Lupus

http://lup.sagepub.com

Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus

M. Aydemir, V. Yazisiz, I. Basarici, AB Avci, F. Erbasan, A. Belgi and E. Terzioglu

Lupus 2010; 19; 255 originally published online Dec 16, 2009;
DOI: 10.1177/0961203309351540

The online version of this article can be found at:
http://lup.sagepub.com/cgi/content/abstract/19/3/255

Published by:
SAGE
http://www.sagepublications.com

Additional services and information for *Lupus* can be found at:

Email Alerts: http://lup.sagepub.com/cgi/alerts

Subscriptions: http://lup.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.co.uk/journalsPermissions.nav

Citations http://lup.sagepub.com/cgi/content/refs/19/3/255

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

Lupus (2010) 19, 255–261
http://lup.sagepub.com

PAPER

Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus

M Aydemir[1], V Yazisiz[2], I Basarici[3], AB Avci[2], F Erbasan[2], A Belgi[3] and E Terzioglu[2]
[1]Çarşamba Government Hospital, Çarşamba, Samsun, Turkey; [2]Department of Internal Medicine, Division of Rheumatology and Immunology, Akdeniz University, Antalya, Turkey; and [3]Department of Cardiology, Akdeniz University, Antalya, Turkey

Neurological involvement is a well-documented issue in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). However, little is known about the involvement of the autonomic nervous system. This study was conducted to investigate autonomic nervous system dysfunction in patients with RA and SLE. Twenty-six RA patients, 38 SLE patients and 40 healthy controls were recruited from our in- and out-patient departments. Heart rate variability (HRV) parameters (the power of the high- [HF] and low-frequency [LF] band of haemodynamic time series, the ratio between low- and high-frequency components [LF/HF ratio], the power spectral density), baroreflex sensitivity (BRS) and beat-to-beat blood pressures were assessed by a novel non-invasive haemodynamic monitoring tool (Task Force Monitor® [TFM], CNSystems Medizintechnik GmbH, Graz, Austria). Autonomic nervous system dysfunction was determined according to classical Ewing autonomic test battery. Furthermore, we implemented a secondary autonomic test score by modifying the Ewing test battery with additional criteria. Both the classical and modified Ewing test batteries have revealed that the frequencies of autonomic neuropathy were significantly higher in patient groups compared with controls ($p < 0.001$). Evaluation by TFM revealed that deterioration of sophisticated autonomic parameters (such as HRV and BRS) were more pronounced in the patient groups compared with controls. There was a significant association between BRS and Ewing test scores and abnormal BRS results were more frequent in patients with autonomic dysfunction according to Ewing test batteries. No relation was found between autonomic neuropathy and disease duration, disease activity and autoantibody positivity. Consequently, we believe that further large-scale studies investigating cardiovascular autonomic neuropathy in rheumatic diseases should be carried out to verify our findings and manifest clinical consequences beyond these results. *Lupus* (2010) **19,** 255–261.

Key words: baroreflex sensitivity; cardiovascular autonomic neuropathy; Ewing test battery; rheumatoid arthritis; systemic lupus erythematosus

Introduction

The autonomic nervous system consists of neurons that connect the central nervous system to the visceral organs, skin effectors, and the cardiovascular system. Autonomic nerves arise from the sympathetic and parasympathetic nervous system and act in concert to control visceral organs and the circulatory system. Certain abnormalities of autonomic function in the setting of structural cardiovascular disease have been associated with an adverse prognosis, including sudden cardiac death and ventricular arrhythmias.[1]

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are autoimmune diseases involving multiple organ systems. Arrhythmias and sudden cardiac death are rare but important manifestations of cardiac involvement in autoimmune rheumatic diseases.[2] In patients with SLE and RA, sinus tachycardia, atrial fibrillation and atrial ectopic beats are the major cardiac arrhythmias.[3] Patients may sometimes present symptoms and signs of circulatory dysfunction and peripheral sensorimotor polyneuropathy.[4] In SLE and RA, although involvement of the peripheral nervous system and central nervous system are well described, there is a paucity of literature on the involvement of the autonomic nervous system.[5–11]

