

CARDIOVASCULAR PARASYMPATHETIC NERVOUS SYSTEM DYSFUNCTION IN FEMALE RHEUMATOID ARTHRITIS PATIENTS

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Abstract : The autonomic dysfunction has been reported in patients with (rheumatoid arthritis) RA and systemic lupus erythematosus (SLE) like connective tissue disorders and it may be due to the vasculitis of vasa nervorum and secondary amyloidosis. The pathogenesis may also have an immune component that affects autonomic functions. In the present study, three standard cardiovascular parasympathetic function tests were performed in 207 RA patients and in 106 healthy controls. 14.45% patients were presented with symptoms related to cardiovascular autonomic dysfunction. Heart rate variation to deep breathing (DBD), standing (30:15 ratio), Valsalva ratio (VR) were found to be significantly reduced in RA patients and was weakly associated with female RA patients ($r=0.165$, $p=0.018$) and was not correlated to disease duration, RF positivity & severity of the disease. In conclusion, this study has confirmed the presence of significant subclinical cardiovascular parasympathetic nervous dysfunction in RA patients and its positive association with female gender. Hence, inclusion of cardiovascular autonomic function tests in the routine clinical examination may be helpful in the early detection of autonomic dysfunction in RA.

Key words : rheumatoid arthritis parasympathetic dysfunction
cardiovascular autonomic tests autonomic dysfunction

INTRODUCTION

Rheumatoid arthritis (RA) has been defined as a chronic systemic inflammatory disorder (1-4) characterized by deforming symmetrical polyarthritis of varying extent and severity, associated with synovitis of

joint and tendon sheaths, articular cartilage loss, erosion of juxta-articular bone (5-7), and in most patients, there is presence of IgM rheumatoid factor in the blood (8). Reports on the prevalence of autonomic dysfunction in RA are discordant, ranging from 0% to over 90% according to different authors (4).

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Discrepancies might be related to the use of different criteria for the diagnosis of autonomic dysfunction and the range of abnormality could be due to the inclusion of different number of tests (4). In 1963, Kalliomaki et al showed a deficient sweating response to an intradermal injection of nicotine in patients with RA (1). In 1965, Bennett and Scott found areas of deficient sweating corresponding to cutaneous sensory disease in patients with sero-positivity RA with peripheral neuropathy (9). In three of their patients a deficient sweating response was found in the absence of peripheral neuropathy, suggesting the presence of a lone autonomic neuropathy.

Edmonds et al in their studies confirmed that the patients with seropositive and seronegative RA had significant abnormal autonomic functions suggesting, autonomic neuropathy occurs commonly in RA hitherto suspected (3). The studies by Lagana et al (10) and S Moule et al (4) concluded that autonomic neuropathy may be present in any kind of connective tissue disorders even in preclinical stage, suggesting that auto-antibodies directed against autonomic nervous system structures might play a role in the pathogenesis of the autonomic dysfunction. Toussirot et al (11) stated that the ANS function was affected in RA with a same frequency as found in literature but remained primarily subclinical and probably isolated from other peripheral and central nervous system damage.

Several studies are available in literature regarding sympathetic nervous system status in RA and SLE like connective tissue disorders. Only recently parasympathetic nervous status in RA has been investigated

(12, 13). But, these reports appear to be inconclusive. Hence, we have performed the present study for assessment of detailed parasympathetic nervous system functions in rheumatoid arthritis patients. The integrity of the autonomic nervous system can be assessed with several tests including cardiovascular, sweating, pupillary reflex, lacrimation and skin tests. However, cardiovascular reflex tests have been most widely used, as they are non-invasive, reproducible, relatively easy and safer tests to perform (5, 7, 14-16, 17). The primary objective of the present study was to assess the parasympathetic nervous system status in the RA patients by using three standard tests and to correlate the findings with the age, sex, disease duration and sero-positivity.

