Deterioration of Heart Rate Recovery Index in Patients with Systemic Lupus Erythematosus

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ABSTRACT. **Objective.** Systemic lupus erythematosus (SLE) is an autoimmune disorder resulting in multisystemic inflammatory damage. It is reported that cardiovascular diseases (CVD) are responsible for 20%–30% of deaths in patients with SLE. Heart rate recovery after exercise is a function of vagal reactivation, and its impairment is an independent prognostic indicator for cardiovascular and all-cause mortality. The aim of our study was to evaluate the heart rate recovery index in patients with SLE.
Methods. The study population included 48 patients with SLE (35 women, mean age 46.3 ± 12.8 yrs, mean disease duration 6.0 ± 2.3 yrs) and 44 healthy controls (30 women, mean age 45.7 ± 12.9 yrs). Basal electrocardiography, echocardiography, and treadmill exercise testing were performed on all patients and controls. The heart rate recovery index was defined as the reduction in the heart rate from the rate at peak exercise to the rate at the first minute (HRR_1), second minute (HRR_2), third minute (HRR_3), and fifth minute (HRR_5) after stopping exercise stress testing.
Results. There were significant differences in HRR_1 and HRR_2 indices between patients with SLE and the control group (24.1 ± 6.5 vs 33.3 ± 9.3; $p < 0.001$, and 44.6 ± 13.3 vs 53.7 ± 9.9; $p < 0.001$, respectively). Similarly, HRR_3 and HRR_5 indices of the recovery period were lower in patients with SLE, compared with indices in the control group (57.6 ± 13.0 vs 64.9 ± 11.7; $p = 0.006$, and 67.2 ± 12.3 vs 75.0 ± 15.4; $p = 0.009$, respectively). Effort capacity was markedly lower (9.0 ± 1.9 vs 11.1 ± 2.3 metabolic equivalents; $p = 0.001$, respectively) among the patients with SLE.
Conclusion. The heart rate recovery index is deteriorated in patients with SLE. When the prognostic significance of the heart rate recovery index is considered, these results may contribute to explain the increased occurrence of cardiac death. It points to the importance of the heart rate recovery index in the identification of high-risk patients. (First Release September 1 2010; J Rheumatol 2010; 37:2511–15; doi:10.3899/jrheum.100163)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS   HEART RATE RECOVERY INDEX
EXERCISE TEST   AUTONOMIC NERVOUS SYSTEM   SUDDEN CARDIAC DEATH

Systemic lupus erythematosus (SLE) is an autoimmune disorder resulting in multisystemic inflammatory damage[1,2]. It is reported that cardiovascular diseases (CVD) are responsible for 20%–30% of deaths in patients with SLE[3,4,5]. Cardiac involvement in patients with SLE can include the pericardium, conduction system, myocardium, valves, and coronary arteries[6,7]. Involvement of the peripheral nervous system and central nervous system in SLE has been well described, but only a few reports of autonomic neuropathy

in this disease have been reported[8,9]. However, studies showed that both sympathetic and parasympathetic pathways are impaired, either singly or together[10].

The autonomic nervous system plays a central role in regulating cardiovascular function. Cardiovascular autonomic nervous system dysfunction is related with significantly increased cardiovascular mortality[11,12,13]. Heart rate recovery (HRR) is an important measure of autonomic nervous system dysfunction and is directly correlated with parasympathetic activity[14]. Impaired HRR during the first minute following exercise was shown to be a prognostic index and independently predicted cardiovascular and all-cause mortality rates[15]. The value for the HRR index was defined as the reduction in the heart rate from the rate at peak exercise to the rate at the first, second, third, and fifth minute after the discontinuation of an exercise stress test. Autonomic dysfunction could contribute to serious arrhythmias in a patient with SLE. The impairment of HRR provides useful clinical information about evaluation of patients with SLE for higher risk of serious arrhythmias.

Previous studies[10,16] investigated the effect of SLE on

autonomic dysfunction, such as Raynaud's phenomenon, sweating abnormalities, and postural hypotension; however, there is no study that evaluates the heart rate recovery index. Our aim was to evaluate the heart rate recovery index in patients with SLE.