Correspondence to: Ender Terzioglu, MD, Prof., Akdeniz Üniversitesi Tıp Fakültesi Hastanesi, Dumlupınar Bulvarı, 07070 Arapsuyu / Antalya, Turkey. Email: ender2504@gmail.com
Received 17 July 2009; accepted 15 September 2009

© The Author(s) 2010 Reprints and permissions: http://www.sagepub.co.uk/journalsPermissions.nav
10.1177/0961203309351540

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

The function and characteristics of the autonomic nervous system can be evaluated by physiological and pharmacological tests. Tests of cardiovascular reflexes are sensitive, reproducible, simple, non-invasive and allow extensive evaluation of cardiovascular autonomic neuropathy (CAN). These tests include measurement of resting heart rate, heart rate and blood pressure responses to standing, handgrip or valsalva manoeuvres, heart rate variability (HRV) and baroreflex sensitivity (BRS).[12] The aim of this study was to define the frequency and spectrum of autonomic nervous system dysfunction (ANSD) in patients with SLE and RA, utilizing both traditional and novel sophisticated cardiovascular autonomic tests.

Materials and methods

Study population

The study population consisted of 36 RA, 38 SLE patients and 40 unrelated, ethnicity- and sex-matched healthy control subjects. We included those patients that fulfilled the classification criteria for RA[13] and SLE[14] provided by the American College of Rheumatology. The characteristics of patients and healthy controls are summarized in Table 1. Informed consent was obtained from all cases, and this study was approved by the ethical committee of Akdeniz University. Patients with pregnancy, diabetes, uraemia, hepatic failure, porphyria, amyloidosis, alcoholism, ischaemic heart disease, cardiomyopathy, arrhythmia, cerebrovascular events, Parkinsonism, multiple sclerosis, cyanocobalamin deficiency, or patients on medication that influences blood pressure or heart rate were excluded from the study. In addiction, SLE and RA patients with secondary Sjögren's syndrome, fibromyalgia and vasculitis that are known to cause neuropathy were not included in this study. Control subjects were selected from healthy persons who did not have any symptoms of ANSD, and were not taking any medication.

Table 1 Baseline characteristics of the study population

	RA (n = 36)	*SLE (n = 38)*	*Controls (n = 40)*
Age (years)	48.7 ± 12.5	38.4 ± 11.3	42.5 ± 12.5†
Sex (M/F)	6/30	6/32	9/31
Height (cm)	164 ± 7	163 ± 8	165 ± 7
Body weight (kg)	69 ± 13	66 ± 13	71 ± 13
BMI (kg/cm2)	25.0 ± 4.0	24.4 ± 3.5	26 ± 4.6
Hb (gr/dl)	13.1 ± 1.0	13.0 ± 1.2	12.9 ± 0.9
Glucose (mg/dL)	90 ± 19	81 ± 11	90 ± 10†
Cr (mg/dl)	0.8 ± 0.7	0.7 ± 0.2	0.7 ± 0.1
ESR (mm/h)	33 ± 24	29 ± 15	19 ± 7.7†
CRP (mg/dL)	1.1 ± 1.7	0.56 ± 0.7	0.48 ± 0.4†
TG (mg/dL)	112 ± 65	113 ± 61	100.9 ± 33
LDL (mg/dL)	105 ± 32	103 ± 28	96.5 ± 30
Age at onset (years)	37.2 ± 14.3	30.6 ± 10.0	
Disease duration (years)	11.2 ± 10.0	6.9 ± 5.0	
SLEDAI	–	5.28 ± 1.9	
DAS28	4.1 ± 1.2	–	
Ig M RF (n, %)	27 (%75)	–	

†$p < 0.05$

Values are shown as mean ± SD.

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; M, male; F, female; BMI, body mass index; Hb, haemoglobin; Cr, serum creatine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TG, triglyceride; LDL, low-density lipoprotein; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; DAS28, Disease Activity Score; RF, rheumatoid factor.

