabetes (3), and early detection is extremely important.

Recovery of the heart rate immediately after exercise is mediated by vagal reactivation (4), with slow heart rate recovery (HRR) being a predictor of all-cause mortality (5) and sudden death (6). The relationship between slow HRR and SMI in diabetes is unclear, so this study was performed to clarify the relationship in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

—A total of 98 consecutive patients with type 2 diabetes and no chest symptoms were studied. They had electrocardiographic abnormalities or at least two risk factors for CAD in addition to diabetes, and presented to Toshiba Hospital between September 2005 and December 2008. Patients were excluded if they had a pacemaker, congestive heart failure, cardiomyopathy, β-blocker or digitalis therapy, congenital valvular heart disease, or left bundle branch block. As a result, 87 patients underwent a treadmill test and single-photon emission computed tomography (SPECT) with thallium scintigraphy.

Exercise stress tests were done on a motorized treadmill (Quinton Q-STRESS TM55, Cardiac Science, Bothell, WA) using the standard Bruce protocol. Patients were encouraged to perform maximal exercise. Testing was terminated after the patient reached the target heart rate (based on age) or because of fatigue, dyspnea, leg discomfort, systolic blood pressure >250 mmHg, ventricular tachycardia, or ischemic electrocardiographic changes. After peak workload was achieved, HRR was calculated as the decrease of the heart rate from its peak during exercise to that at 1 min after finishing the exercise.

Thallium SPECT imaging (Toshiba GCA-7200A, Tokyo, Japan) was performed according to the standards of the American Society of Nuclear Cardiology (7). Rest and stress images were obtained on the same day. Myocardial perfusion abnormalities were judged by two cardiologists, and SMI was diagnosed from abnormal myocardial perfusion images without associated symptoms. Patients with abnormal myocardial perfusion underwent coronary angiography (Toshiba Infinix Celeve-I INFX-8000C), and significant stenosis was defined as ≥75% diameter stenosis.

Statistical analysis

Continuous variables are presented as the mean ± SD. Differences between groups were compared with Student *t* test or the χ^2 test. Analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC), and significance was accepted at $P < 0.05$.

RESULTS

—The patients were divided into groups with or without SMI. Patients were 64 ± 10 years old, 21 were women (24.1%), and the mean BMI was 24.0 ± 3.2 kg/m^2. The mean duration of diabetes was 9.8 ± 6.6 years, 11 patients (12.6%) had a history of cardiovascular disease, and the mean HbA_{1c} was 7.4 ± 1.7%.

The mean resting heart rate was 83.7 ± 12.0 bpm, maximum heart rate was 138.0 ± 14.2 bpm, 1-min postexercise heart rate was 113.9 ± 14.4 bpm, 3-min postexercise heart rate was 91.9 ± 12.0 bpm, and mean maximum workload was 8.2 ± 2.1 METs. The exercise end point was leg fatigue in 29 (33%), diagnostic ST segment changes in 42 (48%), or shortness of breath in 17 (18%). Sixty patients (69%) achieved their target heart rate (≥85% of [220 − age]).

During the treadmill test, 42 patients (48%) showed ST depression, and 41 (47%) with abnormal perfusion defects on scintigraphy were diagnosed as having SMI. Thirty patients (34%) showed significant stenosis on coronary angiography.

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Comparison of the SMI and non–SMI groups

There were no differences of clinical characteristics between the two groups (Table 1). The 1- and 3-min heart rates were similar in both groups, but the SMI group showed slower HRR (18 ± 6 vs. 30 ± 12 bpm; $P < 0.0001$) along with a higher resting heart rate ($P = 0.01$), lower maximum heart rate ($P < 0.001$), lower rate pressure product ($P = 0.0032$), and lower max METs. The number of patients who achieved the target heart rate was not significantly different between the two groups ($P = 0.13$).

Multivariate logistic regression analysis was performed to assess parameters significantly associated with myocardial ischemia, using the following variables: HRR, max METs, resting heart rate, maximum heart rate, rate pressure product, HbA_{1c}, use of sulfonamides, and history of cardiovascular disease. As a result, HRR was significantly associated with SMI (odds ratio 0.83 [95% CI 0.75–0.92], $P = 0.0006$) and was also significantly associated with significant angiographic stenosis, even after adjustment for the above covariates (0.84 [0.75–0.94]; $P = 0.0017$).

CONCLUSIONS

—Many physicians screen asymptomatic persons by stress testing, but it has a low specificity (8). Furthermore, it has been reported that a decrease of the chronotropic reserve predicts CAD (9).