MATERIALS AND METHODS

Study population. In 69 consecutive outpatients, the diagnosis of sarcoidosis was established according to the criteria of the American College of Rheumatology for classification of SLE[17]. Patients who had coronary artery disease (n = 2), diabetes mellitus (n = 4), hypertension (n = 8), orthopedic disorders (n = 2), and 8 patients who smoked were excluded from the study. In addition, 5 patients failed to complete the exercise test and were excluded: 2 complained of shortness of breath and 3 complained of fatigue. As a result, the study population included 48 patients with SLE (35 women; mean age 46.3 ± 12.8 yrs; mean disease duration 6.0 ± 2.3 yrs) and 44 healthy subjects as controls (14 men; mean age 45.7 ± 12.9 yrs).

The activity of SLE was determined by erythrocyte sedimentation rate (ESR) and the SLEDAI score (Systemic Lupus Erythematosus Disease Activity Index)[18]. Age, sex, body mass index, and biochemical measurements were recorded: fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. The demographic characteristics and clinical features of the patients and controls are given in Table 1.

All patients were under followup with the nephrology department, and renal involvement was determined in 43 patients; 36 patients had mesangial and 7 patients had focal proliferative glomerulonephritis in renal biopsy examinations. Fourteen patients had a history of pericarditis and/or chronic pericardial effusion. Neither lung nor gastrointestinal organ involvement was determined in patients.

Patients had no symptoms of heart disease except palpitation. Seven had palpitation complaints and 2 of them had been using low-dose verapamil (80 mg). All patients were symptom-free at the time of the study and had not been receiving verapamil therapy for 2 weeks.

In all subjects, we performed 12-lead electrocardiography (ECG) at 25 mm/s (paper speed), and we performed transthoracic echocardiography by means of a GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-MHz transducer. The control subjects had no cardiovascular or any other organ system disease and presented with normal physical examination, chest radiograph, electrocardiogram, and 2-dimensional and Doppler echocardiogram.

Patients were excluded from the study if they had 1 of the following: hemoglobin < 10 g/dl; pregnancy; diseases interfering with the autonomic nervous system including diabetes mellitus, renal, and liver diseases, Parkinson's disease, porphyria, and amyloidosis; CVD including hypertension, ischemic heart disease, left ventricle ejection fraction < 50%, severe valvular regurgitation, moderate or severe valvular stenosis, cardiomyopathy and cardiac arrhythmia; neurological diseases; chronic obstructive pulmonary disease; or a smoking habit.

Our study complied with the Declaration of Helsinki and was approved by the Ethics Committee and the institutional review board of Erciyes University Medical School. Each patient gave informed consent.

Exercise testing. All patients underwent treadmill testing using the Bruce protocol. The predicted peak heart rate was calculated as 220 minus age, and the aim was to reach at least 85% of the age-predicted heart rates. The end of exercise was flagged, and at least 5 min of postexercise heart rate recorded with the subject at rest. Qualified exercise physiologists and/or cardiology fellows prospectively collected physiologic and hemodynamic data during testing, including symptoms, heart rate, heart rhythm, blood pressure, and estimated functional capacity in metabolic equivalents (METS; where 1 MET = 3.5 ml/kg/min of oxygen consumption). Heart rate recovery indices were defined as the reduction in the heart rate from the rate at peak exercise to the rate at first, second, third, and fifth minute after

Table 1. Demographic and clinical features of the patients and the controls (mean ± SD)