MATERIALS AND METHODS

207 patients with RA from the Rheumatology Clinic, Coimbatore Medical College Hospital, Coimbatore as subjects and 106 age and sex matched healthy persons from college and hospital staffs, and also healthy persons from patient attendees as controls were recruited for the study. The Diagnosis of RA was made by using the ACR criteria. The study was done for a period of one and half years extending from Jan 2006 to June 2007. The study was approved by the ethical committee of Coimbatore Medical College, Coimbatore. Informed consent was obtained from all the study subjects and controls before beginning the study. Name, age, sex, nativity and also the information about demographic social and cultural factors were all recorded. A complete preliminary clinical examination was made in each of the cases and controls. All of them were checked for symptoms and signs of possible autonomic

nervous system dysfunction including dizziness, headache, palpitation, blurred vision, fainting/syncopal attack, perspiration, Raynaud's phenomena. A complete neurological examination including the examination of peripheral reflexes and distal sensation in the legs was also done in each of the patients. Basal BP and heart rate was recorded. All patients and controls were confirmed to have a normal sinus rhythm, without evidence of a conduction defect in a standard electrocardiograph (ECG). The tests were performed under standardized conditions, in the morning between 8 am to 10 am.

Brief Methodology

Subjects

Inclusion Criteria: Ra patients aged between 20 to 60 years, both males and females who were attending the Rheumatology Clinic, Coimbatore Medical College and Hospital, Coimbatore during the study period were recruited for the study.

Exclusion Criteria: The following patients were excluded from the study

1. Patients with chronic diseases such as diabetes mellitus, renal failure, amyloidosis and other diseases known to interfere with autonomic nervous system.
2. Patients with drug treatment which are known to affect the autonomic nervous system including diuretics, antiarrhythmics, neuroleptics, antiepileptics and anti-hypertensive drugs.
3. Patients with hemoglobin level below 10 gm/dl.

4. Patients with diseases including hypertension, ischemic heart diseases, congestive cardiac failure, valvular heart diseases, cardiomyopathy, cardiac arrhythmias.
5. Patients with neurological diseases such as multiple sclerosis, gullian Barrie syndrome.
6. Pregnant patients.

Controls

Controls were selected from healthy hospital and college staffs and also healthy persons accompanying the patients. The criterion for age matching was fixed with an age difference of less than 3 years for each of the matched pairs.

CVS parasympathetic tests

The three standard tests used to measure the cardiovascular parasympathetic nervous system functions were Heart rate response to deep breathing, (Deep breathing difference: DBD), Immediate heart rate response to standing (the 30:15ratio), Valsalva ratio (VR).

1. **Heart rate response to deep breathing, (Deep breathing difference: DBD):**

The participant in lying position was asked to breathe quietly and deeply at six breaths a minute (five seconds in and five seconds out) for one minute. An electrocardiogram was recorded continuously throughout the period of deep breathing and the onset of each inspiration and expiration were marked. The maximum and minimum R-R intervals during each breathing cycle

were measured and converted to beats per minute. The result is then expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles, in beats per minute. A difference of 15 beats or more was considered to be normal, mean values between 11 to 14 beats per minute as borderline, and values of 10 beats or less per minute as abnormal (11, 18, 19, 20, 21, 22).

2. Heart rate response to standing (30:15 ratio)

With the participant lying quietly on the bed the heart rate was recorded continuously on an electrocardiograph. The participant was then asked to stand up unaided and the point of starting to stand is marked on the electrocardiogram. The shortest R-R intervals at or around the 15th beat and the longest R-R interval at or around the 30th beat after starting to stand were measured, the heart rate response was expressed as the 30:15 ratio. Values of 1.04 and above were normal, those between 1.01 and 1.03 as borderline and values of 1.00 and less were considered abnormal (15,23,24,25,26).

3. Heart rate response to Valsalva manoeuvre (Valsalva ratio)

The participant sitting comfortably on the bed was asked to blow into mouthpiece connected to a mercury manometer and hold it at a pressure of 40 mm of Hg for 15 seconds while a continuous electrocardiogram was recorded. The ECG was continued to be recorded even after release of pressure at the end of 15 seconds. The result was expressed as the ratio of longest R-R interval after the manoeuvre and to the shortest R-R interval during the manoeuvre. The mean

of three valsalva ratios is taken as the final value. A ratio of 1:21 or more was taken as normal and values between 1.11 to 1.20 as borderline and values of 1.10 or less were taken as abnormal (25, 26, and 27).

