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Original Article

Effects of cardiac rehabilitation on cardiac autonomic functions in ankylosing spondylitis patients: A randomized controlled study

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Abstract

Aim: Ankylosing spondylitis (AS) is a systemic chronic inflammatory disease that has various adverse effects on cardiac autonomic functions. On the other hand, there is no data regarding the effects of cardiac rehabilitation on cardiac autonomic functions in AS patients. In this study, we aimed to investigate the effects of cardiac rehabilitation on cardiac autonomic nervous system parameters in patients with AS.

Materials and Methods: This study was designed as a prospective randomized controlled trial. The study was carried out in December 2015 - August 2016. 34 patients who fulfilled the modified New York criteria were enrolled in the study. Patients were randomly assigned into case and control groups each consisting of 17 patients. The cardiac rehabilitation program was applied to the case group for eight weeks. Patient evaluation with clinical assessment, echocardiography, and exercise stress testing was performed before and after treatment.

Results: A total of 34 patients made the final study population (37.35± 5.22 years, 55.9% male). There were no significant differences regarding the baseline characteristics between case and control groups. Patients in the case group had better MET levels, exercise time, resting heart rate, and chronotropic reserve than the control patients following cardiac rehabilitation.

Conclusion: Our results indicate that significant improvement in cardiac autonomic functions can be obtained in AS patients when the cardiac rehabilitation program is combined with the medical treatment.

Keywords: Ankylosing spondylitis; cardiac rehabilitation; chronotropic reserve; heart rate recovery

INTRODUCTION

Ankylosing spondylitis (AS) is a systemic chronic inflammatory disease and typically encountered in young males. It primarily affects the sacroiliac and vertebral joints. The pathophysiology of AS has not been clearly identified yet (1). Constitutional symptoms and extra-articular signs related to the involvement of other organ systems (cardiovascular, pulmonary, genitourinary, neurological, and gastrointestinal) can be seen in AS (2).

Heart abnormalities are seen in 10-30% of AS patients and can present as aortitis, aortic regurgitation, myocarditis, myocardial fibrosis, and pericarditis (2). Sinus node dysfunction and atrioventricular conduction abnormalities are rarely encountered (3). Cardiac autonomic functions in AS patients have also been evaluated in several studies (4,5). These studies measured heart rate variability, sympathetic skin response and autonomic cardiac baroreflexes to assess cardiac autonomic functions and reported increased sympathetic activity in AS patients (4,5).

Although anti-inflammatory medications make up the essential treatment in AS, physical treatment can also provide numerous benefits (6). Physical treatment in AS aims to ameliorate pain and stiffness, improve mobility, prevent disability, enhance the quality of life, and prevent structural injury. Exercise was shown to exert anti-inflammatory effects via direct and indirect mechanisms in AS and supportively, a cardiovascular exercise in AS patients was reported to enhance physical fitness and reduce disease activity (7). Niedermann et al. revealed that regular exercise at least 3 times a week resulted in significantly higher fitness levels and lower disease

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activity reflected in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores at 3-months follow-up (7).

Previous studies reported cardiac autonomic benefits in different patient groups with cardiac rehabilitation; most commonly assessed using heart rate variability (HRV) and heart rate recovery (HRR) measures. These benefits were reflected with increased vagal tone after training and enhanced sympathetic drive, lowered vagal influence, or both at peak exertion (8,9).

Although current exercise recommendations in AS focus on spine flexibility exercises, cardiovascular training might prove to be beneficial in AS patients as suggested by Niedermann et al. (7). Evidence concerning the impact of cardiac rehabilitation on cardiac autonomic functions in AS patients is scarce. In this study, we aimed to investigate the effect of cardiac rehabilitation on AS disease activity (reflected in BASDAI, BASFI scores, and CRP levels), functional capacity (reflected in METs), and cardiac autonomic nervous system indices (reflected in resting heart rate, chronotropic reserve, and HRR) in patients with AS.

MATERIALS and METHODS

Study Population

Thirty-four patients (20- 45 years) who were diagnosed with AS according to modified New York criteria between December 2015- August 2016 at the Department of Physical Medicine and Rehabilitation were included in this randomized controlled prospective study (10). Pregnant women; smokers; patients diagnosed with chronic kidney disease, chronic liver disease, diabetes mellitus, malignancies, neurological diseases (such as Parkinson's disease), cardiac diseases (such as cardiac arrhythmias, cardiomyopathies, reduced left ventricular ejection fraction, moderate-severe valvular regurgitation, ischemic heart disease), chronic obstructive pulmonary disease; patients with a prior history of total hip replacement and those currently treated with atrioventricular node blockers were not included in the study. Patients who meet the inclusion criteria were randomized by simple randomization method. We used a random number generator and assigned each patient to the case or control group.

