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ORIGINAL ARTICLE

The autonomic dysfunction in patients with ankylosing spondylitis: a clinical and electrophysiological study

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Abstract The aim of this study was to determine autonomic nervous system (ANS) functions by using clinical and electrophysiological tests in patients with ankylosing spondylitis (AS). Twenty AS and 20 healthy control subjects were recruited. Demographic data, symptoms related with ANS, and neurological findings were recorded. Clinical measurements including the heart rate variation with deep breathing (HRV), heart rate response to standing (HRS), systolic blood pressure response to standing, and diastolic blood pressure response to isometric exercise were obtained to assess parasympathetic and sympathetic functions of the subjects. The electrophysiological assessments of ANS were performed by sympathetic skin response (SSR) and R–R interval variation (RRIV) measurements for the sympathetic and parasympathetic functions, respectively. Patients with AS were subdivided into two groups depending on the activity of disease. The difference between the groups and relationship between ANS variables and clinical entities were determined. Fifteen male and five female AS patients with a mean age of 38±8.05 years and 14 male and six female healthy control subjects with a mean age of 40±9.8 years were included in the study. All the subjects were totally symptom free for ANS involvement and had normal neurological examination findings. The levels of HRV, HRS, and the mean RRIV values were significantly lower in AS patients than in control subjects. The clinical ANS parameters of the patients having more active disease were lower than in subjects with mild disease in regard to HRV values and SSR amplitudes and higher in regard to SSR latencies. The HRV values were found to be correlated with the mean scores of Bath ankylosing spondylitis disease activity index (BASDAI) and C-reactive protein (CRP) levels, and the mean latencies of SSR were correlated with BASDAI scores and CRP levels. In conclusion, our study indicates a subclinical mainly parasympathetic dysfunction of ANS in patients with AS which can be related with disease activity.

Keywords Ankylosing spondylitis · Autonomic nervous system · SSR · RRIV · Quality of life

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Introduction

Ankylosing spondylitis (AS) is an inflammatory disorder of the spine that affects skeletal and extraskeletal tissues. Extraarticular involvement including neurologic and cardiac manifestations may be observed. Cardiovascular complications of AS often featuring aortic regurgitation, conduction defects, and less commonly arrhythmias can be seen in 5–10% of patients with this condition [1, 2]. Nervous system involvement is not well defined, rarely peripheral neuropathies and cauda equina syndrome as well as delayed visual, somatosensory, and brainstem-evoked potentials have previously been reported [2–4]. However, only a few studies investigated the autonomic nervous system (ANS) involvement and indicated conflicting results with different degrees of involvement [5, 6].

Autonomic neuropathy is a third form of neurological involvement, observed in inflammatory rheumatic conditions.

ANS is the portion of nervous system that controls the functions of the body organs and systems including body temperature, heart rate, bowel and bladder tone, etc. It works below the level of consciousness and is activated by centers located in the central nervous system [7]. In previous studies, various techniques, some of which have assessed isolated components of ANS or response to stressor events, had been used [5–10]. Several clinical and electrophysiological noninvasive tests reflecting both sympathetic and parasympathetic activities can be used for a simple assessment of generalized autonomic nerve function. Cardiovascular tests including heart rate variation with deep breathing (HRV), heart rate response to standing (HRS), blood pressure responses to change in posture, and blood pressure variation to isometric exercises can be measured to confirm a clinical diagnosis of autonomic neuropathy and to assess the relative involvement of sympathetic and parasympathetic pathways [11].

The aim of this study was to investigate ANS functions by using clinical and electrophysiological tests of autonomic function in patients with AS. We also examined the relations between the disease activity parameters and indicators of autonomic activity.

Materials and method

We included 20 consecutive AS outpatients from the Physical Medicine and Rehabilitation Clinic, Ankara Training and Research Hospital. All patients fulfilled the modified New York criteria for AS [12]. The control subjects were 20 healthy male and female recruited from hospital staff within ±2 years of the same age. The study was approved by the local ethical committee and all participants gave informed consent prior to testing. Exclusion criteria for patients and controls were systemic diseases that may affect the nervous system or cardiovascular function such as diabetes mellitus, hypo–hyperthyroidism, uremia, cardiac failure, cardiac arrhythmia, or subjects using any medications that would influence the ANS or cardiovascular function. An informative handout advising stopping caffeine and alcohol intake and having restorative sleep 1 day before the study was given to the patients and controls. The subjects were asked to avoid activities that would affect blood pressure like running, jumping, etc. at least 2 h before the testing.

