

ASSESSMENT OF AUTONOMIC FUNCTION IN RHEUMATOID ARTHRITIS PATIENTS USING TILT-TABLE TEST IN A TERTIARY CARE TEACHING HOSPITALDr. P. V. Saraswathi* and Dr. Amudhan Arvind²¹Associate Professor of Physiology, Government Medical College & ESI Hospital Varadharajapuram Coimbatore - 641015.²(Pharmacology) Assistant Professor, Department of pharmacology, Government Dharmapuri Medical College, Dharmapuri.***Corresponding Author: Dr. P. V. Saraswathi**

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory disorder affecting primarily the peripheral joints. This disorder not only affects the joints but also many systems like the Respiratory, Cardiovascular and the Nervous system particularly autonomic nervous system involvement has been commonly encountered among the RA patients. **Aim and Objectives:** This study was aimed at investigating the various functions of the autonomic nervous system in RA patients and to explore the possible relation between the autonomic nervous system dysfunction with the patient's age, gender, and disease duration and sero-positivity status of RA. **Materials and methodology:** This cross sectional study was conducted in a tertiary care hospital among 207 RA patients attending the Rheumatology clinic. Age matched control group included 106 persons. Two tests were used to assess the autonomic function namely the Tilt table test and Postural BP. **Results:** Although both parasympathetic and sympathetic divisions are affected in rheumatoid arthritis, parasympathetic division suffers more than the sympathetic division. None of our patients who showed an abnormal blood pressure response to tilting were suffered from the symptoms of orthostatic hypotension. Altered autonomic responses has shown significant positive correlation to female RA patients with longer disease duration and sero-positivity and does not show any relationship to the age of the patients. **Conclusion:** The early detection and treatment of autonomic neuropathy will not only help to reduce the mortality but also certainly improve the quality of life and reduce the sufferings in RA patients.

KEYWORDS: Rheumatoid arthritis, Autonomic dysfunction, tilt table test, orthostatic hypotension.**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disorder. It affects principally the joints and is usually accompanied by one or more of extra-articular manifestations as rheumatoid nodules, normochromic normocytic anaemia and neuropathy.^[1,2] Neuropathies are estimated to be the commonest neurological extra-articular feature. The neuropathic affection among RA patients includes mononeuropathy (entrapment neuropathy e.g. carpal tunnel syndrome), mononeuritis multiplex, peripheral polyneuropathy and autonomic neuropathy (AN).^[3-5] Autonomic neuropathy results from the affection of the sympathetic and/or parasympathetic nerve fibres. Autonomic neuropathy manifests clinically as cold, clammy, cyanotic extremities, peripheral vasospasm, palpitation, orthostatic hypotension, syncopal attacks and sexual dysfunction.^[6,7]

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, lacrimation and pupil size assessment tests have been most widely used as they are non-invasive and safer tests to perform.^[8] This study was aimed at investigating the various functions of the autonomic nervous system in RA patients and to explore the possible relation between the autonomic nervous system dysfunction with the patient's age, gender, and disease duration and sero-positivity status of RA.

MATERIALS AND METHODOLOGY

In our study 207 consecutive patients with RA from the Rheumatology Clinic, Coimbatore Medical College Hospital, Coimbatore and 106 age and sex matched controls from healthy hospital and college staffs, persons accompanying the patients were recruited to 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. Informed consent was obtained from all the study subjects before

beginning the study. 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 included for the study. Those patients with chronic diseases such as diabetes mellitus, renal failure, amyloidosis and other diseases known to interfere with autonomic nervous system, patients with drug treatment which are known to affect the autonomic nervous system including diuretics, antiarrhythmic, Neuroleptics and antiepileptic and anti-hypertensive drugs, patients with Hemoglobin level below 10gm/dl, patients with a history of ophthalmopathy as well as those using eye drops interfering with the autonomic nervous system, patients with diseases including Hypertension, Ischemic heart diseases, Congestive cardiac failure, Valvular Heart diseases, Cardiomyopathy, Cardiac Arrhythmias, patients with neurological diseases such as multiple sclerosis, Gullian- barrie syndrome and pregnant patients were excluded from study.

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. 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, and 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 are confirmed to have a normal sinus rhythm, without evidence of a conduction defect in a standard electrocardiograph (ECG). The tests are performed under standardized conditions, in the morning, after a period of relaxation. Tobacco, alcohol and medications are not allowed before the tests. Tests used to measure the sympathetic function were blood pressure response to standing (postural BP), Tilt table test-Blood pressure changes. Similarly parasympathetic nerve function was assessed by Tilt table test-heart rate response.

These tests involved variation in heart rate and blood pressure to variety of stimuli. Heart rate changes were studied to assess the integrity of parasympathetic functions and changes in blood pressure for those of sympathetic functions⁹. Blood pressure was recorded manually using sphygmomanometer. Beat to beat heart

rate was measured using BPL CARDIART 6108T electro cardiograph. Below was the detailed method how the tests were done.