Study Protocol

Eligible patients were randomized into case and control groups (each including 17 patients). Control group received a home exercise program (stretching of pectoral muscles, augmenting muscular strength of back, abdominal respiration, pursed-lip respiration, and deep breathing exercises) for 30 minutes/ day that lasted 8 weeks. The case group received 24 sessions of cardiac rehabilitation for 60 minutes/ day that lasted 8 weeks (3 days a week) in addition to home exercise program. The home exercise program was described by physicians. The cardiac rehabilitation program using Ergoline ergometer exercise bike (Ergoselect 200P, Ergoline, Bitz, Germany) was coached by physicians and nurses. The study was approved by the local ethical committee and was carried out in accordance with the principles outlined in the Declaration of Helsinki (No. NEÜ-KAEK 2015/285). Written informed consent was obtained from all participants.

Detailed medical history and physical examination findings (including range of motion in cervical spine, lumbar spine, shoulder, elbow, hand, finger, hip, knee, feet joints; motor and sensory examinations; deep tendon reflexes and pathological reflexes) were recorded for all patients. The evaluation was performed by the same physician for each patient.

Assessment of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), acute phase reactant levels (C- reactive protein [CRP]), electrocardiography, echocardiography and exercise stress test (GE T2100 Treadmill, CardioSoft v6.7 Diagnostic System, GE Healthcare, Finland) were performed both before and after exercise programs. Exercise capacity was measured using the maximal workload achieved during exercise stress test (EST) and expressed as metabolic equivalents of task (METs). The chronotropic reserve and HRR indices were also calculated using EST. The chronotropic reserve was calculated using the formula CI = {[Heart rate at peak exercise − resting heart rate]/[(220 − age) − resting heart rate)]}x100. HRR indices were calculated by subtracting 1st (HRR1) and 2nd (HRR2) minute heart rates following EST from the maximal heart rate during EST. The evaluation was performed by the same cardiologist for each patient.

Cardiac Rehabilitation Program

The aerobic exercise program was individualized for each patient taking the baseline exercise stress test results into account. In addition, exercise program was revised each week following weekly assessments.

The first and last five minutes of the cardiac rehabilitation group was spared for warm-up and cooling, respectively. Target heart rate interval was calculated using the age-based formula [to take a percentage (70%-85%) of the maximal or peak heart rate]. 90% of the maximal heart rate was permitted at the most. Cycle ergometer training was followed by stretching and augmentation exercises. Augmentation exercises were individualized referring to one- repetition maximum (1RM). Maximum load that three separate major muscle groups in the upper and lower extremities can lift for a single repetition was determined. The workout included biceps, triceps, and deltoid muscle groups in the upper extremities; quadriceps, hamstring, and abductor muscle groups in the lower extremities. Isotonic exercises were performed at an intensity of 75% 1RM at a training volume of 3-sets of 10-repetitions. Duration of the cardiac rehabilitation program was 3 days per week which lasted for 8 weeks. At the end of the eighth week, the patients were recommended to continue home exercise program.

Home Exercise Program

Patients were recommended to perform a home exercise program, composed of 20- 45 min brisk walking 3 days a week followed by stretching and augmentation exercises for a total duration of 24 weeks. The program was individualized for each patient. Phone interviews were performed each week to assess and promote the patients' compliance with the home exercise program.

Statistical Analysis

Shapiro- Wilk test was used to test whether parameters were normally distributed. Normally distributed continuous parameters were presented as mean± standard deviation and skewed continuous parameters were expressed as median (range defined as minimum-maximum). Categorical data were presented as frequency and percentages. Normally distributed parameters were compared using the Student's t- test in two independent samples and paired sample t- test in two dependent samples. The Mann- Whitney U test and Wilcoxon signed-rank tests were used to compare skewed continuous parameters between two independent and dependent groups, respectively. Categorical data was compared using the Chi-square and Fisher's exact tests. Statistical analyses were performed using Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

A total of 34 patients made the final study population [37.35± 5.22 years, 55.9% male]. Baseline characteristics of the study population are given in Table 1. Age, gender, height, weight, body mass index (BMI), disease duration, peripheral joint involvement, history of uveitis or medications did not differ significantly among the two groups (p>0.05) (Table 1). In addition, none of the patients had extra-articular manifestations (Table 1).