Demographic characteristics including age, sex, body mass index (BMI), drug intake, and disease duration were recorded. Clinical autonomic symptoms including feelings of faintness in orthostatic change of posture, distal vasomotor dysfunction, sweating abnormalities, and gastrointestinal, genital, or urinary disorders were evaluated in all participants. A detailed neurological examination was performed in the patient and control groups. Blood samples of the AS patients were taken to determine hemoglobin, erythrocyte sedimentation rate using the Westergren method, and C-reactive protein (CRP) by turbidimetric method. We used Bath ankylosing spondylitis disease activity index (BASDAI) to determine the activity of disease [13]. The patients were divided into two groups according to disease activity. A score of ≤6 was defined as mild to moderate disease activity and a score of >6 defines severe disease activity. Nottingham Health Profile (NHP) was used to assess quality of life (QoL) in the patient and control groups [14].

Clinical measurements assessing parasympathetic and sympathetic functions were performed. For parasympathetic function, the HRV was measured by asking the patient to breathe in and out six times, each breath being held in and out for 5 s. The maximum and minimum beats during each cycle was measured and the final result was the mean difference between the maximum and minimum heart rates over the three respiratory cycles [8, 11]. Also, the HRS was used to assess the parasympathetic function. The immediate increase in heart rate with standing was measured by asking the patient to stand after lying quietly for about 10 min. The increase in the heart rate as a response to change in posture was measured [8, 11].

The systolic blood pressure response to standing (SBP) was measured to assess sympathetic and partly parasympathetic functions. The SBP was measured as the difference between the resting supine measurement and that obtained immediately after standing. The mean of three readings taken at 1-min intervals was used for analysis [8, 11]. In addition, diastolic blood pressure response to isometric exercise (DBP) was obtained to assess sympathetic function of the subjects. The DBP was recorded by first measuring the maximum voluntary contraction using a hand grip dynamometer, after which the patient was asked to maintain a third of the maximum for as long as possible up to 5 min, while he was sitting in an upright position. The diastolic blood pressure was measured three times before and at 1-min intervals during the hand grip phase. The result was expressed as the difference between the maximum reading during the test and the mean of the pretest readings [8, 11].

Electrophysiological assessments

The electrophysiological assessments of ANS function were performed by sympathetic skin response (SSR) and R–R interval variation (RRIV), which were recorded according to the methods described Shahani et al. [15, 16]. All subjects were studied in the supine position using the equipment Nihon Kohden Neuropack M1 QP-954 BK (Tokyo, Japan) by the same physician (SK) who was blinded to subjects' identity and clinical data. All study sessions were completed in the morning at least 2 h after a light breakfast in a quiet semidarkened room with an

ambient temperature between 23°C and 26°C and an extremity skin temperature over 31°C. All the clinical and electrophysiological tests of ANS were performed on the same day.

RRIV was used for parasympathetic function and was recorded using the disk electrodes placed on the chest wall across the cardiac position with a ground electrode on the right axial line at the lowest rib. Using the triggering mode and adjusting, the sweep speed two QRS (mainly R waves) of electrocardiography were simultaneously displayed on the screen. Because the first displayed complex represented the triggering potential, the variation in timing of the second complex represents the variation in the R–R interval. Twenty traces were recorded and superimposed and a printout was made for subsequent measurement. Five groups of 20 sweeps were recorded at rest and two during forced deep breathing at six breaths per minute. The band pass was 20–1,000 Hz, the sensitivity 0.5 mV, and the sweep duration was 0.2–1 s. The range in the 20 pairs of R–R intervals was termed as (a) and the mean R–R interval was termed as (b). The RRIV was expressed as a percentage of the average R–R interval using the formula RRIV=a/b×100 [15, 16]. The recordings and calculations were performed by the computer software.