A brief explanation of the study was provided, anthropometric measures (weight, height, and body mass index [BMI]) and blood pressures were assessed. Clinical examinations of all subjects in the study, as well as the control groups, were performed before the tests and all participants were found to be in a stable condition. RA activity was determined with DAS28 score.[15] The activity of SLE was determined with a SLEDAI score.[16]

Non-invasive cardiac autonomic function evaluation by Task Force Monitor®

All tests were performed under standardized conditions in climate-controlled rooms in the morning, after a period of relaxation. Tobacco, alcohol, caffeine and medications were not allowed before the tests. Non-invasive cardiovascular recordings were performed using a dedicated device (Task Force Monitor® [TFM], CNSystems, Medizintechnik, Graz, Austria). This system provides continuous non-invasive blood pressure measurement via a vascular unloading device (finger plethysmography) on a beat-to-beat basis which is cross-checked with periodic automatic oscillometric brachial blood pressure measurements. Also a six-channel electrocardiogram (ECG) recording is utilized for determination of RR intervals to calculate real-time HRV by an autoregressive model. In addition, an impedance cardiography module incorporated into the system allows non-invasive continuous haemodynamic monitoring of the subjects (but this unit was not used because the issue was out of context). Therefore, utilization of TFM has afforded us both basic haemodynamic and autonomic parameters involving heart rate, systolic and diastolic blood pressure (SBP and DBP), the power of the high- (HF: 0.15–0.4 Hz) and low-frequency (LF: 0.04–0.15 Hz) band spectral analysis of heart

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

rate, the total power spectral density (PSD), and BRS which were calculated for every heart beat in real time. Also, the capability to review the raw data of every individual heart beat was facilitated by the analysis of the Ewing test battery.

BRS is described as the extent of heart rate modification in disproportional relation to change in arterial blood pressure. It is suggested that the downward tilting BRS test provided a physiological, non-invasive method for determining BRS and might be a useful index of reflex cardiac vagal and sympathetic function.[17] Based on the 'sequence method' the TFM automatically calculates the 'slope' (the steepness of the regression line between blood pressure change in mmHg and the RR interval change in ms regardless of the down or up-events) which we used to define BRS. BRS less than 10 ms/mmHg was considered as pathologic.[18,19]

The head-up tilt test, in which changes in blood pressure and heart rate are measured as the patient changes position from lying to standing, is an established method of evaluating the function of the autonomic nervous system.[20] Therefore in addition to acquiring supine data we performed brief tilting (60°) to gain heart rate and blood pressure responses to standing. All acquired data were evaluated according to the TFM recommendations[21] and reference values from previous studies.[22]

Table 2 Original and modified Ewing battery

	Normal (Score = 0)	*Borderline (Score = 1)*	*Abnormal (Score = 2)*
1) Tests reflecting parasympathetic function			
a) Heart rate response to Valsalva manoeuvre (Valsalva Ratio)	≥1.21	1.11–1.2	≤1.1
b) Heart rate variation during deep breathing (R-R Interval) (Max-Min) (bpm)	≥15	11–14	≤10
c) Immediate heart rate response to standing (30:15 ratio)	≥1.04	1.01–1.03	≤1.0
d) Inspiration/expiration heart rate (E/I ratio) during deep breathing	≥1.2	1–1.1	≤1
2) Tests reflecting sympathetic function			
a) Blood pressure response to standing (Decrease of systolic blood pressure, mm/Hg)	≤10	11–19	≥20
b) Blood pressure response to sustained handgrip (Increase of diastolic blood pressure, mm/Hg)	≥16	10–15	≤10
c) Blood pressure response to standing (Decrease of diastolic blood pressure, mm/Hg)	≤5	5–9	≥10
Ewing battery score = (1a + 1b + 1c + 2a + 2b)	0–1	2–3	≥4
Modified Ewing battery score = (1 a + 1 b + 1 c + 1 d + 2a + 2b + 2c)	0–1	2–4	≥5

