Cardiovascular autonomic functions and sympathetic skin responses in connective tissue diseases*

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In this study; we investigated cardiovascular autonomic functions in patients with rheumatoid arthritis (RA), progressive systemic sclerosis (PSS) and systemic lupus erythematosus (SLE). Among these patients, 20 cases with RA were further investigated in respect to symphathetic skin responses (SSR). Eighty three patients (48 with RA, 16 with PSS, 19 with SLE) and 20 healthy controls were recruited in this randomised study. Heart-rate (R-R interval) variation during deep breathing, heart-rate response to Valsalva maneuver, immediate heart rate response to standing, systolic blood pressure response to standing and diastolic blood pressure response to sustained hand grip were used as determinants of autonomic functions in our cases. As described in "materials and methods", E/I ratio (heart rate in deep expiration versus deep inspiration), Valsalva ratio and 30/15 ratio were calculated. While there was no significant difference between patients groups and normal controls in respect to E/I ratio; Valsalva ratio was found to be significantly lower in PSS group when compared with normal controls ($p<0.05$). 30/15 ratio was also significantly lower in all three subgroups of patients, compared with normal controls (RA: $p<0.001$; PSS: $p<0.001$; SLE: $p<0.05$). Only in patients with RA, decrement in systolic blood pressure in response to standing, was found to be significantly higher than normal controls ($p<0.05$). On the other hand; diastolic blood pressure response to sustained hand grip was, significantly lower than control group, in all three subgroups ($p<0.01$). Among 20 RA patients who were tested for sympathetic skin potentials, no response were observed in 4 patients (20%) and peripheral neuropathy (PNP) was detected only in 1 of them. Among these 4 patients with loss of sympathetic skin responses; PNP was present in only one of them and impaired systolic blood pressure response to standing was detected in three of them. In conclusion; as shown in this study, all three collagen vascular diseases might present with varying degrees of autonomic involvement. In patients with RA; absence of SSR correlates with the presence of orthostatic hypotension which is an indicator of sympathetic dysfunction, but no such correlation could be found between SSR and PNP. [Turk J Med Res 1995, 13(3): 106-110]

Key Words: Connective tissue diseases, Autonomic functions, Peripheral neuropathy

From histologic point of view, autonomic neuropathies are characterized by neuronal degeneration; and like peripheric neuropathies, they may be primary, idiopathic or may occur as a complication of various diseases (1). They have been reported to occur during the course of diabetes mellitus, chronic renal failure, various neurologic diseases and malignancies (2-6). Connective tissue diseases are chronic diseases of unknown etiology, involving many organs and systems, thus causing various symptoms. Among this group; rheumatoid arthritis (RA), progressiv systemic sclerosis (PSS), systemic lupus erythematosus, polymyositis and dermatomyositis are the most widespread diseases. In scleroderma; constipation, diarrhea and eusophageal motility disturbances are considered having a pathogenesis involving autonomic dysfunction. However; in RA, SLE and other connective tissue diseases, vasculitis and ischemic neuropathy have been hold responsible from the extra-articular complications (7). Although, peripheric neuropathy is a frequent extra-articular complication of RA, the effects of RA, on autonomic nervous system, have not been well delineated. So, in this study, we aimed to investigate cardiovascular autonomic functions in patients with RA, PSS and SLE using standardised, non-invasive clinical and electrocardiographic tests. We also examined sympathetic skin responses in some patients with RA.

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Table 1. Characteristics of different groups

	RA	PSS	SLE	Control
Number of patients	48	16	19	20
Age (years)	44.2±14.0	49.5+14.1	43.9±10.0	45.6±18.1
Female/Male	43/5	13/3	18/1	17/3

MATERIALS AND METHODS

83 patients (48 RA, 16 PSS, 19 SLE) being followed up by our rheumatology outpatient clinic and 20 healthy controls were recruited in this study. Patients with heart failure, hypertension, ischemic cardiomyopathy, diabetes mellitus, renal failure, malignancy, pneumopathy and amiloidosis were excluded. In order to be admitted in this study; patients should not have used sympathomimetic, parasympatholytic or cardioactive drugs during the last 10 days and should have been steroid free, at least during the last year. The characteristics of patients and healthy controls were outlined in Table 1.