Characteristics	Patients with SLE, n = 48	Controls, n = 44	p
Age, yrs	46.3 ± 12.8	45.7 ± 12.9	0.84
Women, men	33/15	30/14	0.95
Body mass index, kg/m^2	26.2 ± 2.2	26.4 ± 2.8	0.77
Heart rate, beats/min	90.0 ± 14.5	86.2 ± 12.3	0.18
Fasting glucose, mg/dl	96.7 ± 7.8	95.0 ± 9.5	0.34
Total cholesterol, mg/dl	168.6 ± 33.0	164.8 ± 32.6	0.58
HDL cholesterol, mg/dl	36.6 ± 5.7	38.3 ± 6.3	0.29
LDL cholesterol, mg/dl	115.1 ± 21.9	116.5 ± 19.0	0.75
Plasma triglycerides, mg/dl	120.8 ± 50.1	125.3 ± 70.8	0.72
Systolic BP, mm Hg	124.7 ± 16.5	123.4 ± 15.5	0.84
Diastolic BP, mm Hg	76.6 ± 11.5	74.4 ± 13.6	0.40
Clinical features			
Duration of SLE, yrs	6.0 ± 2.3	—	
SLEDAI score	5.0 ± 1.7	—	
Palpitation, n (%)	7 (14.6)	—	
Raynaud disease, n (%)	5 (10.4)	—	
Perspiration, n (%)	6 (12.5)	—	
Medications, n (%)			
Oral corticosteroids	37 (77)	—	
Hydroxychloroquine	5 (10.4)	—	
Azathioprine	8 (16.6)	—	
Cyclophosphamide	7 (14.6)	—	
Mycophenolate mofetil	6 (12.5)	—	

SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BP: blood pressure.

the end of the exercise stress test; these results were indicated as HRR_1, HRR_2, HRR_3, and HRR_5, respectively.

Statistical analysis. Continuous variables were given as mean ± SD; categorical variables were defined as percentages. An independent-samples t test was used to compare the study variables between patients with SLE who used corticosteroids (CS) and patients with SLE who did not use CS, and between patients with SLE and controls. A probability value of $p < 0.05$ was considered significant. All statistical analyses were carried out using SPSS software (version 15.0 for Windows; SPSS, Chicago, IL, USA).

RESULTS

The baseline characteristics of the study groups are shown in Table 1. In the patient group, the mean duration of the disease was 6.0 ± 2.3 years. According to the basic clinical and demographic characteristics, both groups of the study were similar with respect to age, creatinine (mg/dl), body mass index, and fasting glucose and cholesterol levels. All subjects were normotensive, and no significant differences were observed in systolic or diastolic blood pressures and resting heart rates between the 2 groups. All patients and controls had sinus rhythm and normal 12-lead ECG results at rest. All completed the exercise stress test without rhythm abnormalities, ischemic changes, or other complications. Clinical features of patients with SLE are also given in Table 1.

The mean SLEDAI score and duration of the disease (years), ESR (mm/h), and medication used in patients with SLE are shown in Table 1. Seventy-seven percent of patients

were taking CS. We performed subgroup analysis to examine possible effects of CS use on hemodynamic measures and heart rate variability indices. It was determined that there was no significant difference in heart rate or systolic and diastolic blood pressure between patients who used CS and patients who did not (91.0 ± 10.0 vs 88 ± 14.0, 125.0 ± 7.5 vs 122.7 ± 15.0, 73.8 ± 14.5 vs 75.1 ± 8.5, respectively; $p > 0.05$). Heart rate variability indices, HRR_1, HRR_2, HRR_3, and HRR_5 were also similar between patients taking CS and patients not taking CS (25.4 ± 2.5 vs 25.0 ± 5.3, 45.8 ± 15.3 vs 44.6 ± 9.4, 56.8 ± 5.5 vs 58.6 ± 18.0, 68.2 ± 10.0 vs 66.9 ± 11.5, respectively; $p > 0.05$).

Comparisons of the baseline echocardiographic values among patients with SLE and the controls are summarized in Table 2. No differences were found regarding left ventricular diameters, ejection fraction, and left ventricular mass. There was no difference in right ventricular diastolic diameter and pulmonary artery systolic pressure (PASP) between groups. In the patient group, PASP was measured between 20 and 30 mm Hg in 24 patients and between 15 and 20 mm Hg in 20 patients, and under 15 mm Hg in 4 patients in echocardiographic evaluation. Right heart catheterization was performed on 24 patients who had PASP > 20 mm Hg and similar results were obtained with echocardiography. Right heart catheterization was not performed in patients who had PASP < 20 mm Hg. No patient had a diag-

Table 2. Comparison of variables from echocardiography and exercise stress tests of patients and controls (mean ± SD).