SSR was used to measure the sympathetic function. SSR recordings were performed using disc electrodes attached to the palm and dorsum of the right hand. The same device and the electrical stimuli as single square wave pulses of 0.1-s duration and 10–20-mA intensity were applied to the dominant median nerve at the wrist portion. Latency and amplitude of the response were analyzed. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection of the signal baseline, and the amplitude was measured peak to peak [15–16].

Statistical analysis

The analysis of the demographic data was conducted by descriptive statistics. Results were expressed as mean±SD (range). Differences between the groups were assessed by Mann Whitney *U*. The mean values of SSR and RRIV were compared using Mann Whitney *U* test. Spearman correlation analysis was used to evaluate the correlation between ANS parameters and clinical entity parameters. A two-sided $p<0.05$ was considered statistically significant. The software used was SPSS for Windows 11.0 version.

Results

Twenty patients with AS (15 male, five female) with a mean age of 38±8.05 years and 20 healthy control subjects (14 male, six female) with a mean age of 40±9.8 years were included in the study. All the subjects were totally symptom free for ANS involvement and subjects in both groups had normal neurological examination findings. There were no significant differences between AS and control subjects in the parameters including age, sex, and BMI. The demographic and clinical data of the AS and control subjects are summarized in Table 1. In AS group, all but two of the patients were taking nonsteroidal anti-inflammatory drugs (NSAIDs). Fifteen patients were on sulphasalazine treatment (2 g/day) and two patients were receiving methotrexate (15 mg/week). All the scores of NHP subscales were significantly higher in AS group than in healthy control subjects, as expected, indicating a decreased QoL, in patients with AS ($p<0.01$).

The clinical measurements of ANS in both groups are shown in Table 2. The levels of HRV and HRS were significantly lower in AS patients than in control subjects, suggesting a dysautonomia in parasympathetic functions. The mean SBP and DBP values, showing mainly sympathetic nervous function, were not significantly different in patients with AS compared to control subjects. The electrophysiological test results including SSR and RRIV are shown in Table 3. There was no difference between the SSR measurements (latencies and amplitudes) of the patients and control subjects. The mean RRIV values of the AS patients were statistically lower than in healthy controls which is suggestive of dysfunction of parasympathetic nervous system.

Patients with AS were subdivided into two groups depending on the activity of disease. There were 11 patients with a BASDAI score greater than 6, indicating a severely

Table 1 The clinical and demographical characteristics of AS patients and control subjects

Variable	AS group $n=20$	Control $n=20$
Age (yr) (mean)±SD	38.0±8.5	40±9.8
F/M	5/15	6/14
BMI (kg/m^2)	25.3±4.2	25.5±3.9
Duration of disease (year)	9.75±6.5	–
ESR (mean±SD)mm/h	27.6±16.6	–
CRP (mean±SD)mgr/dl	2.1±2.0	–
VAS pain	5.8±2.9	–
BASDAI score	5.5±2.6	–
NHP		
Pain	49.2±34.2	22.2±21.05
Physical activity	39.3±26.0	10.4±9.6
Energy	57.5±43.7	16.2±13.4
Sleep	37.0±29.2	11.2±10.9
Social isolation	25.0±21.0	5±2.4
Emotional reaction	43.1±32.8	20±19.2

AS Ankylosing spondylitis, *F* female, *M* male, *BMI* body mass index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *VAS* visual analog scale, *BASDAI* Bath ankylosing spondylitis disease activity index, *NHP* Nottingham Health Profile

Table 2 The results of the clinical the ANS tests of patients and control subjects

	AS group n=20	Control group n=20	p value
HRV	5.9±4.9	9.7±3.3	0.00
Baseline HR	78.2±9.3	77.0±7.4	0.59
After deep breath HR	84.1±10.4	86.7±8.6	0.45
HRS	8.8±5.4	14±7	0.00
Supine HR	79.1±11.5	74.1±8.3	0.06
Standing HR	87.9±14.9	88.1±12.6	0.69
SBP	15.0±8.8	12.2±7.4	0.34
Supine BP	74.2±10.2	69.0±5.5	0.07
Standing BP	89.2±11.6	81.2±10.2	0.39
DBP	12.4±9.7	7±4.5	0.10
Before handgrip BP	63.1±13.8	57.6±7.2	0.06
After handgrip BP	75.5±17.2	64.6±10.7	0.05