Cardiovascular autonomic functions were investigated using those clinical and electrocardiographic tests, all standardised in previous studies dealing with diabethic autonomic neuropathy (1,8):

1) Heart-rate (R-R interval) variation during deep breathing: *Normally the heart rate varies contiunally but this depends on an intact parasympathetic nerve supply. Following a resting period of 5 minutes, the patient was instructed to make deep inspirations, 6 times a minute in supine position and during this period ECG was continiously recorded and expirium and inspirium intervals were plotted on the tracing. The ratio of longest RR interval during expiration versus the shortest RR interval during inspiration revealed "E/I ratio".*

2) Heart-rate response to Valsalva maneuver: *During the strain period of the Valsalva maneuver the blood pressure decreases and the heart rate rises. After release, the blood pressure rises, overshooting its resting value and the heart slows. This maneuver was performed by instructing the patients to moke a forceful expiration while their mouths were closed and noses clamped. Flushing on the face and distension of neck veins were accepted as indicators of a succesful manoeuvre. This manoeuvre was made for 15 seconds and repeated three times. During valsalva maneuver and for 30 seconds following the maneuver, ECG was continuously recorded. "Valsalva ratio" was calculated by dividing the longest RR interval within the 30 seconds-period, by the shortest RR interval during the maneuver.*

3) Immediate heart-rate response to standing: *During the change from lying to standing, a characteristic immediate rapid increase in heart rate occurs which is maximal at about the 15th beat after standing. After a resting period of 5 minutes in supine position, the patient was instructed to stand up, while continuous ECG recording was performed. "30/15" ratio was calculated by dividing RR interval of 30th QRS complex by the RR interval of 15th QRS complex.*

4) ***Systolic blood pressure response to standing:*** *On standing, pooling of blood in the legs causes a fall in blood pressure which is normally rapidly corrected by peripheral vasoconstriction. After a resting period of 5 minutes in supine position, blood pressure was checked and this measurement was repeated just after having the patient stood up, and the difference in systolic blood pressure was recorded.*

5) ***Diastolic blood pressure response to sustained handgrip:*** *During sustained handgrip, a sharp rise in blood pressure is expected. The patients were instructed to perform a sustained grip to the sphyngomonometer covering the left arm with their right hand; and the change in diastolic blood pressure following this effort was recorded.*

The results were considered to be pathologic if the E/I ratio <1.10, Valsalva ratio <1.10, 30/15 ratio <1.00, systolic blood pressure response to erect posture >30 mmHg and diastolic blood pressure response to grasping maneuver <10 mmHg.

Sympathetic skin potentials, were measured by a time-dependent recording method, described by Knezevic and Bafada (10). Ag/AgCI EEG surface electrodes with a diameter of 1 cm were placed on palmar and volar aspects of both hands as well as on plantar and dorsal surfaces of both feet. These electrodes were connected with DISA 1500 digital EMG system, and operated within 0.5-2 Hz frequency limits with a sensitivity of 0.5-2 mV, in analytic time period of 500 ms/DIV. Contralateral fibular and median nerves were stimulated by shock waves of 40 mili amper for periods of 0.2 ms. The stimulant was applied in a randomized pattern and at least 1 minute of rest was supplied between two consecutive stimulants. For each region, at least 5 responses were recorded and the response with shortest latency and greatest amplitude was taken into account for evaluation. Latency of each autonomic skin potentials was found by measuring the time interval from stimulus artefact to the beginning of potential; on the other hand the amplitude was calculated by measuring the spike to spike distance.

Statistical evaluation: Unidirectional variance analysis were used for comparing the parametric data of each group, while chi-square or Fischer's exact test were used for comparing non-parametric data.