Blood pressure response to standing (Postural changes): The participant's blood pressure was measured with a sphygmomanometer while he was lying down quietly and again when he stands up. The postural fall in blood pressure was taken as the difference between the systolic blood pressure lying and the systolic blood pressure standing. A postural fall of systolic blood pressure of 10 mm of Hg or less was taken as normal; values between 11 to 29 mm of Hg as border line, and those of 30 mm of Hg and more were taken as abnormal.^[10]

Tilt table test

The test subject was made to lie on a hand operated tilt table the heart rate and blood pressure were monitored by using BPL Electro Cardio Graph and Sphygmomanometer for 5 to 15 minutes while the patient lies quietly. Once the stable recording was made, the head of the table was tilted up to 60° and the heart rate and blood pressure were monitored for up to 30-45 minutes. Normal response was a brief, transient decrease in BP accompanied by increase in heart rate. There was a return to near-baseline rates and pressures and this was maintained throughout the period of tilting. The result was considered abnormal if the fall in blood pressure more than 30 mm of mercury and borderline result was if the fall in blood pressure was between 11 to 29 mm of mercury and the fall of blood pressure up to 10mm of mercury was considered as normal. The shortest RR interval at or around the 15th beat or the longest R-R interval at or around the 30th beat soon after tilting the table are noted, the heart rate response was expressed as the 30: 15 ratio. Values of 1.04 and above or normal, those between 1.01 and 1.03 as border line and values of 1.00 and less were considered abnormal.^[11]

SPSS version 21 was used to analysis the data. The test values were reported as means \pm SD. Independent 't' test was used to compare the means. Correlation of effects of age, gender, sero-positivity and disease duration on autonomic reflexes was done with Spearman and Pearson's R correlation tests.

RESULTS

We analyzed the different autonomic function tests which we conducted in RA cases; increased number of abnormal results were found in tilt table test – both BP and heart rate, postural BP in few cases. Maximum number of abnormal results was found in tilt table HR changes.

Table. 1: AFT Results in Cases and Controls.

Sl. No.	Tests	Groups (Values are in numbers)					
		CASES n=207			CONTROLS n=106		
		Normal	Border Line	Abnormal	Normal	Border Line	Abnormal
1	Tilt table HR	17	-	190	106	-	-
2	Postural BP-systolic	165	34	8	80	26	-
3	Postural BP-diastolic	192	12	2	106	-	-
4	Tilt table BP-systolic	165	34	8	79	27	-
5	Tilt table BP- diastolic	193	12	2	104	2	-
S. No	Tests	Groups				p Value	
		Cases		Controls			
		Mean	SD	Mean	SD		
1	Tilt table HR	0.953	0.251	1.334	0.086	<0.001*	
2	Postural BP-systolic	9.70	8.586	8.73	3.585	0.190	
3	Postural BP-diastolic	4.74	8.747	6.64	3.562	0.007*	
4	Tilt table BP-systolic	9.70	8.586	9.08	3.601	0.367	
5	Tilt table BP- diastolic	4.70	8.746	7.60	3.507	<0.001*	

Further analysis was done comparing the autonomic function test results with age and sex by evaluating the influence of age and sex over the autonomic function in rheumatoid arthritis patients and the results were as given below.

Table 2 & 3: Effect of Variants – Age & Sex on AFT Results in RA Cases.

Sl. No	Tests	RA Cases <40 Years (n=86)		RA cases >40 years (n=121)		't'	p
		Mean	SD	Mean	SD		
1	Tilt table HR	0.9914	0.37886	0.9270	0.06889	-1.829	0.068
2	Postural BP-systolic	8.5814	7.53886	10.4959	9.20609	1.587	0.114
3	Postural BP-diastolic	3.6977	7.53669	5.4876	9.47463	1.455	0.147
4	Tilt table BP-systolic	8.5814	7.53886	10.4959	9.20609	1.587	0.114
5	Tilt tabl BP- diastolic	0.0814	0.21503	0.0372	0.13174	-1.830	0.069

Sl. No	Tests	RA Cases Females (n=152)		RA cases Males (n=55)		't'	p
		Mean	SD	Mean	SD		
1	Tilt table HR	0.9673	0.29080	0.9175	0.05904	-1.259	0.210
2	Postural BP-systolic	10.0000	8.32395	6.8519	6.39105	-2.545	0.012
3	Postural BP-diastolic	5.2980	7.77839	8.0000	5.57773	2.364	0.019
4	Tilt table BP-systolic	10.0000	8.47207	16.1273	9.19753	4.492	<0.0001*
5	Tilt table BP- diastolic	5.2667	1.65547	5.0727	1.11976	-0.804	0.422

Finally we compared the relation between different type of autonomic damage with RA factor status and duration of disease. Both diminished heart rate variation and abnormal blood pressure changes were found to be more among RA Factor Positive RA Patients with longer disease duration.

Table. 4: Comparison of RA Factor, Disease Duration With Autonomic Status in RA Cases.