Our findings indicated that slow HRR after exercise strongly predicts SMI in patients with type 2 diabetes. Slow HRR similarly predicts myocardial ischemia at the microvascular and macrovascular levels.

Possible mechanisms of SMI include autonomic denervation of the myocardium (10–12), a higher pain threshold during exercise testing (13), higher β-endorphin levels (14), and increased production of anti-inflammatory cytokines that may block pain transmission and increase the neural activation threshold (15).

The prevalence of SMI may exceed 20% among asymptomatic patients with type 2 diabetes (3). In this study, the prevalence was a high 47%, probably because our cohort included patients with electrocardiogram abnormalities, at least two risk factors for CAD in addition to diabetes, or a history of CAD (13%).

Table 1—*Comparison of the SMI and non–SMI patients*

Variable	SMI patients ($n = 41$)	Non–SMI patients ($n = 46$)	OR (95% CI)	*P* value*	
				Univariate	Multivariate
Female sex	8 (20)	13 (28)	—	0.34	—
Age (years)	66 ± 11	62 ± 10	—	0.14	—
BMI (kg/m^2)	24.0 ± 3.3	24.1 ± 3.1	—	0.9	—
Duration of diabetes (years)	11.0 ± 6.3	10.3 ± 9.1	—	0.82	—
Current smoker	13 (32)	22 (48)	—	0.13	—
Family history of diabetes	20 (49)	33 (72)	—	0.19	—
Hypertension	30 (73)	36 (78)	—	0.45	—
Hyperlipidemia	29 (71)	27 (59)	—	0.18	—
Cardiovascular disease	6 (15)	5 (11)	1.01 (0.15–6.87)	0.6	0.99
Diabetic treatment					
Diet only	8 (20)	11 (24)	—	0.62	—
Oral hypoglycemic agent	23 (56)	25 (54)	—	0.87	—
Use of sulfonamides	16 (39)	17 (37)	1.02 (0.31–3.4)	0.84	0.97
Insulin	10 (24)	10 (22)	—	0.77	—
ACE inhibitors or ARB	28 (68)	24 (52)	—	0.13	—
Statins	24 (59)	21 (46)	—	0.23	—
Calcium channel blockers	11 (27)	9 (20)	—	0.42	—
Serum cholesterol (mmol/L)					
Total	4.97 ± 1.01	4.97 ± 0.88	—	0.96	—
LDL	2.77 ± 0.88	2.82 ± 0.72	—	0.72	—
Serum triglycerides (mmol/L)	3.65 ± 2.09	4.34 ± 2.95	—	0.2	
HbA_{1c} (%)	7.6 ± 1.8	6.9 ± 1.3	0.7 (0.47–1.04)	0.05	0.08
Heart rate (bpm)					
Resting	87 ± 11	81 ± 12	1.01 (0.95–1.08)	0.01	0.67
Maximum	133 ± 14	143 ± 13	0.98 (0.91–1.05)	<0.001	0.54
1-min	115 ± 14	113 ± 15	—	0.45	—
3-min	95 ± 12	90 ± 11	—	0.05	—
Recovery	18 ± 6	30 ± 12	0.83 (0.75–0.92)	<0.0001	0.0006
Maximum METs	7.2 ± 2.1	9.0 ± 1.7	0.79 (0.56–1.12)	<0.0001	0.19
Rate pressure product	25,316 ± 4,739	28,368 ± 4,641	1.0 (0.99–1.01)	0.0032	0.41
Achievement of THR	25 (61)	35 (76)	—	0.13	—

Data are mean ± SD or number (%). ARB, angiotensin-receptor blocker; OR, odds ratio; THR, target heart rate. *The *t* test or χ^2 test was used to assess differences between the SMI group and non–SMI group. Multivariate logistic regression analysis was performed to identify the parameters significantly associated with myocardial ischemia using heart rate recovery, max METs, resting heart rate, maximum heart rate, rate pressure product, HbA_{1c}, use of sulfonamides, and history of cardiovascular disease.

This study had the limitations of being performed at a single institution and in a small patient population. Accordingly, the relation between HRR and SMI should be assessed by a larger study with pathophysiologic data in the future.

Although it is possible that our results were influenced by the difference of exercise parameters between the two groups, we conclude that HRR is useful for easy detection of SMI in high-risk type 2 diabetic patients to allow primary prevention and that HRR is significantly associated with SMI even after adjustment for the influence of exercise parameters.

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T.Ya. contributed to all study processes, including data research and manuscript preparation. T.Yo. contributed to discussion and wrote, reviewed, and edited the manuscript. K.M., T.L., and F.S contributed to discussion.

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