THE STUDY OF AUTONOMIC FUNCTION TESTS IN PATIENTS OF RHEUMATOID ARTHRITIS BY CARDIOVASCULAR ANALYSIS SYSTEM

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Background and objectives: In patients of Rheumatoid Arthritis (RA) although peripheral and central nervous system involvement has been well recognized[1], autonomic nervous system (ANS) involvement has rarely been studied and has shown conflicting results. This study was conducted to investigate ANS dysfunction in patients of RA by CANWin using classical Ewing autonomic battery tests. **Methods:** 50 patients of RA between the age group of 20-70 years along with 25 healthy age and sex matched controls were evaluated by 4 parasympathetic tests including resting heart rate (HR), HR response to deep breathing, standing and valsalva maneuver; and 2 sympathetic tests consisting of blood pressure response to standing and sustained hand grip (SHG) by CANWin analysis system (Window based). **Results:** Heart rate response to deep breathing (E:I), standing (30:15 ratio) and valsalva showed very significant results in patients of RA as compared to that of controls ($P<0.01$). 10% of RA patients showed fall in systolic BP on standing by more than 20 mm Hg as compared to controls (0%) with significant p-value of <0.05. 20% of RA patients showed abnormal low rise in diastolic BP on SHG with significant p-value of <0.05. **Interpretation** & **Conclusions:** This study has confirmed the presence of cardiac autonomic nervous system dysfunctions including both sympathetic and parasympathetic, in patients of RA.

Key Words: Rheumatoid Arthritis (RA), CANWin analysis system (Window based), ANS dysfunction

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Introduction:

Rheumatoid Arthritis is a chronic multisystem disease of unknown aetiology characterized by persistent inflammatory synovitis, usually involving peripheral joints in symmetric distribution and in some cases, extra articular involvement[2] such as anemia, weight loss, rheumatoid nodules, rheumatoid vasculitis, etc. Rheumatoid arthritis can begin at any age, but has its peak between 35 to 55 years of age[3]. The prevalence of RA is around 1% worldwide and that of India is 0.9% with women suffering 3-5 times more than men[4].

Rheumatoid arthritis is a form of autoimmunity, and is strongly associated with the inherited tissue type Major histocompatibility complex (MHC) antigen HLA-DR4 (most specifically DR0401 and 0404)[5]. Epidemiological studies have confirmed potential association between RA and two herpes virus infections: Epstein-Barr virus (EBV) and Human Herpes Virus 6 (HHV-6). Immunoregulatory properties of Vitamin-D have been suggested with the discovery of the vitamin D receptor (VDR) in the cells of the immune system and association of greater intake of vitamin D with a lower risk of RA, as well as correlation of significant clinical improvement with the immunomodulating potential in vitamin D-treated RA patients[6].

In patients of RA, peripheral nervous system is the main target and central nervous system (CNS) involvement is rare. Autonomic neuropathy may be present in any kind of connective tissue disorders even in pre-clinical stage. Cardiovascular ANS assessment in RA has been studied by few investigators and there have been conflicting results because of the ways in which controls were selected and the criteria used to determine ANS dysfunction. In 1965 **Bennett et al** studied the thermo-regulatory sweating response to warm water immersion and the local sweating response to intradermal injection of acetyl choline and concluded that clinical sensory neuropathy in RA is usually accompanied by an autonomic neuropathy of postganglionic type[7]. In 1979 **Edmonds et al** investigated the cardiovascular reflexes, by using the tests described for parasympathetic nerve function and concluded that significantly more patients with RA had abnormal autonomic function when compared to the control groups[8]. **Leden et al**

in 1983 reported increased resting heart rate in all RA patients and significant abnormal response to orthostatic stress in severe RA patients[9]. **Louthrenoo W, Ruttanaupawan et al** in 1999 concluded that 47% of the RA patients had symptoms suggesting ANS dysfunction without any correlation with disease duration, or raised ESR[10]. **Dina C. Janse van Rensburg et al**, 2012 concluded that the RA group had a significant higher resting heart rate compared to the control group in both the supine and standing position, and also a poorer response to posture change[11]. Many previous studies had evaluated sympathetic nervous system involvement by using only a single test like sweating response, orthostatic test, pupillary reflex, lacrimation and skin tests, but these were not considered conclusive. However, cardiovascular reflex tests are being used most widely now as they are non-invasive, results are easy to reproduce and they reflect the state of ANS throughout the body. The objective of present study was to evaluate the autonomic function tests in patients of RA by simple bedside and objective cardiovascular reflex tests which includes six tests proposed by Ewing.

Material & Method:

The present study was carried out in the Department of Physiology in collaboration with Department of Medicine, Dr. S.N. Medical College by using **CAN Win Analysis System** on 50 patients having rheumatoid arthritis diagnosed on the basis of criteria developed by American College of Rheumatology in 1987 along with twenty five (25) healthy age and sex matched controls of Western Rajasthan. The procedures were in accordance with the ethical standards of the committee of the institute. Patients were checked for symptoms and signs of possible autonomic dysfunctions including orthostatic hypotension (light headedness, blurred vision, sensation of weakness and unsteadiness, fainting or syncope on standing), perspiration, palpitations and Raynaud's phenomenon.

CAN Win-PC is a Windows based Cardiac Autonomic Neuropathy (CAN) Analysis System with interpretation and detects Cardiac Autonomic Neuropathy based on Ewing battery of tests. This device can detect SNS and PNS damage and diagnose CAN by carrying out CAN tests in a hassle-free way. The system uses Tacho Cardio Gram (TCG) and automatic Non-Invasive Blood Pressure (NiBP) to conduct a battery of six tests. Being fully automatic, CAN Win eliminates the need of manual recordings, readings and calculations.