RESULTS

No statistically significant difference in respect to age and sex distribution was detected between patient and control groups, whose epidemiologic data was given in Table 1. Due to inconvenient clinical status, blood

Table 2. Cardiovascular autonomic function test results in patient and control groups

Test	RA n=48	PSS n=16	SLE n=19	Control n=20
E/I ratio	1.27±0.14	1.28+0.15	1.30±0.15	1.25+0.16
Valsalva ratio	1.19+0.15	1.13±0.13*	1.18±0.14	1.24±0.11
30/15 ratio	1.03+0.06***'	0.99±0.05***	1.06±0.19*	1.18±0.16
Systolic blood pressure response (mrnHg)'	-11.61±10.46*	-9.06İ12.41	-11.05+10.1	-7.45±6.17
Diastolic blood pressure response (mmHg)'	3.31+2.14"*	4.13+2.36***	4.47±3.40***	14.25±6.75

'Three patients with RA could not be evaluated. In respect to control group *p<0.05, ***p<0.001; in respect to PSS group'<0.05

pressure tests could not be applied to 3 patients with RA.

No difference could be found between patient and control groups in respect to E/I ratio, but Valsalva ratio was found to be significantly lower in PSS group compared with normal controls. All of the three patient groups revealed 30/15 ratios, significantly lower thaTv normal controls and a significant difference was also detected between RA group and the PSS group where this ratio was the lowest. Systolic blood pressure response to standing (the decrement in systolic blood pressure), was significantly higher only in RA group; in the other two groups this change could not reach statistical significance. Diastolic blood pressure response to sustained handgrip was significantly lower in all patient groups than normal controls as shown in Table 2. The distribution of cases with pathologic responses was outlined in Table 3.

In 20 patients with RA, EMG examination was performed and SSR was detected. In general evaluation; no statistically significant difference could be shown between patient groups and normal controls In respect to latency and amplitudes of sympathetic skin potentials. In four patients SSR could not be detected. EMG revealed polyneuropathy with segmental demyelinization in one of these patients; however the EMG was normal in the other three patients. In a patient who showed a marked reduction in amplitudes of SSR, EMG revealed moderate mixed polyneuropathy. SSR was found to be normal in another patient with mild thenar atrophy and bilateral carpal tunnel syndrome confirmed by EMG. One of the patients whom no SSR from hands and feet could be detected, complained of impotance, flushing and sweating. Another patient with no SSR in his feet, experienced voiding incontinance. The other two patients without SSR, and the rest of the group had no complain related with autonomic dysfunction.

Of the four patients without SSR, 3 of them had pathologic systolic blood pressure responses to standing (i.e. 30 mmHg or more fall). Among patients in whom SSR were obtained, blood pressure tests could not be made in one patient, while they were found to be within normal limits in other 15 patients.

Table3. Distribution of cases with pathologic cardiovascular autonomic function tests

Test	Pathology criterion	RA	PSS	SLE
E/I ratio	<1.10	4/48* (8/3)	1/16 (6/3)	0/19 (0)
Valsalva ratio	<1.10	15/48 (31.3)	6/16 (37.5)	5/19 (26.3)
30/15 ratio	<1.00	22/48 (45.8)	9/16 (56.3)	5/19 (26.3)
Systolic blood pressure response response	>-30 mmHg	5/45 (11.1)	1/16 (6.3)	1/19 (5.3)
Diastolic blood pressure response	<10 mmHg	45/45 (100)	16/6 (100)	18/19 (94.7

•Number of cases with pathologic test results/total number of cases tested (%)