No of AFT with abnormal results	Profiles			
	Ra Factor status		Disease duration	
	Positive n=157	Negative n=50	< 5yrs n=160	> 5 yrs n=47
Tilt Table HR (n=190)	157(100%)	33(66%)	143(89%)	47(100%)
Postural BP- Systole (n= 8)	8(5.095%)	0	0	8(17.02%)
Postural BP- Diastole (n= 2)	2(1.27%)	0	0	2(4.26%)
Tilt Table BP- Systole (n= 8)	8(5.095%)	0	0	8(17.02%)
Tilt Table BP Diastole (n=2)	2(1.27%)	0	0	2(4.26%)

DISCUSSION

We conducted a case control study to assess the autonomic nervous system status in Rheumatoid Arthritis patients (n=207) and controls (n=106) involving posture induced cardiovascular autonomic reflex tests using TILT TABLE.

In our study, mean heart rate variation difference in tilt table test was 0.9538, (p value <0.001) found to be significantly diminished in 91.79% of RA patients which is higher than in Leden *et al*^[14] study (41.17%) and in contrast to the studies of Bekkelund *et al*^[13], and Piha *et al*^[15] which found no ANS abnormality.

In Further analysis, our study revealed the damage occurred in both the divisions of autonomic nervous system in Ra patients and it is in a sub clinical state unassociated with clinical symptoms and signs. Parasympathetic suffers more damage comparing to sympathetic division (91.79% VS 4.83%).

The abnormal systolic blood pressure change that occurred during tilting affected only 3.86% of our RA patients which was significantly associated with female gender (p <0.0001), as in our previous study where we used different set of bedside clinical tests to assess exclusively the parasympathetic division. Like in our previous study age of the RA patients did not have any effect on the autonomic damage.^[12] But disease duration and RF status had shown a positive influence on the autonomic damage in our patients like studies done by V.Sandhu *et al*^[16] and Castro EM *et al*^[17], in which blunted autonomic cardiovascular reflexes were positively associated to RF status, and also to Geenen *et al*^[18] study whose patients showed a significantly shorter PEP (the Pre-Ejection-Period- reflecting elevated Sympathetic Nervous System activity) was most pronounced in those with chronic active disease. Significant abnormal BP changes (either systole or diastole) were found only in 4.83% of our RA patients.

The pathogenesis of the ANS 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. The presence of circulating auto antibodies 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 auto-antibodies in the pathogenesis of ANS dysfunction remains to be determined. The abnormal cardiovascular responsiveness found in our study suggests that these patients are prone to develop a sub clinical form of autonomic neuropathy. As a consequence, the assessment of cardiovascular autonomic function in patients with RA should be part of their clinical evaluation, autonomic impairment being a potential,

poor, prognostic factor in other diseases, such as diabetes and ischemic heart diseases.^[19]

Dudley-Golding *et al*^[20], and Ewing D J *et al*^[21] reported a definite relation between peripheral and autonomic neuropathy in diabetics and we observed a similar association in our study. 10.63 % of our RA patients had shown clinical evidence of peripheral neuropathy and all of them showed early changes of parasympathetic damage, were strongly associated to RF, disease duration and gender. Peripheral neuropathy is thought to be due to vasculitis in rheumatoid disease.^[13] And possibly an autonomic neuropathy occurs for the same reason and even precede the development of peripheral neuropathy. The possible pathogenesis factor involved in altered ANS function in RA include primary disturbance of the ANS present in the preclinical phase or a secondary response to the inflammatory process or to auto-antibodies directed against ANS structures.^[21] The defects in regulatory processes which are fundamental to RA may lie in the immune system, the nervous system, the endocrine system or the interactions of these. A better understanding of neuro-endocrine immune interactions holds the promise of new approaches to the treatment of RA with the use of hormones, neurotransmitters, neuro-peptides and or their antagonists. The presence of an autonomic neuropathy has been an established poor prognostic factor in diabetics, since the frequency of unexplained cardio-respiratory arrests particularly during anesthesia and in the immediate post-operative period appears to be increased in these patients¹. This may also apply in RA and long term follow up of RA patients is essential to determine whether such risk factors exist in rheumatoid autonomic neuropathy.

CONCLUSION

Rheumatoid arthritis patients are affected by asymptomatic autonomic neuropathy. Although both parasympathetic and sympathetic divisions are affected in rheumatoid arthritis, parasympathetic division suffers more than the sympathetic division. None of our patients who showed an abnormal blood pressure response to tilting were suffered from the symptoms of orthostatic hypotension. Altered autonomic responses has shown significant positive correlation to female RA patients with longer disease duration and sero-positivity and does not show any relationship to the age of the patients. Peripheral neuropathy occurs in RA patients with parasympathetic dysfunction. Simple bed side tests which are used to study the autonomic reflexes can provide an objective guide to whether or not autonomic damage is present and to what degree. Tilt table test will certainly be helpful to rule out the orthostatic hypotension among RA patients and also will be useful in detecting any subclinical damage involving postural blood pressure reflexes in them. The early detection and treatment of autonomic neuropathy will not only help to reduce the mortality but also certainly improve the quality of life and reduce the sufferings in RA patients.

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