Table 1. Descriptive and clinical characteristics of the study population (n= 34). SD: Standard deviation

	Case (n=17)	Control (n=17)	p value
Age (year), ±SD	38.00±4.68	36.71±5.78	0.478
Gender, n (%)			
Male	8 (47.1)	11 (64.7)	0.300
Female	9 (52.9)	6 (35.3)	
Height (m), ±SD	1.68±0.05	1.67±0.10	0.833
Weight (kg), ±SD	80.71±18.15	75.24±16.57	0.366
BMI (kg/m^2), ±SD	28.78±6.60	26.94±5.11	0.369
Duration of disease (years), median (min-max)	5 (2-26)	6 (1-20)	0.658
Peripheral joint involvement, n (%)	1 (5.9)	0	1.000
Extraarticular manifestations, n (%)	0	0	-
History of uveitis, n (%)	1 (5.9)	1 (5.9)	1.000
Prescribed medications, n (%)			
NSAID+ conventional DMARD	8 (47.1)	6 (35.3)	0.486
NSAID+ biological DMARD	9 (52.9)	11 (64.7)	

BMI: Body Mass Index, DMARD: Disease-Modifying Antirheumatic Drugs; NSAID: Non- Steroidal Anti- Inflammatory Drugs

BASDAI and BASFI scores and CRP levels before and after treatment are shown in Table 2. BASDAI score was significantly higher in the case group compared to the control group before treatment (p<0.05). On the other hand, there was no significant difference between groups regarding BASDAI score after treatment (p>0.05). In addition, BASFI score and CRP levels were similar in the case and control groups both before and after treatment (p>0.05). BASDAI, BASFI scores, and CRP levels did not differ in any of the groups before and after treatment (p >0.05).

Transthoracic echocardiography findings before and after treatment are given in Table 3. Systolic pulmonary artery pressure (sPAP) was significantly lower in the case group than the control group following cardiac rehabilitation (p<0.05). On the other hand, right ventricular end-diastolic diameter, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left ventricular ejection fraction were not significantly different between case and control groups both before and after treatment (p> 0.05).

Exercise stress test results before and after treatment are shown in Table 4. In the case group, resting heart rate, maximum heart rate, exercise duration, and maximum METs showed a significant change after cardiac rehabilitation. Maximum heart rate, exercise duration, and maximum METs were significantly increased, whereas resting heart rate was significantly decreased in the case group after rehabilitation (p<0.05). On the other hand, none of these parameters changed significantly in the control group before and after treatment (p >0.05).

Table 2. Levels of CRP, BASDAI and BASFI scores before and after treatment (n= 34). SD: Standard deviation

	Case (n=17)	Control (n=17)	p value
BASDAI, ±SD			
Before treatment	5.63±2.06	4.02±2.34	0.041
After treatment	4.92±1.53	4.08±2.65	0.265
Δ BASDAI	-0.71±2.24	0.05±1.20	0.223
p value	0.208	0.329	
BASFI, ±SD			
Before treatment	3.85±2.22	3.65±2.50	0.801
After treatment	3.59±2.07	4.26±3.60	0.510
Δ BASFI	-0.26±1.06	0.62±2.22	0.152
p value	0.489	0.858	
CRP, median (min- max)			
Before treatment	2.3 (2.0-21.9)	2.7 (0-22.7)	0.838
After treatment	2.1 (2.0-20.3)	2.0 (0-27.9)	0.708
Δ CRP	0 [(-6.70)-6.50]	0 [(-3.40)-5.20]	0.812
p value	0.508	0.753	

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C- reactive protein

Table 3. Transthoracic echocardiographic findings before and after treatment (n= 34). SD: Standard deviation