DISCUSSION

Autonomic neuropathy has been reported to occur during the courses of diabetes mellitus, chronic renal failure, various neurologic diseases and in some malig-. nancies. It causes postural hypotension, sweating disturbances, delay in gastric emptying, nocturnal diarrhea, voiding disturbances and impotence (1-6). Autonomic neuropathy can be diagnosed by showing neural degeneration in sural nerve biopsy (1). However, since clinical findings generally occur late in the course of autonomic neuropathy and performing surai nerve biopsy is not a practical issue, more conveniant investigations have been searched. Since detection of autonomic nervous system activation by means of direct neurophysiological measurements proves to be a difficult process, investigating autonomic functions indirectly, by the help of some physiological reflexes which are controlled by autonomic nervous system, is more practical (1). The cardiovascular non-invasive tests, which we used in this study, have been used widely in investigating autonomic dysfunction in various diseases and these tests have been shown to have a high correlation with the organic autonomic neuropathy in diabethic patients (1,3,5,8,9,11). E/I ratio, Valsalva

ratio, cardiac rate, response rate to standing (30/15 ratio) are markers of parasympathetic activation, while tests dealing with blood pressure responses to standing and diastolic blood pressure response to sustained handgrip reflect sympathetic system activation (6). Among these tests, the one investigating diastolic blood pressure response to sustained handgrip, requires intact hand and wrist functions. However; in connective tissue diseases, deterioration of hand grasping due to small joint involvement, interferes with the efficiency of the test. Really, systolic blood pressure response to standing, reflecting sympathetic functions, was found to be pathologic in 11.1% of RA patients, 6.3% of PSS patients and 5.3% of SLE patients. However, this test was reported to be pathologic in all patients with RA and PSS and in 94.7% of those with SLE. This implies that; although, this test has a significant positivity in all three patient groups, it has a limited utility due to impaired hand functions.

Peripheric neuropathy is one of the well known extra-articular complications in connective tissue diseases (12). Kalliomaki et al, who performed the original studies about autonomic functions, found an impairment in sweating response to intradermal nicotine enjection (13). Bennet and Scott also detected impaired sweating response in three RA patients without peripheric neuropathy (14). On the other hand, Edmonds et al found a good correlation between peripheric and autonomic neuropathy, and claimed that RA patients with autonomic neuropathy, had a more agressive and active disease course (15). Leden et al investigated the change in cardiac rate and blood pressure in RA patients, by having them immediately stood and come into 90 degree erect posture from supine position using a special apparatus (11). When compared with normal controls, mild RA patients revealed no significant difference, while those having an agressive disease course accompanied by peripheric neuropathy showed impaired changes in cardiac rate and blood pressure.

In previous studies relating connective tissue diseases, autonomic function tests have been investigated by means of cardiovascular autonomic function tests, but sypathetic skin responses have not been detected (11,16,17). In 20 patients with RA, whom we also investigated sympathetic skin responses, 4 of them revealed no response, while only one of them had peripheric neuropathy. Besides this, in a case with low SSR amplitudes, mild mixed polyneuropathy was detected in EMG. On the other hand, in 3 of 4 patients whom no SSR was observed, systolic blood pressure was pathologic. According to our findings, although there is a partial correlation between SSR and orthostatic hypotension reflecting cardiovascular sympathetic functions, no such correlation could be found between SSR and PNP. In general evaluation; systolic blood pressure response to standing was significantly different in RA patients than normal controls. The ratio of patients with abnormal results was also higher in RA patients than the other two patient groups. These findings indicate that, sympathetic involvement is more prevalent in RA patients than PSS and SLE.

Eusophagus motility dysfunction, constipation and diarrhea, occuring in PSS patients as a result of gastrointestinal involvement, are claimed to be due to autonomic dysfunction. Klimuk et al, investigated their patients, 10 with CREST syndrome and 4 with diffuse scleroderma, by non-invasive methods and concluded that autonomic dysfunction is frequently seen in PSS (18). In another study, where peripheric nervous system involvement was also investigated in PSS, 3 patients were found to have autonomic dysfunction of varying degrees (17). In 16 patients with the diagnosis of CREST syndrome, Suarez-Almazor et al, found 30/15 ratio and blood pressure response to erect posture to be different than control group but no such significant difference could be shown in other cardiovascular autonomic tests (16). We also have to keep in mind that in CREST variant of PSS, visceral involvement is less frequent. In our PSS patients, we found both Valsalva and 30/15 ratios significantly lower than the control group; 30/15 ratio was also found to be lower than the RA group as well. On the other hand, the incidence of pathologic test results was higher in PSS group than the other two patient groups. These observations point out that; parasympathetic involvement is most widespread in PSS, among the connective tissue disease we examined in this study.