Autonomic test batteries

Autonomic function was assessed by a battery of five simple and non-invasive cardiovascular reflex tests, as suggested by Ewing *et al.*[23] The original Ewing battery to assess cardiovascular function consists of three tests reflecting cardiac parasympathetic damage; 1. heart rate response to the Valsalva manoeuvre (Valsalva ratio); 2. heart rate variation during deep breathing (expiration/inspiration [E/I] difference); 3. heart rate response to standing (30:15 ratio or Ewing ratio); and two tests implying cardiovascular sympathetic damage; 1. SBP response to standing; 2. blood pressure response to sustained handgrip. Regarding the reference values each test was evaluated with a score of '0' for normal, '1' for borderline, and '2' for abnormal results, and the sum of these five scores accounted for the Ewing score. Eventually the Ewing's battery scores ranged between 0 and 10. Autonomic involvement was categorized as normal (score 0–1), borderline (2–3) or abnormal (≥4) (Table 2). Moreover, we modified the original Ewing battery by adding two tests reflecting cardiac autonomic function: 1. inspiration/expiration HRV during deep breathing (E/I ratio), which reflects parasympathetic damage; 2. DBP response to standing, which reflects sympathetic damage. The modified Ewing battery score was calculated as normal (score 0–1), borderline (2–4), and abnormal (≥5) (Table 2). Significantly all of the autonomic function tests mentioned below were performed three times within appropriate resting periods (>5 minutes) between each repetition and the mean of three measurements was utilized in the statistical analysis.

Heart rate response to Valsalva manoeuvre

The ratio of longest RR interval after the manoeuvre (release phase) and the shortest RR interval during the manoeuvre (strain phase) is calculated as the Valsalva ratio.

Heart rate variation during deep breathing

Patients were asked to control their breathing so as to reach a rhythm of six deep breaths per minute with a cycle length of 10 seconds. The absolute heart rate difference (E/I difference) between the

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

longest RR interval during expirium and shortest RR interval during inspirium and their quotient (and E/I ratio) were calculated.

Heart rate response to standing
Participants were asked to stand up after a 10 minutes resting period in supine position while simultaneous ECG and beat-to-beat blood pressures were recorded. The quotient of the shortest RR interval around the 15th beat just after standing and the longest RR interval around the 30th beat after standing is considered as the 30:15 ratio.

Blood pressure response to standing
As described above the patients were asked to stand up for 3 minutes after a 10 minute resting period in a supine position. The SBP and DBP just before standing and 3 minutes after active standing were determined to define postural change in blood pressure to evaluate orthostatic intolerance.

Blood pressure response to sustained handgrip
Three consecutive (within 5 minute resting periods) handgrip tests were performed by the patients for 2 minutes while beat-to-beat blood pressure was recorded simultaneously. The absolute difference between the highest DBP during handgrip and the basal DBP just before the handgrip is noted.

Statistical analysis

SPSS package software (Version 13, SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous data were expressed as mean ± SD, whereas categorical variables were expressed as percentages. Comparisons between two categories were made using Student's *t*-test for continuous variables. To analyse non-parametric data, a Mann–Whitney *U*-test or Kruskal–Wallis test were used as appropriate. The analysis of variance (ANOVA) test was used to compare the continuous variables of ANSD for the three groups. Spearman's correlation was performed to examine correlations between categorical variables. Logistic regression analysis was used to find the correlation of cardiovascular ANSD with disease activity and disease duration. The values of $p < 0.05$ were considered as statistically significant.

Results

Basic haemodynamic data, spectral analysis of HRV and BRS derived by TFM

Basic haemodynamic and autonomic parameters of three groups acquired by TFM are summarized in Table 3.

Heart rate
Patients with SLE and RA had significantly higher mean supine position heart rates when compared with healthy controls. Compared with resting values, there was no significant difference in the increment of heart rate during the tilt test in patients or controls.

Blood pressure
Both SBP and DBP values after tilt test were higher compared with supine position in each group. However, there were no significant differences in SBP and/or DBP among the three groups in either supine or tilt position.