	Case (n=17)	Control (n=17)	p value
RVEDD, median (min- max)			
Before treatment	32 (28-42)	32 (25-35)	0.919
After treatment	32 (28-42)	33 (24-37)	0.563
Δ RVEDD	0 [(-2)-5]	1 [(-2)-7]	0.245
p value	0.287	**0.034**	
LVEDD (mm), ±SD			
Before treatment	43.18±4.38	43.82±4.28	0.666
After treatment	44.41±4.49	44.53±4.61	0.940
Δ LVEDD	1.24±2.41	0.71±2.57	0.540
p value	0.051	0.274	
LVESD (mm), ±SD			
Before treatment	26.18±3.63	25.71±3.87	0.717
After treatment	25.24±3.36	25.76±3.90	0.674
Δ LVESD	-0.94±2.73	0.59±2.41	0.266
p value	0.174	0.921	
LVEF (%), ±SD			
Before treatment	60±0	60.29±1.21	0.325
After treatment	60.29±1.21	60±0	0.325
Δ LVEF	0.29±1.21	-0.29±1.21	0.167
p value	0.332	0.332	
sPAP (mmHg), ±SD			
Before treatment	25.18±3.64	26.53±2.79	0.233
After treatment	24.82±3.54	27.88±4.11	0.026
Δ sPAP	-0.35±3.41	1.35±4.0	0.190
p value	0.675	0.182	

LVEDD: Left Ventricular end- Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; LVESD: Left Ventricular end- Systolic Diameter; RVEDD: Right Ventricular end- Diastolic Diameter; sPAP: Systolic Pulmonary Artery Pressure

Table 4. Exercise test results before and after treatment (n= 34). SD: Standard deviation			
	Case (n=17) ±SD	Control (n=17) ±SD	p value
Resting heart rate (bpm)			
Before treatment	91.71±6.26	93.24±7.86	0.607
After treatment	86.76±8.33	91.88±8.98	0.095
Δ Resting heart rate	-4.94±8.93	-1.35±3.43	0.132
p value	**0.037**	**0.123**	
Maximum heart rate (bpm)			
Before treatment	156.29±13.72	173.00±18.40	0.005
After treatment	163.41±11.64	170.41±16.60	0.164
Δ Maximum heart rate	7.12±12.75	-2.59±12.80	0.034
p value	**0.035**	0.417	
Exercise duration (min)			
Before treatment	9.21±3.24	9.79±2.80	0.579
After treatment	10.29±3.34	9.64±2.64	0.532
Δ Exercise duration	1.09±1.65	-0.15±1.42	0.026
p value	**0.015**	0.675	
Maximum METs			
Before treatment	10.08±2.84	11.02±2.83	0.340
After treatment	12.12±3.36	11.30±2.28	0.412
Δ Maximum METs	2.04±1.76	0.28±1.41	0.003
p value	**<0.001**	0.422	
Heart rate at 1st minute of rest (bpm)			
Before treatment	133.47±16.59	151.29±18.82	0.006
After treatment	140.29±13.07	148.71±16.15	0.105
Δ Heart rate at 1st minute of rest	6.82±20.17	-2.59±12.69	0.113
p value	0.182	0.413	
Heart rate at 2nd minute of rest (bpm)			
Before treatment	117.71±17.74	134.12±19.65	0.016
After treatment	121.24±11.36	130.76±15.08	0.046
Δ Heart rate at 2ndminute of rest	3.53±18.45	-3.35±12.71	0.214
p value	0.442	0.293	
Bpm: Beats Per Minute; min: Minute			

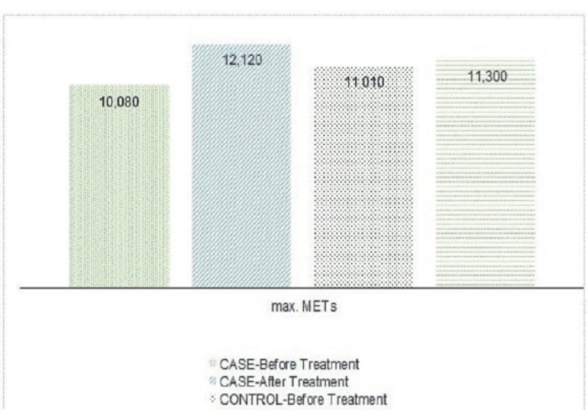

Figure 1. Maximum METs before and after treatment in the study population

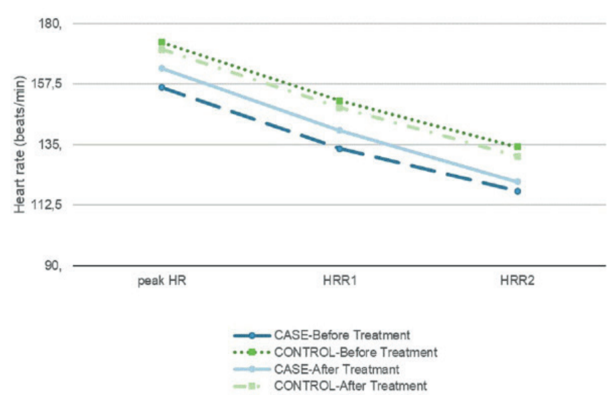

Figure 2. Maximum heart rate during exercise test and heart rate at the first and second minutes of rest

