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Abnormal heart rate recovery on exercise in ankylosing spondylitis

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ABSTRACT

Objectives: This study evaluated the heart rate recovery response in ankylosing spondylitis (AS) patients and control subjects.
Background: Delayed heart rate recovery after exercise reflects AD and independently predicts adverse cardiac outcome.
Methods: Fifty-one patients with AS and 50 age- and matched controls received electrocardiography, echocardiography, and treadmill exercise testing. The heart rate recovery (HRR) index was calculated as the reduction in heart rate from the rate at peak exercise to the rate at the 1st (HRR_1), 2nd (HRR_2), 3rd (HRR_3) and 5th (HRR_5) minute after the cessation of exercise stress testing.
Results: There were significant differences in HRR_1 and HRR_2 indices between patients and controls (24.8 ± 12.1 vs 34.9 ± 11.0; $p < 0.001$ and 41.2 ± 14.2 vs 54.3 ± 11.8; $p < 0.001$, beats/min, respectively). Similarly, HRR_3 and HRR_5 indices were lower in patients than controls (51.3 ± 15.1 vs 65.2 ± 14.0; $p < 0.001$ and 61.0 ± 14.2 vs 76.1 ± 14.8; $p < 0.001$). In addition, exercise capacity was markedly lower (8.1 ± 2.0 vs 10.5 ± 2.5 METs; $p < 0.001$) in AS than controls.
Conclusion: The HRR index is impaired in AS patients, implying the occurrence of autonomic dysfunction even without active joint disease or frank cardiac involvement.

1. Introduction

Ankylosing spondylitis (AS) is a systemic inflammatory disorder that affects mainly young men with a predilection of sacroiliac joints and spine [1]. Well-known cardiac manifestations include aortitis, myocarditis, myocardial fibrosis and pericarditis [2,3]. In addition, sinus node dysfunction, atrial and ventricular arrhythmias were rarely reported [4,5]. However, data was scant about the presence of autonomic dysfunction (AD) in AS. The autonomic nervous system plays a central role in the regulation of cardiovascular function and AD is independently related to increased cardiovascular mortality [6,7]. Heart rate recovery (HRR) correlates directly to parasympathetic activity [8,9] and its impairment indicates the presence of AD. Impaired HRR during the first minute following exercise, in particular, has been shown to be an important and independent prognosticator for increased cardiovascular and all-cause mortality rates [10,11]. The study aimed to evaluate the heart rate recovery response after exercise in AS patients as compared to matched controls.

2. Methods

2.1. Study population

The study population included 51 patients with AS and 50 matched controls. Patients were consecutively recruited from the outpatient rheumatology clinic and all fulfilled the modified New York Criteria for the classification of AS [12]. Age- and gender-matched controls were recruited from the hospital visitors or staffs. Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [13]. Age, gender, body mass index and biochemical measurements (fasting blood glucose, lipid profiles, C-reactive protein [CRP]) were recorded from all subjects.

All participants received 12-lead electrocardiography (ECG) at 25 mm/s (paper speed) and transthoracic echocardiography by means of a GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-MHz transducer. All the controls had normal physical examinations, no known cardiovascular or any other systemic diseases, and normal electrocardiographic and echocardiographic exams. Patients were excluded from the study if they (i) were pregnant; (ii) were taking atrioventricular nodal blockers; (iii) had diseases interfering with the autonomic nervous system, including diabetes mellitus, renal and liver diseases, Parkinson's disease; (iv) had known cardiovascular diseases including hypertension, ischemic heart disease, left ventricle (LV) ejection fraction lower than 50%, moderate or severe valvular regurgitation, cardiomyopathy and cardiac arrhythmia; (v) had active joint disease; or (vi) had neurological diseases and chronic obstructive pulmonary disease. We have also excluded smokers in both groups. This study complied with the Declaration of Helsinki, was approved by the Local

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Ethics Committee of Erciyes University, School of Medicine, and informed consent was obtained from each participant.

2.2. Exercise testing

All subjects underwent exercise treadmill testing using the Bruce protocol. The predicted peak heart rate was calculated as (220 − age) beats/min and the aim of exercise was to reach at least 85% of the age-predicted heart rates. The end of exercise was flagged, and at least 5 min of post-exercise heart rate was recorded with the subject at rest. Qualified exercise physiologists and/or cardiology fellows prospectively collected physiologic and hemodynamic data during testing, including development of symptoms, heart rate, heart rhythm, blood pressure, and estimated functional capacity in metabolic equivalents (METs; where 1 MET = 3.5 ml/kg per 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 the 1st-, 2nd-, 3rd- and 5th-minute after the cessation of exercise stress test; these results were indicated as HRR_1, HRR_2, HRR_3 and HRR_5 respectively. All the qualified exercise physiologists and/or cardiology fellows were blind to the clinical and laboratory data of the patients and controls.

2.3. 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 continuous variables and chi-square or Fisher's exact test for categorical variables between patients and controls. A probability value of $p < 0.05$ was considered statistically significant, and two-tailed p values were used for all statistics. All statistical analyses were performed using dedicated software (SPSS, version 15.0 for Windows; SPSS, Chicago, IL).

3. Results

The baseline characteristics of the study groups are shown in Table 1. Patients and controls were matched regarding age, gender as well as basic clinical and laboratory characteristics. Patients had higher CRP levels as expected. Two study groups had comparable systolic or diastolic blood pressures as well as resting heart rates. All of them were in sinus rhythm and had normal 12-lead ECG results at rest. All subjects completed the exercise stress tests without new-onset rhythm abnormalities, ischemic changes, or other complications. The mean BASDAI scores, symptoms duration (years) and medications of AS patients were shown in Table 2.