Table 3 Results of basic haemodynamic and heart rate variability data and baroreflex sensitivity during supine position and tilt test

	Supine				*Tilt*			
	RA	*SLE*	*Control*	*P*	*RA*	*SLE*	*Control*	*P*
HR (bpm)	77.6 ± 12	77.2 ± 11	71.5 ± 8.4	0.027	89.9 ± 15	89.2 ± 15	83.6 ± 11	0.059
SBP(mmHg)	115 ± 12	109 ± 12	109 ± 10	0.068	124 ± 16	117 ± 13	117 ± 12	0.070
DBP(mmHg)	75 ± 8	72 ± 9	74 ± 9	0.461	86 ± 10	84 ± 11	84 ± 11	0.765
LF (ms^2)	135 ± 163	202 ± 305	214 ± 208	0.016	136 ± 162	180 ± 211†	295 ± 215†	<0.001
HF (ms^2)	115 ± 159	211 ± 461	156 ± 182	0.130	71 ± 100‡	105 ± 256‡	116 ± 134	0.006
LF/HF	1.5 ± 1.1	2.3 ± 3.3	1.7 ± 1.4	0.373	3.5 ± 6.58	3.3 ± 3.3	3.9 ± 3.9†	0.135
BRS (ms/mmHg)	8.9 ± 5.1	10.9 ± 6.7	13.5 ± 7.3	0.002	6.1 ± 4.1	6.8 ± 4.2	6.9 ± 2.3†	0.048

†$p < 0.05$ Supine vs Tilt,
‡$p < 0.001$ Supine vs Tilt,
Values are shown as mean ± SD.
HR, heart rate; SBP, systolic blood pressure; DBF, diastolic blood pressure; LF, low-frequency power; HF, high-frequency power; BRS, baroreflex sensitivity.

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

Spectral analyses of heart rate variability

The LF value in the supine position was significantly higher in the controls compared with SLE and RA patients. While the LF values in SLE decreased immediately, the LF values of controls increased after the tilt position. The LF values did not change significantly by tilting of RA patients. HF values in all groups were similar in the supine position, and significantly decreased after the tilt test. Decreases in HF values were significantly prominent in patient groups, especially in SLE patients. Compared with baseline values LF/HF increased after tilting in all groups. The increase was higher in the controls compared with patients groups.

BRS

In the supine position, the average BRS values were 8.9 ± 5.1, 10.9 ± 6.7 and 13.5 ± 7.3 ms/mmHg in RA, SLE patients and controls, respectively. The BRS values of RA and SLE patients was smaller than those of healthy controls. After the tilt test, the average BRS values significantly decreased in all groups. The most pronounced decreases were observed in healthy controls (-6.5 ± 6.4 ms/mmHg) (Table 3). According to BRS ≤ 10 ms/mmHg, 27 of the RA patients (75%), 23 of the SLE patients (60%) and 12 of the controls (30%) had ANSD (Table 4).

Results of the Ewing battery (original and modified)

The results of the cardiovascular autonomic tests are shown in Table 4. The frequencies of abnormal results were significantly higher in patient groups than for the controls. Twenty-two (61%) RA patients and 18 (47%) SLE patients were diagnosed as ANSD with the original Ewing battery. However these ratios were higher (75% and 68%, respectively) and similar to the rates of abnormal BRS when modified Ewing battery was applied as the criteria of cardiovascular ANSD. Regarding each criteria the difference between the three groups (both for patients and controls) was statistically significant ($p < 0.001$). The results of individual tests revealed that the functions of sympathetic and parasympathetic neurons were impaired either alone or together. The differences in parasympathetic and sympathetic tests between patient and control groups were statistically significant ($p < 0.05$).

There was no statistically significant correlation between ANSD and age, gender or BMI in the RA and SLE patients. None of the above test results correlated with SLEDAI in SLE patients, and DAS28 scores in RA patients. The duration of the disease and onset age of disease did not affect ANSD in either disease (data not shown).

Table 4 Frequency of autonomic neuropathy in patients with SLE, RA and healthy controls

	Autonomic neuropathy (n, %)			
	RA	*SLE*	*Controls*	*P*
Ewing battery (Original)	22(61%)	18(47%)	4(10%)	<0.001
Modified Ewing battery	27(75%)	26(68%)	12(30%)	<0.001
BRS (≤l0ms/mmHg)	27(75%)	23(60%)	12(30%)	<0.001

Table 5 Comparison of Ewing battery scores (original and modified) with baroreflex sensitivity

	Original Ewing battery		*Modified Ewing battery*	
Autonomic neuropathy (+)	*RA(22)*	*SLE(18)*	*RA (27)*	*SLE (26)*
BRS (ms/mmHg)				
≤10	20 (91%)	12 (66%)	22 (81.5%)	17 (65%)
>10	2 (9%)	6 (33%)	5 (18.5%)	9 (35%)
	rho = −0.294 *		rho = −0.302 *	
	$p = 0.002$		$p = 0.001$	

*Spearman's correlation.