Maximum METs before and after treatment in the study population are shown in Figure 1. Furthermore, heart rate at both first and second minutes of rest following maximal exertion was found to be similar in case and control groups before and after treatment (p>0.05). Maximum heart rate and heart rate at the first and second minutes of rest are shown in Figure 2.

Heart rate recovery (HRR) indices and chronotropic reserve before and after treatment are shown in Table 5. There was no significant difference between case and control groups both before and after treatment regarding HRR indices (p> 0.05). Despite there was a significant difference regarding chronotropic reserve between case and control groups before treatment (p<0.05), chronotropic reserve of the case group increased significantly after treatment and the difference was disappeared (p>0.05). On the other hand, chronotropic reserve did not change significantly in the control group after treatment (p>0.05). The HRR indices and chronotropic reserve before and after treatment in case and control groups are shown in Figure 3.

Table 5. Heart rate recovery indices before and after treatment (n= 34). SD: Standard deviation

	Case (n=17) ±SD	Control (n=17) ±SD	p value
Heart rate recovery index at first minute of rest (bpm)			
Before treatment	22.82±11.89	21.71±6.54	0.736
After treatment	23.12±6.94	21.71±6.73	0.551
Δ HRRI 1	0.29±10.66	0.00±6.89	0.924
p value	0.911	1.000	
Heart rate recovery index at second minute of rest (bpm)			
Before treatment	38.59±13.20	38.88±13.92	0.950
After treatment	42.18±8.32	39.65±10.06	0.430
Δ HRRI 2	3.59±8.99	0.76±12.63	0.458
p value	0.119	0.806	
Chronotropic reserve			
Before treatment	85.95±8.06	94.31±9.08	0.008
After treatment	89.81±6.22	92.93±8.16	0.218
Δ Chronotropic reserve	3.85±6.92	-1.38±7.13	0.037
p value	**0.036**	0.437	

Bpm, beats per minute

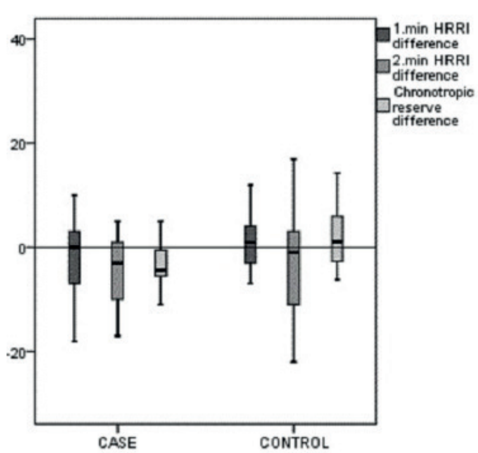

Figure 3. Differences in heart rate recovery indices and chronotropic reserve before and after treatment in case and control groups

DISCUSSION

Cardiac disturbances are common in AS patients and these patients may also have cardiac autonomic dysfunction which was shown to be associated with increased morbidity and mortality (2,4). However, data regarding the impact of current treatment modalities on cardiac autonomic functions in AS patients is relatively scarce. In the current randomized controlled study, we demonstrated for the first time that cardiac rehabilitation increases maximal exercise capacity and chronotropic reserve and decreases resting heart rate in AS patients. These findings suggest an improvement in cardiac autonomic functions in AS patients following cardiac rehabilitation program.

Recommendations regarding physical exercise in AS management have changed dramatically in the last decades. Previously, physical exercise was not recommended in AS patients due to its possible negative impact on the disease activity. However, it has been suggested to improve aerobic capacity and further attenuate disease activity in recent years (7). In our study, physical exercise was well-tolerated by the participants. Despite improved fitness, we did not detect a significant change in disease activity after cardiac rehabilitation.