ANS Autonomic nervous system, *AS* ankylosing spondylitis, *HRV* heart rate variation with deep slow breathing, *HRS* heart rate response to standing, *SBP* systolic blood pressure response to standing, *DBP* diastolic blood pressure response to isometric exercise

active disease. The clinical ANS parameters of the patients having more active disease were significantly lower than in subjects with mild disease in regard to HRV values and SSR amplitudes and higher in regard to SSR latencies (Table 4).

In our study, when we compared the results of clinical and electrophysiologically determined ANS tests, we observed higher values of SBP (13.9±8.3 vs 18.4±10.6) and SSR latencies (1.6±0.2 vs 0.6±0.3) and HRV (10.7± 1.4 vs 8.3±4.7), DBP (8.8±4.1 vs 4.5±3.8), and SSR amplitudes (2.9±1.4 vs 1.5±1.1) in female subjects than in male subjects in AS and control groups, respectively ($p<$ 0.05). Subgroup analyses of female AS patients with female controls indicated significant differences in HRV and RRIV values. In the comparison of male patients with male control subjects, we observed higher values of DBP in patients with AS than in control subjects (Table 5).

The HRV values indicating the parasympathetic function were found to be correlated with the mean score of BASDAI and CRP levels, suggesting that patients with active disease may have dysfunction in parasympathetic nervous system. Also, the mean latencies of SSR were correlated with BASDAI scores and CRP levels as well as with physical subscales of NHP. No other correlation was found between clinical and electrophysiological ANS parameters and patients' clinical entities (Table 6).

Table 3 The electrophysiological ANS test results of the patients and control subjects

	AS group n=20	Control group n=20	p
SSR (median) latency (ms)	1.5±0.2	1.4±0.1	0.10
SSR (median) amplitude (mV)	2.5±2.02	2.4±1.4	0.92
RRIV	1.3±1.2	2.1±1.4	0.04

ANS Autonomic nervous system, *SSR* sympathetic skin response, *RRIV* R–R interval variation

Discussion

As far as we have known, our study is the first to use both clinical and electrophysiological tests in assessing the ANS function in AS patients. In our study, we have found significant differences in values of HRV and HRS suggesting a dysfunction in parasympathetic pathways. Also, we have determined significant difference in electrophysiologically determined RRIV levels, between the AS and control subjects, supporting this dysfunction. The latencies and amplitudes of the SSR were similar between AS patients and healthy control subjects. When we compared the patients according to disease activity, we observed that clinical HRV levels and electrophysiologically determined SSR latencies were significantly different between each group, indicating the dysautonomia in patients with clinical and biological signs of more active disease. Our study population were completely asymptomatic in terms of cardiovascular and neurological manifestations. Therefore, we can mention a subclinical dysautonomia in patients with AS, which seem to be more noticeable with active disease.

There is debate as to whether or not gender differences exist in sympathetic reflex responses; most reports suggest that males demonstrate greater cardiovascular responses to various stressors and susceptibility for orthostatic intolerance was more common in women than in men, while women were reported to have greater vagal cardiac control at rest and greater parasympathetic withdrawal during head uptilt [17–19]. There are no data about the expected

Table 4 The results of clinical and electrophysiological tests of ANS in AS patients according to disease activity

	BASDAI>6, n=11	BASDAI≤6, n=9	p
DBP	11.0±7.7	14.1±12.1	0.55
SBP	13.9±6.3	16.4±11.5	0.88
HRV	4.0±3.5	8.1±5.7	0.04
HRS	8.2±4.1	9.4±7.0	0.88
SSR (median) latency (ms)	1.7±0.1	1.4±0.2	0.04
SSR (median) amplitude (mV)	1.1±0.4	3.6±1.1	0.03
RRIV	1.3±1.4	1.3±1.1	0.66