Statistical analysis

SPSS version 15 for Windows program was used to analyze the data. The test values were reported as means \pm SD. Independent t test was used to compare the means. Correlation of age, gender, seropositivity and disease duration on parasympathetic autonomic reflexes was done with Spearman and Pearson's correlation tests. The test results were statistically analyzed and their CVS parasympathetic function status was categorized into normal, early parasympathetic damage, definite parasympathetic damage according to Ewing's D.J criteria, which was published in the article Diagnosis, and Management of Diabetic Autonomic Neuropathy (28). In all the three tests borderline values were included with normals during statistical analysis

Normal : all the tests were normal

Early Parasympathetic Damage : anyone of the three tests were abnormal

Definite Parasympathetic Damage : at least two of the three tests were abnormal.

RESULTS

Demographic and Clinical profiles are summarized in Tables I & II. In this study the mean age of the subjects were found to be 42.60; with female preponderance. The male female ratio being 55:152 and the

TABLE I: Demographic data of subjects and controls.

Profile (n=207)	Values	Profile	Groups		P Value	
			Subjects n=207	Controls n=106		
Age (in years)	42.60±9.23	Age in	<40 (n)	86 (41.55%)	39 (36.79%)	0.416
Sex male (n)	55	years	>40 (n)	121 (58.45%)	67 (63.21%)	
Female (n)	152	Sex	Male (n)	55 (26.57%)	23 (21.70%)	0.339
Disease duration (in years)	3.41±2.43		Female (n)	152 (73.43%)	83 (78.30%)	
Rheumatoid factor (% positivity)	75.85					
HB % (in gm %)	11.20±.54					
ESR (mm/hr)	42.58±26					

The subjects were comparable to the controls both in age and sex.

TABLE II: Basal HR, BP and CVS parasympathetic test results of subjects & controls.

Study group type	Variables in Mean±SD			Parasympathetic tests results in Means±SD		
	Basal heart rate	Basal systolic BP	Basal diastolic BP	DBD	30:15 ratio	VR
Subjects (207)	81.48±8.84	112.65±15.79	74.26±7.022	8.01±4.539	0.9538±0.2510	1.0654±0.08913
Controls (106)	72.34±2.54	111.32±15.58	75.94±5.98	18.75±3.02	1.3349±0.08624	1.3292±0.08391
P value	0.000*	0.047*	0.367	<0.001*	<0.001*	<0.001*

Data expressed are mean±SD. DBD: Deep breathing difference; VR: Valsalva ratio.

percentage of the females were 73.43 and about 76% of them were found to be with seropositivity. The mean disease duration was 3.41 years. The mean hemoglobin of the studied subjects was 11.20 grams % with the range extending between 12.6 – 10. The mean ESR of them was 43mm per hour with the range of 135-10 mm/hr. 14.49 percentages of subjects were found to be with symptoms suggesting autonomic dysfunction. The most common symptoms were frequent perspiration and palpitation. About 18% of studied RA cases were had symptoms suggesting symptoms of dry eyes. 10.63% of the patients were affected by peripheral neuropathy. The subjects had significantly elevated mean basal heart rate (81.48) compared to the controls (72.34) and their mean basal systolic BP was 112.65 and basal diastolic BP was 74.26 (Table II). Similarly RA cases with abnormal parasympathetic results had shown

a significant increase in their mean basal heart rate (85.32) than both the RA cases with normal CVS parasympathetic function and controls.

TABLE III: CVS parasympathetic test results in subjects (n=207).

Tests	Normal	Border line	Abnormal
DBD	12	35	160
30:15 ratio	17	—	190
Valsalva ratio	10	39	158
CVS parasympathetic tests (n=3)		18.20	81.80
Autonomic status	Subjects n=207		Controls n=106
Early Parasympathetic damage	190 (91.79%)		—
Late Parasympathetic damage	148 (71.50%)		—

Borderline values were included in normal values for statistical analysis. Maximum abnormality was found in 30:15 ratio.

TABLE IV : Correlation of age, gender, disease duration, RF status and CVS parasympathetic test results in subjects.