Variables	Patients with SLE, n = 48	Controls, n = 44	p
Echocardiographic findings			
RVEDD, mm	32.9 ± 4.7	32.4 ± 4.0	0.53
LVEDD, mm	46.3 ± 3.9	46.0 ± 4.0	0.77
LVESD, mm	29.5 ± 3.1	29.0 ± 2.8	0.49
IVSD, mm	10.4 ± 1.6	10.4 ± 1.5	0.90
LVPWD, mm	10.0 ± 2.2	9.8 ± 1.5	0.74
LVEF, %	65.6 ± 5.7	67.3 ± 6.0	0.16
Left atrial size, mm	31.2 ± 3.8	30.4 ± 4.0	0.35
Left ventricular mass, g	156.8 ± 18.9	150.1 ± 23.5	0.13
PASP, mm Hg	26.3 ± 5.1	25.3 ± 5.6	0.37
Exercise stress test findings			
Exercise time, min	8.7 ± 2.7	9.5 ± 2.1	0.13
Maximal heart rate, beats/min	166.0 ± 13.6	169.1 ± 14.6	0.30
Maximal systolic BP, mm Hg	166.5 ± 23.5	170.3 ± 23.1	0.44
Maximal diastolic BP, mm Hg	78.0 ± 13.1	79.5 ± 17.1	0.63
Maximal, METS	9.0 ± 1.9	11.1 ± 2.3	0.001
HRR_1	24.1 ± 6.5	33.3 ± 9.3	< 0.001
HRR_2	44.6 ± 13.3	53.7 ± 9.9	< 0.001
HRR_3	57.6 ± 13.0	64.9 ± 11.7	0.006
HRR_5	67.2 ± 12.3	75.0 ± 15.4	0.009

SLE: systemic lupus erythematosus; RVEDD: right ventricular end-diastolic diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVSD: interventricular septum diameter; LVPWD: left ventricular posterior wall diameter; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; BP: blood pressure; METS: metabolic equivalents (1 MET = 3.5 ml/kg/min of oxygen consumption); HRR: heart rate recovery index.

nosis of pulmonary hypertension after clinical evaluation, echocardiographic examination, and catheterization.

Comparisons of the maximal heart rate, maximal systolic and diastolic blood pressure, exercise duration, and metabolic equivalents attained during the exercise stress test among patients with SLE and controls are summarized in Table 2. According to these results, the first-minute and second-minute HRR indices of patients with SLE were significantly lower than those of the control group (24.1 ± 6.5 vs 33.3 ± 9.3; p < 0.001, and 44.6 ± 13.3 vs 53.7 ± 9.9; p < 0.001, respectively). Similarly, HRR indices after the third and fifth minutes of the recovery period were significantly lower in patients with SLE compared with those indices in the control group (57.6 ± 13.0 vs 64.9 ± 11.7; p = 0.006, and 67.2 ± 12.3 vs 75.0 ± 15.4; p = 0.009). On the other hand, we found that METS attained during the exercise stress test of patients with SLE were significantly lower than those of the controls (9.0 ± 1.9 vs 11.1 ± 2.3 METS; p = 0.001).

DISCUSSION

We have demonstrated that heart rate recovery indices were impaired in the first, second, third, and fifth minutes of the recovery period after maximal exercise testing in patients with SLE compared to controls. We also observed that effort capacity was significantly lower in patients with SLE. To our knowledge, this is the first study that shows an impaired heart rate recovery index among patients with SLE.