ANS Autonomic nervous system, *DBP* diastolic blood pressure response to isometric exercise, *SBP* systolic blood pressure response to standing, *HRV* heart rate variation with deep slow breathing, *HRS* heart rate response to standing, *SSR* sympathetic skin response, *RRIV* R–R interval variation

Table 5 The results of ANS tests regarding to gender in patients with AS and control subjects

	HRV	HRS	SBP	DBP	SSRL	SSRA	RRIV
Male AS	5.7±5.4*	8.6±5.8	13.9±8.3	14.8±9.7	1.6±0.2	2.3±1.7	1.6±1.4*
Control	8.3±4.7*	13.1±8.1	13.9±7.3	4.5±3.8	1.5±0.1	1.5±1.1	1.4±0.7*
Female AS	6.4±3.2	9.2±4.8	18.4±10,6	5.4±6,5*	1.3±0.1	3.3±2.5	0.6±0.3
Control	10.7±1.4	14.6±6.3	11.2±7.5	8.8±4.1*	1.4±0.1	2.9±1.4	3.1±3.0

ANS Autonomic nervous system, *DBP* diastolic blood pressure response to isometric exercise, *SBP* systolic blood pressure response to standing, *HRV* heart rate variation with deep slow breathing, *HRS* heart rate response to standing, *SSRL* sympathetic skin response latency, *SSRA* sympathetic skin response amplitude, *RRIV* R–R interval variation
*$p<0.05$, Mann Whitney *U*

difference between the results of ANS tests in males and females with AS in the literature. In our study, we have found significant differences between male and female subjects in regard to parasympathetic and sympathetic test results in AS and control groups. But we could not compare our data with the results of previous studies as the population groups and the tests used to assess ANS involvement are different from our study and our study group is so small for definite deductions regarding gender differences.

The lack of significant difference between AS and control subjects in SSR variables may argue against any marked abnormality in sympathetic autonomic system. Although no difference was observed between the active and inactive patients regarding the electrophysiologically determined sympathetic functions, we determined a relationship between parameters of disease activity and SSR, which may indicate a dysfunction also, in sympathetic pathways in patients with active rheumatic disease. The reason for the absence of a difference between active and inactive AS patients in regard to SSR variables may be explained by the small number of patients analyzed according to disease activity.

As our patients had no clinical autonomic symptoms and findings, the changes in autonomic control do not seem to be due to peripheral or central nervous system involvement. The abnormality in autonomic cardiovascular reflexes may be due to physical deconditioning as a result of inactivity [8, 20]. But our study group was all ambulant, which also suggests that deconditioning due to immobility is not the complete explanation for our findings. In addition, all of our AS patients were on NSAIDs and most of them were using sulphasalazine. Although these medications are known to have no direct effects on ANS function, some rare occurrence of water-retaining effect has been described with NSAIDs [5], but in our study none of our patients had any clinical evidence of edema or extracellular volume disorder. On the other hand, as AS patients get older, they get more cardiac and other systemic complications, which might contribute to autonomic dysfunction [6]. But none of our patients had a history or clinical finding of cardiac complications. AS patients have thoracic limitations and the effects of these limitations on the results of some of the ANS tests cannot be excluded in our study. Also, the small sample size may limit the power of the study to detect small effects and interactions between covariates. Further larger studies with improved assessments of ANS involvement may be required in evaluating patients with AS.

Testing and quantifying ANS function is an important but difficult area of clinical neurophysiology. Different laboratory approaches can be used to investigate the ANS function [5–11]. However, as most of these tests are complex and not suitable for routine evaluation, physicians

Table 6 The correlation coefficients between the ANS parameters and some clinical variables of the AS patients

	DBP	SBP	HRV	HRS	SSRL	RRIV
Age	0.27	0.24	0.40	0.01	0.09	0.01
Disease duration	0.32	0.31	0.12	0.25	0.23	0.38
BASDAI scores	0.13	0.05	−0.47*	0.10	0.52*	0.21
CRP	0.41	0.32	−0.44*	0.18	0.60*	0.27
NHP						
Pain	0.17	0.24	0.38	0.01	0.44	0.03
Physical activity	0.01	0.23	0.32	0.12	0.55*	0.33
Energy	0.38	0.07	0.13	0.32	0.55*	0.20