Tests	Age			Gender			Disease Duration			RF status		
	Correlation value (r)	P value	Inference	Correlation value (r)	P value	Inference	Correlation value (r)	P value	Inference	Correlation value (r)	P value	Inference
Early PSD	-0.033	0.632	ns	0.095	0.174	ns	0.006	0.933	ns	-0.045	0.515	ns
Definite PSD	-0.039	0.577	ns	0.165	0.018	s	0.057	0.412	ns	-0.002	0.978	ns

s: significant; PSD: parasympathetic damage; ns: Not significant. Tests used were Pearson's r and Spearman's correlation. Late parasympathetic autonomic damage had shown significant positive correlation to gender (r=0;165, p=0.018).

Parasympathetic function tests are summarized in Tables III & IV. 81.80 % of the studied cases had abnormal results of parasympathetic dysfunction (PSD). Maximum abnormal test results were found in 30:15 ratio heart rates (91.79%) (Table III). About 66.18% of female patients were shown early PSD and 49.28 % of female patients were affected by definite PSD, whereas only 25.60 of male RA patients were affected by early PSD & 22.22% of male RA patients were shown definite PSD (Tables III & IV).

DISCUSSION

This case-control study to assess the parasympathetic autonomic nervous system status in rheumatoid arthritis patients (n=207) and controls (n=106) was conducted using three standard parasympathetic autonomic function tests. It is known that abnormal responses to autonomic function tests may precede appearance of clinical symptoms in diabetics with autonomic neuropathy (13, 28). In the present study, 14.49% RA patients had symptoms that could be attributed to an autonomic neuropathy, which is similar to the study of Edmonds et al (3), but higher than Piha et al study

(11.76%) (16), and lower than the report of Luthrenoo et al (47%) (12), Tan et al (16.67%) (17), and in contrast Bekkelund et al (30) and Berendregt et al (31) found no autonomic dysfunction symptoms in RA patients.

In our study, the basal heart rate was found to be significantly elevated in RA patients and in RA patients with abnormal CVS parasympathetic test results which is similar to the report of Leden et al (13) and Piha et al (29). The elevated basal heart rate may be due to peripheral parasympathetic efferent vagal damage, which is a proved factor in diseases like diabetes (23). The same might be applied to RA because of its chronic nature. This was supported by our CVS parasympathetic test results. However, abnormal heart rate control may also be based on central nervous dysfunction. The elevated heart rate in RA may be due to decreased parasympathetic tone, which in turn, may be due to increased central sympathetic activity, inhibiting the parasympathetic vasomotor center (12, 32, 33).

In the present study, heart rate variation to deep breathing, 30:15 ratio, Valsalva ratio (Means were 8.01, 0.9538, 1.0654, respectively,

and p values were <0.001) were found to be significantly diminished in 81.80% RA patients which is similar to the findings of Toussiroot et al (11) (60%), Geenen et al (34) (50%) and higher than Leden et al (13) and Edmonds et al (3), Tan et al (17) and in contrast, studies of Bekkelund et al (11), and Piha et al (29) and Tumiati B et al (35) found no CVS ANS abnormality. The pathologic CVS parasympathetic reflex tests in our RA patients (81.80%) was weakly associated to female gender [CV (correlation value) (r) = 0.165, p=0.018] and no correlation to age, disease duration and RF status and in contrast to the report of Sandhu et al (32) and Castro et al (36) in which blunted autonomic cardiovascular reflexes were positively associated to RF status.

The pathogenesis of the autonomic dysfunction in patients with RA is not clearly understood. Vasculitis of the vasa-nervorum and secondary amyloidosis has been proposed.

The pathogenesis may have an immune component. This is supported by improvement of acute autonomic neuropathy after treatment with immunosuppressive drugs in patient with SLE (4,37). The presence of circulating autoantibodies against nerve growth factor, cervical ganglia and the vagus nerve has been recently demonstrated in RA and SLE patients who had cardiovascular dysfunction. The significance of these autoantibodies in the pathogenesis of autonomic dysfunction remains to be determined. The abnormal cardiovascular parasympathetic reactivities observed in our study suggest that these patients are prone to develop a subclinical form of autonomic neuropathy. Hence, further study should be conducted for the detailed assessment of cardiovascular autonomic functions in patients with RA and these autonomic testing could be the part of their routine clinical evaluation in RA to reduce the autonomic morbidity in these patients.

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