Comparison of baroreflex sensitivity with Ewing batteries for ANDS

The original Ewing autonomic neuropathy test was related to the result of BRS (Spearman's rho = –0.294, $p = 0.002$). BRS was lower than 10 ms/mmHg in 91% of the RA patients and 66% of the SLE patients who had been diagnosed with autonomic neuropathy by original Ewing battery. Similarly, there was a negative correlation between modified Ewing battery and BRS (Spearman's rho = –0.302, $p = 0.001$) (Table 5).

Discussion

In this present study, we have investigated the frequency of cardiac autonomic dysfunction in patients with RA and SLE. Three different methods were applied for this purpose, including the measurement of autonomic parameters by TFM, Ewing battery and BRS. The main finding of this study is that autonomic dysfunction is common in patients with SLE and RA, compared with healthy controls. Cardiovascular autonomic tests were pathologic in 61–75% of the RA patients and 47–68% of the

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

SLE patients. Furthermore, BRS values supported the results obtained by Ewing battery tests in both patient groups. However, there was no correlation between the presence of ANSD and important features of the diseases, including disease duration and activity.

Some authors consider the Ewing tests to be moderately sensitive for CAN, and propose that sensitivity may be improved with HRV measures or BRS. Tank *et al.*[19] also found that HRV and BRS were not very successful in identifying diabetic patients with mild CAN, and marked discrepancies were present between BRS and conventional CAN test results.[24] The CAN was concomitantly assessed by several measures in this study. All utilized measures were in agreement to indicate a more diseased autonomic function in patient groups compared with controls. This is in accordance with the findings of other authors, who used different autonomic test methods and scoring systems. We modified the Ewing battery score since we propose that it is difficult to diagnose borderline autonomic neuropathy with the original Ewing score. We added the E/I ratio demonstrating parasympathetic disorder and DBP change reflecting sympathetic dysfunction to tests in the original Ewing battery test. The percentage of autonomic neuropathy was increased to 75% from 61% in RA patients and to 68% from 47% in SLE patients with modified Ewing score. This difference demonstrates that original Ewing battery score is not sufficient in detecting some of the patients with autonomic neuropathy. The modified Ewing battery score seems to be more sensitive in detecting autonomic dysfunction than the original Ewing Battery score.

The arterial baroreflex is the most important physiological mechanism reacting to sudden alterations in blood pressure. BRS reflects the parallel fluctuations of arterial pressure and heart rate, determining the function of the arterial baroreflex. Assessment of the modulation of BRS during a tilt test appears to be a sensitive tool for the early detection of CAN.[25] Ninety-one percent of the RA patients and 66% of the SLE patients with abnormal Ewing battery tests had a pathological BRS if the threshold of $\leq$10 ms/mmHg was used. Similar findings have been not observed in RA patients in the modified Ewing battery tests. In addition, impaired modulation of BRS after a tilt test in patients with RA and SLE was seen in this study. These results may indicate defective sympathetic activation during orthostatic challenge in patients with RA and SLE.