ANS Autonomic nervous system, *DBP* diastolic blood pressure response to isometric exercise, *SBP* systolic blood pressure response to standing, *HRV* heart rate variation with deep slow breathing, *HRS* heart rate response to standing, *SSRL* sympathetic skin response latency, *RRIV* R–R interval variation, *NHP* Nottingham Health Profile
*$p<0.05$, Spearman correlation matrix

may underestimate the autonomic involvement in AS patients. SSR and R–R interval are two simple noninvasive electrophysiological tests which can be easily performed in the electromyography laboratory [15, 16]. These two tests have been shown to be valuable in determining the ANS involvement in some inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia syndrome [7, 10, 21, 22]. In our study, we have found abnormal RRIV values in AS patients than in healthy controls which indicate the presence of parasympathetic ANS dysfunction. In addition, we observed that ANS dysfunction especially the parasympathetic integrity may be a feature of AS at least during the active period of the disease, which was confirmed by clinical and electrophysiological tests results. As this is the first study evaluating ANS function by electrophysiological methods including RRIV and SSR tests, we could not compare our results with any data, except clinical tests assessing ANS function in AS patients [5, 6].

There are only two studies in the literature evaluating the ANS in patients with AS with contradictory results [5, 6]. Previous data [5] demonstrated a change in autonomic nervous system function of AS patients, with a decreased parasympathetic activity, as evidenced by higher heart rate and lower baroreflex slope. These changes were mainly observed in their patients with more active disease. On the other hand, some authors [6] investigated the involvement of ANS function by using power spectral analysis of heart rate variability in AS patients and demonstrated no evidence of ANS involvement in their patient group. Our results were consistent with those of Toussirot et al. [5]. The discrepancy between our data and those of others [6] could be explained by the differences in study group properties, the disease activity levels, or the different clinical approaches in investigating the ANS function.

There have been a number of studies showing ANS dysfunction in chronic inflammatory joint disease and connective tissue disorders [7–11, 21–24] with different degrees of impairment. It was previously reported that dysfunction of the cholinergic anti-inflammatory pathway may predispose some individuals to excessive inflammatory responses. As a support for this concept; patients with autoimmune diseases, including diabetes, rheumatoid arthritis, Behcet, lupus, and other inflammatory diseases including Crohn's disease and sepsis are associated with ANS dysfunction [24]. This dysfunction was mainly reported to be due to secondary complications of inflammation in nerves leading to suppressive nerve signaling but other mechanisms have also been postulated. As seen, the mechanisms are certainly complex but in recent years, an alternative explanation was suggested: It was possible that dysfunction in this pathway was a proximal or even primary event that enables or allows the overproduction of cytokines in response to an otherwise innocuous stimulus [25, 26]. Whether the inflammatory process in AS is a consequence of autonomic dysfunction requires further studies, which will provide additional insight on the pathogenesis of inflammatory diseases.

In conclusion, our study indicates a subclinical dysfunction of ANS, particularly the parasympathetic division in patients with AS, which can be related with disease activity. Abnormalities of ANS are responsible for high morbidity and early recognition of autonomic dysfunction may be very important. Therefore, clinical and electrophysiological methods to detect asymptomatic autonomic neuropathy are suggested to identify AS patients at high risk for symptomatic dysautonomia and to increase their quality of life.