Hoyle et al detected autonomic neuropathy in two patients with the diagnosis of SLE and mixed connective tissue disease respectively and reported on the improvement of gastrointestinal, cardiovascular and genitourinary symptoms of these patients with steroid therapy (19). A South African group performed a battery of sophisticated autonomic tests on 15 patients with SLE and Raynaud's phenomenon. Of these, 13 had at least one abnormal evaluation. This implies that subtle autonomic dysfunction is present more often than clinically appreciated. Maddison's group evaluated 23 outpatients with mild SLE using standardized autonomic testing (21). Mild abnormalities were found in 3 (13%) with SLE but in no controls.

Our findings indicate that in SLE autonomic functions are *less* disturbed than in RA and PSS. In SLE cases, only 30/15 ratio is found to be significantly lower than the control group. According to these results, when patients with abnormal sympathetic or parasympathetic test results are considered, SLE group is the least affected group, with the lowest frequency of autonomic dysfunction.

In conclusion, in patients with RA, there is a correlation between SSR and orthostatic hypotension reflecting autonomic dysfunction, but no such correlation could be shown between SSR and PNP. Parasympathetic dysfunction has been observed most

frequently in PSS patients. While sympathetic dysfunction is frequent in patients with RA, SLE is the group with least autonomic dysfunction.

Bağ dokusu hastalıklarında kardîyovasküler otonomik fonksiyonlar ve sempatik deri cevapları

Bu çalışmada romatoid artritli (RA), progresif sistemik sklerozlu (PSS) ve sistemik lupus eritematozlu (SLE) hastalarda kardîyovasküler otonomik fonksiyonları inceledik. Bunlardan RA'li 20 hasta sempatik deri cevapları (SDC) yönünden de incelendi. Bu randomize çalışmaya 83 hasta (48'i RA, 16'sı PSS ve 19'u SLE) ve 20 sağlıklı kontrol alındı. Derin inspirasyon esnasında kalp hızı (R-R aralığı), valsalva manevrasına kalp hızı cevabı, ayağa kalkma anındaki kalp hızı ve sistolikkan basıncı cevabı ve devamlı elle yakalamaya diastolik kan basıncı cevabı vakalarımızda otonomik fonksiyonlar için parametre olarak alındı. E/I oranı (derin expirasyonda kalp hızının derin inspirasyondakine oranı), Valsalva oranı ve 30/15 oranı hesaplandı. E/I oranı açısından hasta ve kontrol grupları arasında anlamlı fark bulunamazken PSS grubunda Valsalva oranı kontrol grubundakinden daha düşük bulundu (p<0.05). Ayrıca 30/15 oranı her üç hasta grubunda kontrol grubuna göre anlamlı derecede düşük idi (RA: p<0.001; PSS: p<0.001; SLE: p<0.05). Sadece RA'li hastalarda ayağa kalkışta sistolik kan basıncı azalması kontrol grubundakine göre daha fazla idi (p<0.05). Diğer bir deyişle, devamlı el sıkmada diastolik kan basıncı hasta gruplarında kontrol grubuna göre anlamlı derecede düşük idi (p<0.01). Sempatik deri potansiyelleri yönünden test edilen 20 RA'li hastadan 4 tanesinde (%20) cevap izlenmezken, sadece 1 tanesinde periferik nöropati (PNP) izlendi. Sempatik deri cevabı kaybolan 4 hastadan sadece 1 tanesinde PNP vardı ve ayağa kalkışta sistolik kan basıncı azalması ise 3 tanesinde sağlandı. Sonuç olarak her üç bağ dokusu hastalığında değişik derecelerde otonomik tutulum olduğunu söyleyebiliriz. RA'li hastalarda SDC'nin olmayışı sempatik disfonksiyonun göstergesi olan ortostatik hipotansiyonla korelasyon gösterirken, SDC ile PNP arasında benzer korelasyon saptanmamıştır.
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