Physical exercise has also been proposed to modulate autonomic functions in different patient groups (9,11). To evaluate cardiac autonomic functions, we assessed heart rate during and after physical exercise. Heart rate recovery index (HRRI) is an indicator of vagal activity, whereas chronotropic response is a reflection of both sympathetic and parasympathetic tones (11,12). Impaired HRRI was a strong independent predictor of both any- cause and CV- related mortality in several studies (13-16). AS patients were reported to have significantly reduced HRRI compared to healthy population (12). Herein, we revealed that HRRI at first and second minutes were slightly higher after cardiac rehabilitation compared to baseline values.

In addition to HRRI parameters, resting heart rate and chronotropic reserve are other indicators of cardiac autonomic nervous system functions. We found that there was a significant improvement in chronotropic reserve in AS patients who received cardiac rehabilitation program compared to controls. In addition, resting heart rate was significantly reduced in patients who received cardiac rehabilitation program after treatment. On the other hand, changes in HRRI at first and second minutes of rest were similar between the two groups.

In current clinical practice, there is no standard approach for assessing AS disease activity. BASDAI is the most widely used scoring system to evaluate disease activity. In our study, BASDAI score was significantly higher in the case group compared to controls before treatment. However, the score was greater than 4 in both groups, reflecting an active disease status. We detected a slight improvement in the cardiac rehabilitation group and worsening in the home-exercise group regarding BASDAI score, but these changes did not reach statistical significance. These results were compatible with the findings of a previous study evaluating the efficacy of cardiovascular exercise on AS that did not detect a change in BASDAI score following exercise (7).

Other parameters that are used along with BASDAI score to assess disease activity in AS patients are the acute phase reactants, namely erythrocyte sedimentation rate and CRP. A previous study reported that an increase in acute phase reactants occurs in AS patients with peripheral joint involvement (17). Since we included patients with only axial joint involvement, CRP levels were within the reference range in our study population. In addition, we did not detect any significant difference in CRP levels following cardiac rehabilitation.

For the functional evaluation of AS patients, we preferred using BASFI score. In resemblance to a previous study, BASFI scores did not differ before and after rehabilitation (7). However, BASFI scores tended to improve in the cardiac rehabilitation group and worsen in the home-exercise group.

Exercise capacity is a strong and independent predictor of mortality in the general population (18). In our study, maximum METs and exercise duration improved significantly in the cardiac rehabilitation group. On the other hand, there was no statistically significant change in the home exercise group. We did not evaluate the mortality rates in our study. However, our findings suggest that beneficial effects of cardiac rehabilitation on exercise capacity may be accompanied by improved mortality rates and this association needs to be evaluated in further studies with longer follow- up.

Aerobic physical exercise has been shown to improve pulmonary vasculature via nitric oxide (NO)-mediated vasodilatation in animal models (19). A previous study demonstrated that exercise training was associated with decreased sPAP in connective tissue diseases (20). In the current study, we found that sPAP was significantly lower in the case group than the control group following cardiac rehabilitation.

Mechanisms underlying the beneficial effects of physical exercise programs on autonomic nervous system in AS patients have not been elucidated yet. Routledge et al. have reported that regular exercise modulates autonomic nervous system activity via the renin-angiotensin-aldosterone system and NO-mediated pathways, resulting in an overall decrease in sympathetic activity and an increase in vagal tone (21). These findings should be reproduced in further studies. However, a link between autonomic functions and disease activity in rheumatologic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have already been proposed. According to previous studies, the autonomic nervous system may modulate inflammatory responses, via "cholinergic anti-inflammatory pathway", whose dysfunction due to RA and AS may result in exaggerated immune response (22). Animal studies have also demonstrated anti-inflammatory effects following electrical stimulation of the vagus nerve (23). Therefore, modulating autonomic functions may have further therapeutic implications in the treatment of AS.

LIMITATIONS

Our study has several limitations. First, the study population was relatively small and the follow-up period was relatively short. Second, the instructors did not make any effort to preserve the exercise capacity of the participants. However, it is known that regular face-to-face and phone interviews contribute to the preservation of acquired physical capacity. Furthermore, more accurate and reproducible results could have been obtained if peak oxygen consumption was measured instead of METs for the assessment of exercise capacity.

CONCLUSION

Our findings revealed that cardiac rehabilitation increases maximal exercise capacity and chronotropic reserve and decreases resting heart rate in AS patients. These findings suggest that cardiac rehabilitation can be applied in conjunction with the current medical therapy to improve functional capacity and cardiac autonomic functions in these patients. The impact of cardiac rehabilitation on morbidity and mortality in AS patients, via improving cardiac autonomic functions, needs to be elucidated in further prospective studies.

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