Disclosures None

References

1. Vander Linden S, Van Der Heijde, Brawn J (2005) Ankylosing spondylitis. In: Harris ED, Budd RC, Firestern GS et al (eds) Kelley's textbook of rheumatology, 7th edn. Saunders, Philadelphia, pp 1125–1139
2. O'Neill TW, Bresnihan B (2005) The heart in ankylosing spondylitis. Ann Rheum Dis 51:705–706
3. Tyrell PNM, Davies AM, Evans N (1994) Neurological disturbances in ankylosing spondylitis. Ann Rheum Dis 53:714
4. Pillay N, Hunter T (1986) Delayed evoked potentials in patients with ankylosing spondylitis. J Rheumatol 13:137–141
5. Toussirot E, Bouhaddi MB, Poncet JC et al (1999) Abnormal autonomic cardiovascular control in ankylosing spondylitis. Ann Rheum Dis 58:481–487
6. Yildirir A, Aksoyek S, Calguneri M et al (2001) No evidence of cardiac autonomic involvement in ankylosing spondylitis, as assessed by heart rate variability. Clin Rheumatol 20:185–188
7. Ozgocmen S, Yoldas T, Yigiter R et al (2006) R–R interval variation and sympathetic skin response in fibromyalgia. Arch Med Res 37:630–634
8. Sandhu V, Allen SC (2004) The effects of age, seropositivity and disease duration on autonomic cardiovascular reflexes in patients with rheumatoid arthritis. Int J Clin Pract 58:740–745
9. Evrengül H, Dursunoglu D, Cobankara V et al (2004) Heart rate variability in patients with rheumatoid arthritis. Rheumatol Int 24:198–202
10. Karatas GK, Önder M, Meray J (2002) Autonomic nervous system involvement in Behçet's disease. Rheumatol Int 22:155–159
11. McLeod JG (1999) Evaluation of the autonomic nervous system. In: Aminoff MJ (ed) Electrodiagnosis in clinical neurology. 4th edn. Elsevier, Amsterdam, pp 421–432
12. Vander Linden S, Volkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 27:361–368
13. Garret S, Jenkinson T, Kennedy LG et al (1994) A new approach to defining disease status in ankylosing spondylitis; the bath ankylosing spondylitis disease activity index. J Rheumatol 21:2286–2291
14. Küçükdeveci AA, McKenna SP, Kutlay S et al (2000) The development and psychometric assessment of the Turkish version of the Nottingham health profile. Int J Rehabil Res 23:31–38

15. Shahani BT, Day TJ, Cros D et al (1990) R–R interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol 47:659–664
16. Shahani BT, Halperin JJ, Boulu P et al (1994) Sympathetic skin response. A method of assessing unmyelinated axon dysfunction in peripheral neuropathies. J Neurol Neurosurg Psychiatry 47:536–542
17. Shoemaker JK, Hogeman CS, Khan M et al (2001) Gender affects sympathetic and hemodynamic response to postural stress. Am J Physiol Heart Circ Physiol 281:H2028–H2035
18. Jones PP, Spraul M, Matt KS et al (1996) Gender does not influence sympathetic neural reactivity to stress in healthy humans. Am J Physiol Heart Circ Physiol 270:H350–H357
19. Dart AM, Du XJ, Kingwell BA (2002) Gender, sex hormones and autonomic nervous control of the cardiovascular system. Cardiovasc Res 53:678–687
20. Piha SJ, Voipio-Pulkki L-M (1993) Elevated resting heart rate in rheumatoid arthritis: possible role of deconditioning. Br J Rheum 32:212–215
21. Tan J, Akin S, Beyazova M et al (1993) Sympathetic skin response and R–R interval variation in rheumatoid arthritis. Am J Phys Med Rehabil 72:196–203
22. Gamez-Nava JI, Gonzalez-Lopez L, Ramos Remus C et al (1998) Autonomic dysfunction in patients with systemic lupus erythematosus. J Rheumatol 25:1092–1096
23. Dekkers JC, Geenen R, Godaert GLR et al (2004) Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease. Clin Exp Rheumatol 22:63–70
24. Czura CJ, Tracey JK (2005) Autonomic neural regulation of immunity. J Intern Med 257:156–166
25. Shahabi S, Hassan ZM, Jazani NH et al (2006) Sympathetic nervous system plays an important role in the relationship between immune mediated diseases. Med Hypotheses 67:900–903
26. Goldstein RS, Bruchfeld A, Yang L et al (2007) Cholinergic anti-inflammatory pathway activity and high mobility group box-1 (HMGB1) serum levels in patients with rheumatoid arthritis. Mol Med 13:210–215