The relationship between autonomic neuropathy and peripheral neuropathy was described in patients with diabetes mellitus. The presence of an autonomic neuropathy has been established as a poor prognostic factor in patients with diabetes. A complex interrelationship between neuropathy and angiopathy exists in diabetes mellitus. It is confirmed that CAN was a reflection of diabetic microangiopathy.[26] Similarly, autonomic neuropathy was reported in patients with chronic obstructive pulmonary disease[27] and chronic renal failure on haemodialysis.[28] It is suggested that intraneural hypoxaemia may occur as a pathogenic mechanism in autonomic neuropathy. A study revealed that 57.4% of the RA patients had electrophysiologic evidence of peripheral neuropathy. The presence of vasculitis in the sural nerve biopsies were observed in patients with neuropathy, and only 25% of the patients with electrophysiological evidence of neuropathy were demonstrated to have clinical symptoms or signs of neuropathy.[29] In SLE patients, while peripheral nervous system involvement was seen in 2–18% of cases, ANSD was seen in 6–93% of cases.[9,10,28–30] Although it is well known that autonomic neuropathy is associated with peripheral neuropathy in RA and diabetes mellitus, one cohort of SLE patients did not show a relation between autonomic and peripheral neuropathy.[10] Autonomic neuropathy may exist independently of peripheral neuropathy and there may be other causes for autonomic neuropathy. Neuropathy in RA and SLE may arise secondary to vasculitis, drug toxicity, and rarely to amyloidosis.

In a study reported by Lioté and Osterland.[9] the role of glucocorticoids was questioned and the results of the study revealed that autonomic neuropathy could be related to glucocorticoids in SLE patients. It is speculated that different autoantibodies may be responsible for autonomic neuropathy in autoimmune diseases. No relationship was found between ANSD and anticardiolipin antibodies in SLE.[31] Baerwald *et al.*[32] observed a significant negative correlation between beta 2R and anti-ds-DNA antibody titres in SLE patients.[32] In the present study, we did not detect an association between ANSD and autoantibody positivity (rheumatoid factor (RF) in RA patients, antinuclear antibodies in SLE patients). There was no correlation with disease activity, disease duration and the age of the patients.

A recent study demonstrated that CAN was common in children and adolescents with SLE and juvenile idiopathic arthritis (JIA) patients.[33] Unlike our study, they found that autonomic function test scores had significant positive correlation with the disease activity scores, and SLEDAI

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010

and disease duration were significant clinical predictors of CAN in SLE patients. In addition, it is suggested that serum neuropeptide Y (NPY), a marker of sympathetic function, and vasoactive intestinal peptide (VIP), a marker of parasympathetic function, were significantly lower in lupus and JIA patients than controls.[33] These results indicated that all components of the autonomic nervous system were affected by immunological alterations, and there was a neuroimmunological basis for ANSD in autoimmune diseases.

In conclusion, several methods have become available for the detection of the defects in the autonomic nervous system. In all methods, the frequencies of CAN among RA and SLE patients are common and mostly subclinical. Future research should be focused on pathogenetic mechanisms of the CAN in autoimmune disorders, which may enable physicians to improve overall management of patients with these disorders.