Cardiac involvement in SLE includes all components of the heart[6,7]. Involvement of the nervous system in SLE can mean confusional states, psychosis, anxiety, and affective disorders including seizures, chorea, myelopathy, and headaches[19,20]. The autonomic nervous system plays a central role in regulating cardiovascular function in both patients with disease and healthy individuals. The rise in heart rate during exercise is thought to be due to activation of the sympathetic nervous system and the simultaneous suppression of the parasympathetic nervous system[11]. On the other hand, the fall in heart rate immediately after exercise is considered to be the parasympathetic reactivation together with sympathetic withdrawal[21].

Studies showed that heart rate recovery is a mark of autonomic system function and is directly associated with parasympathetic nervous system activity[22,23,24]. Savin, et al[23] interpreted their findings as indicating that an increment in vagal activation as well as a decrement in sympathetic activation had been detected already during the first minutes of the recovery soon after exercise cessation. Imai, et al[21] showed that short-term and midterm HRR indices (30 s to 2 min) are mediated primarily by vagal reactivation. Kannankeril, et al[25] showed that the parasympathetic effect on heart rate was defined by differences in heart rate with and without atropine. These data demonstrated that the parasympathetic system effects continued during high-intensity exercise, and a large parasympathetic system

effect on heart rate was noted by 1 min, increased at 4 min, and then stayed stable until 10 min in the recovery period. In the literature, heart rate recovery has been studied in various diseases such as heart failure[26], coronary artery disease[27], diabetes mellitus[28], metabolic syndrome[29], obstructive sleep apnea[30], and Behçet's disease[31]. We excluded subjects with coronary artery disease, diabetes mellitus, neurologic diseases, prior cardiovascular event, and current smoking to avoid the effects of these variables on the heart rate recovery index. In addition, both the control group and subjects with SLE had almost similar atherosclerotic risk factors such as blood pressure, age, and lipid profile.

Several studies have determined that the impaired heart rate recovery index after exercise is a powerful and independent predictor of cardiovascular and all-cause mortality[11,12,24]. Cole, et al[11] reported that a delayed decrease in heart rate during the first minute after exercise has been found to be a potent predictor of overall mortality, of the presence or absence of myocardial perfusion defects, and of changes in heart rate during exercise. Jouven, et al[32] showed that an HRR < 25 beats/min after the first minute of the recovery period increased the relative risk by 2.2 for sudden cardiac death, compared with the group with HRR rate > 40 beats/min. Nishime, et al[33] showed that when the heart rate recovery decreased to < 10–12 beats/min, risk of death increases.

Cardiac abnormalities in SLE occur in a high percentage of patients[34,35]. Pericarditis is a very common clinical manifestation in SLE (20%–30% of all patients)[36]. Lioté, et al[10] showed that abnormal cardiovascular autonomic function was observed in patients with SLE. Louthrenoo, et al[16] demonstrated that 19% of patients with SLE had symptoms suggesting autonomic nervous system dysfunction. Although sinus tachycardia, atrial fibrillation, and atrial ectopic beats are frequent, malignant ventricular arrhythmias are rarely reported in SLE[37]. Various laboratory methods to assess autonomic nervous system function may help. However, they often require special equipment and training, so they cannot be easily used for routine evaluation. The heart rate recovery provides a useful method to measure autonomic activity. Our results show that patients with SLE have decreased heart rate recovery indices compared with controls. Hence, autonomic dysfunction might be a risk factor for cardiac death in patients with SLE, and heart rate recovery index analysis might be used for risk stratification.

Heart rate recovery index may be affected by corticosteroids, which may have positive inotropic effects. Corticosteroids are leading drugs among treatments for SLE. In our study, we determined that CS use did not affect HRR indices. Indeed, all of our patients had taken longterm CS therapy, but 27% of them had not been using CS for the last month before the study. In addition, patients were using oral prednisone therapy in low dose, with median dose of 5

mg (range 2–7 mg) per day. As a result, we eradicated positive inotropic effects of CS in the patient group.

The heart rate recovery index is deteriorated in patients with SLE. When the prognostic significance of the heart rate recovery index is considered, these results may explain the increased occurrence of cardiac death in patients with SLE. Our study points to the importance of the heart rate recovery index, a simple measure that can be clinically useful in the identification of high-risk patients.

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