Table 3 compared the echocardiographic and exercise parameters between patients and controls. Both groups had similar LV function and pulmonary arterial systolic pressures. The maximal heart rate, maximal systolic and diastolic blood pressures and exercise duration were similar between 2 groups. However, the heart rate recovery indices were significantly impaired in patients than controls (Fig. 1). Specifically, the 1st- and 2nd-minute HRR indices of patients were significantly lower than those of controls (24.8 ± 12.1 vs 34.9 ± 11.0; $p < 0.001$ and 41.2 ± 14.2 vs 54.3 ± 11.8; $p < 0.001$, respectively). Similar results were observed regarding HRR indices after the 3rd and 5th minute of the recovery period. (Patients versus. controls: 51.3 ± 15.1 vs 65.2 ± 14.0; $p < 0.001$ and 61.0 ± 14.2 vs 76.1 ± 14.8; $p < 0.001$). Exercise functional capacity was markedly lower in patients than controls (8.1 ± 2.0 vs 10.5 ± 2.5 METs; $p < 0.001$).

Table 1
Clinical characteristics of the study population.

	Ankylosing spondylitis (n = 51)	Controls (n = 50)	p value
Age (year)	38.6 ± 11.1	40.4 ± 10.3	0.383
Male	30 (59%)	23 (46%)	0.197
Hypertension	3 (6%)	5 (10%)	0.444
Hyperlipidemia	5 (10%)	8 (16%)	0.353
Fasting glucose (mg/dl)	86.5 ± 10.2	89.3 ± 8.3	0.131
Triglyceride (mg/dl)	113.7 ± 48.9	129.8 ± 70.0	0.181
LDL-cholesterol (mg/dl)	113.2 ± 24.6	107.6 ± 23.4	0.270
HDL-cholesterol (mg/dl)	44.3 ± 9.1	41.6 ± 9.9	0.161
Total Cholesterol (mg/dl)	180.3 ± 32.1	176.1 ± 21.6	0.444
C-reactive protein [CRP] (mg/l)	10.4 ± 5.4	3.8 ± 1.1	<0.001
Systolic blood pressure (mm Hg)	122.7 ± 17.5	124.4 ± 14.5	0.649
Diastolic blood pressure (mm Hg)	79.6 ± 13.5	77.4 ± 15.6	0.442
Baseline heart rate (beats/min)	85.4 ± 12.3	84.4 ± 17.8	0.680
BMI (kg/m^2)	26.2 ± 2.6	25.4 ± 2.7	0.591

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. LDL: Low density lipoprotein, HDL: High density lipoprotein, BMI: Body mass index.

Table 2
Clinical features of patients with ankylosing spondylitis.

	Value
Duration of disease (year)	5.2 ± 3.2
BASDAI score	3.85 ± 2.1
Peripheral involvement	9 (18%)
Uveitis	3 (6%)
Medication	
NSAID	51 (100%)
Methotrexate	1 (1%)
Salazopyrine	11 (22%)
Etanercept	5 (10%)
Adalimumab	6 (12%)

4. Discussion

We demonstrated that heart rate recovery indices were impaired in the 1st, 2nd, 3rd and 5th minutes of the recovery period after maximal exercise testing in AS patients with respect to controls, implying the occurrence of cardiac autonomic dysfunction in otherwise healthy AS patients without active articular or cardiac manifestations.

AS is a chronic inflammatory disease that involves axial skeleton and extra-articular organs, such as the eyes, lungs, neurological system, and heart [1,2,12]. This disease characteristically affects young adults with a peak age of onset between 20 and 30 years [12]. The cardiac involvement in AS including aortitis causing aortic regurgitation, myocarditis causing conduction disturbances, myocardial fibrosis causing abnormalities of left ventricular relaxation and pericarditis [3]. Conduction system abnormalities in these patients usually precede the aortic root disease [14,15]. The involvement in cardiac autonomic nervous system in AS was less established in the literature. The rise in heart rate during

Table 3
Echocardiographic and exercise stress test parameters of the study population.

	Ankylosing spondylitis (n = 51)	Controls (n = 50)	p value
Echocardiographic findings			
Right ventricular end-diastolic diameter (mm)	34.6 ± 4.8	33.4 ± 4.4	0.188
Left ventricular end-diastolic diameter (mm)	47.2 ± 4.8	46.7 ± 4.4	0.561
Left ventricular end-systolic diameter (mm)	30.1 ± 4.1	29.1 ± 2.8	0.173
Left ventricular ejection fraction (%)	65.4 ± 6.0	66.7 ± 5.7	0.265
Left ventricular mass (grams)	155.9 ± 49.9	154.9 ± 61.3	0.933
Pulmonary arterial systolic pressure (mm Hg)	23.9 ± 10.0	22.8 ± 5.2	0.467
Exercise stress test findings			
Exercise time (min)	8.9 ± 2.5	9.4 ± 2.6	0.147
Maximal heart rate (beats/min)	166.4 ± 18.7	168.5 ± 14.3	0.541
Maximal systolic blood pressure (mm Hg)	167.3 ± 22.6	168.6 ± 23.2	0.775
Maximal diastolic blood pressure (mm Hg)	78.5 ± 15.2	79.6 ± 15.4	0.716
Maximal metabolic equivalents (METs)	8.1 ± 2.0	10.5 ± 2.5	<0.001
HRR_1 (beats/min)	24.8 ± 12.1	34.9 ± 11.0	<0.001
HRR_2 (beats/min)	41.2 ± 14.2	54.3 ± 11.8	<0.001
HRR_3 (beats/min)	51.3 ± 15.1	65.2 ± 14.0	<0.001
HRR_5 (beats/min)	61.0 ± 14.2	76.1 ± 14.8	<0.001

Data are expressed as mean ± standard deviation for normally distributed data. HRR: Heart rate recovery.