References

1 Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol* 2008; 51: 1725–1733.
2 Maradit-Kremers H, Crowson CS, Nicola PJ, *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005; 52: 402–411.
3 Seferović PM, Ristić AD, Maksimović R, *et al*. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. *Rheumatology (Oxford)* 2006; 45(Suppl 4): 39–42.
4 Sofat N, Malik O, Higgens CS. Neurological involvement in patients with rheumatic disease. *QJM* 2006; 99: 69–79.
5 Hoyle C, Ewing DJ, Parker AC. Acute autonomic neuropathy in association with systemic lupus erythematosus. *Ann Rheum Dis* 1985; 44: 420–424.
6 Gledhill RF, Dessein PH. Autonomic neuropathy in systemic lupus erythematosus. *J Neurol Neurosurg Psychiatry* 1988; 51: 1238–1240.
7 Edmonds ME, Jones TC, Saunders WA, Sturrock RD. Autonomic neuropathy in rheumatoid arthritis. *Br Med J* 1979; 2: 173–175.
8 Maule S, Quadri R, Mirante D, *et al*. Autonomic nervous dysfunction in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA): possible pathogenic role of autoantibodies to autonomic nervous structures. *Clin Exp Immunol* 1997; 110: 423–427.
9 Lioté F, Osterland CK. Autonomic neuropathy in systemic lupus erythematosus: cardiovascular autonomic function assessment. *Ann Rheum Dis* 1994; 53: 671–674.
10 Shalimar, Handa R, Deepak KK, Bhatia M, Aggarwal P, Pandey RM. Autonomic dysfunction in systemic lupus erythematosus. *Rheumatol Int* 2006; 26: 837–840.
11 Stojanovich L, Milovanovich B, de Luka SR, *et al*. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. *Lupus* 2007; 16: 181–185.
12 Vinik AI, Erbas T. Recognizing and treating diabetic autonomic neuropathy. *Cleve Clin J Med* 2001; 68: 928–930.
13 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315–324.
14 Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271–1277.
15 American College of Rheumatology Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Reduced joint counts in rheumatoid arthritis clinical trials. *Arthritis Rheum* 1994; 37: 463–464.
16 Bombardier C, Gladman DD, Urowitz MB, *et al*. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35: 630–640.
17 Nakagawa M, Takahashi N, Ooie T, *et al*. Development of a new method for assessing the cardiac baroreflex: response to downward tilting in patients with diabetes mellitus. *Heart* 2001; 86: 643–648.
18 Kardos A, Watterich G, de Menezes R, Csanády M, Casadei B, Rudas L. Determinants of spontaneous baroreflex sensitivity in a healthy working population. *Hypertension* 2001; 37: 911–916.
19 Tank J, Baevski RM, Fender A, *et al*. Reference values of indices of spontaneous baroreceptor reflex sensitivity. *Am J Hypertens* 2000; 13: 268–275.
20 Benditt DG, Ferguson DW, Grubb BP, *et al*. Tilt table testing for assessing syncope. An American College of Cardiology Consensus Document. *J Am Coll Cardiol* 1996; 2: 263–275.
21 Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; 17: 354–381.
22 Agelink MW, Malessa R, Baumann B, *et al*. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. *Clin Auton Res* 2001; 11: 99–108.
23 Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985; 8: 491–498.
24 Tank J, Neuke A, Molle A, Jordan J, Weck M. Spontaneous baroreflex sensitivity and heart rate variability are not superior to classic autonomic testing in older patients with type 2 diabetes. *Am J Med Sci* 2001; 322: 24–30.
25 Beitzke M, Pfister P, Fortin J, Skrabal F. Autonomic dysfunction and hemodynamics in vitamin B12 deficiency. *Auton Neurosci* 2002; 97: 45–54.
26 Ziegler D. Diagnosis and treatment of diabetic autonomic neuropathy. *Curr Diab Rep* 2001; 1: 216–227.
27 Stewart AG, Waterhouse JC, Howard P. Cardiovascular autonomic nerve function in patients with hypoxaemic chronic obstructive pulmonary disease. *Eur Respir J* 1991; 4: 1207–1214.
28 Sahin M, Kayatas M, Urun Y, Sennaroglu E, Akdur S. Performing only one cardiovascular reflex test has a high positive predictive value for diagnosing autonomic neuropathy in patients with chronic renal failure on hemodialysis. *Ren Fail* 2006; 28: 383–387.
29 Agarwal V, Singh R, Wiclaf, *et al*. A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. *Clin Rheumatol* 2008; 27: 841–844.
30 Omdal R, Henriksen O, Mellgren SF, Husby G. Peripheral neuropathy in systemic lupus erythematosus. *Neurology* 1991; 41: 808–811.
31 Magaro M, Mirone L, Altomonte L, Zoli A, Angelosante S. Lack of correlation between anticardiolipin antibodies and peripheral autonomic nerve involvement in systemic lupus erythematosus. *Clin Rheumatol* 1992; 11: 231–234.
32 Baerwald C, Graefe C, Muhl C, Von Wichert P, Krause A. Beta 2-adrenergic receptors on peripheral blood mononuclear cells in patients with rheumatic diseases. *Eur J Clin Invest* 1992; 22(Suppl 1): 42–46.
33 El-Sayed ZA, Mostafa GA, Aly GS, El-Shahed GS, El-Aziz MM, El-Emam SM. Cardiovascular autonomic function assessed by autonomic function tests and serum autonomic neuropeptides in Egyptian children and adolescents with rheumatic diseases. *Rheumatology (Oxford)* 2009; 48: 843–848.

Downloaded from http://lup.sagepub.com at Akdeniz Universitesi on April 10, 2010