Exclusion Criteria: Patients with following history and diseases were excluded:

1. Hemoglobin <10 gm%.
2. Pregnancy.
3. Diseases interfering with the autonomic functions including Diabetes mellitus, renal and liver disease and Parkinson's disease.
4. Cardiovascular diseases including hypertension, ischemic heart disease and congestive heart failure.
5. Neurological diseases including multiple sclerosis, polyneuropathy or Guillain Barre Syndrome.
6. Drugs that interfere with the autonomic functions including anti-hypertensive, diuretics, adrenergic drugs, anti-arrhythmics, sedatives, hypnotics and anti-epileptic drugs.

The following non-invasive autonomic function tests were performed by **CAN Win Analysis System.**

A. Tests of predominantly parasympathetic function:-

1. Resting Heart Rate

2. Heart Rate variation during deep breathing (Expiration/Inspiration ratio):

While recording ECG, the subjects were asked to inhale deeply for 5 seconds followed by exhalation for 5 seconds at a rate of 6 breaths per minute. The ratio between longest R-R interval during expiration and shortest R-R interval during inspiration (E/I ratio) in each respiratory cycle is calculated for evaluation. A value of 1.20 or higher was taken as normal[12].

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

The subject was instructed to lie down comfortably and ECG was recorded to calculate the heart rate. Then the subject was instructed to stand up within 3-4 seconds and remained motionless thereafter. The 30:15 is

the ratio of the longest R-R interval at beat 30 during the inspiration/expiration cycle and the shortest R-R interval at beat 15 after standing. It examines the integrity of the efferent parasympathetic branch. The 30:15 ratio of ≥1.04[13] is taken as normal and value of <1.04 is considered abnormal.

4. Heart-rate response to Valsalva maneuver (VM ratio)

The subject was asked to blow out or to expire forcefully through a mouthpiece attached to the sphygmomanometer to maintain the pressure at about 40mm Hg for 15 seconds. The ECG is recorded simultaneously during this maneuver and 15 seconds afterwards to see the RR interval changes. The valsalva ratio = Longest R-R interval after maneuver (after the strain)/ Shortest R-R interval during maneuver (during the strain). The normal valsalva ratio is >1.21[13] and in autonomic dysfunction this ratio is <1.21.

B. Tests of predominantly sympathetic function:-

1. Blood-pressure response to standing

The BP of the subject was recorded at lying down and again when the subject stands up from supine position. In normal subjects systolic blood pressure does not fall by more than 10mm Hg and in autonomic dysfunction it falls by >20-30 mm Hg. Orthostatic hypotension was defined as a fall of ≥20mm Hg in systolic and/or ≥10 mmHg in diastolic blood pressure from lying to standing position[14].

2. Blood-pressure response to Sustained handgrip (SHG)

Initially the subject was asked to exert maximal hand grip strength on hand grip dynamometer with dominant hand. First the maximum voluntary contraction (MVC) (Maximal isometric tension i.e. T_{max}) is determined and then the subjects were asked to press the handgrip dynamometer for at 30% of the maximal voluntary effort. The BP was recorded in contralateral arm and rise in diastolic BP was measured. The value of >15mm Hg rise in diastolic BP is considered as normal response, 11-15 mm Hg as borderline and 10mm Hg or less is considered abnormal (Ewing and Clarke grading)[15].

Various autonomic parameters obtained from patients and controls were compared by Student 't' test (two tailed dependent). P values of < 0.05 were accepted as significant difference between the compared values.

Results:

In the present study, 22% of the patients were in age group of 20-34; 54% in age group of 35-49 and remaining 24% were in the age bracket of 50 and above. The mean age of the patients were found to be 42.50 ± 11.76 with female preponderance. Out of the total patients, 80% were females and 20% were males. The mean age of female patients was 40.60 ± 11.01 and that of male patients was 50.10 ± 12.15. Table: 1 and Graph: 1 summarizes the parasympathetic parameters in RA patients and controls, whereas sympathetic parameters have been summarized in Table: 2 and Graph: 2.

Table: 1 Comparison of parasympathetic parameters in RA patients and controls

Parameter	Group		p-value#
	Patient (Mean±SD)	Control (Mean±SD)	
RHR(bpm)	79.32 ± 11.38	74.08 ± 10.67	0.059 (NS)
E:I(DBT)	1.19 ± 0.22	1.35 ± 0.23	0.0056 (VS)
30:15 (L/S)	0.95 ± 0.14	1.10 ± 0.30	0.0048 (VS)
Valsalva Ratio	1.75 ± 0.87	2.64 ± 1.68	0.0033 (VS)
#p value significant <0.05, NS- non-significant VS-very significant			

Graph: 1 Comparison of parasympathetic parameters in RA patients and controls

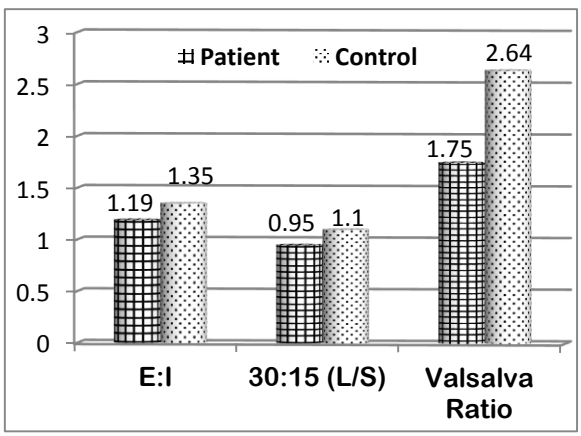
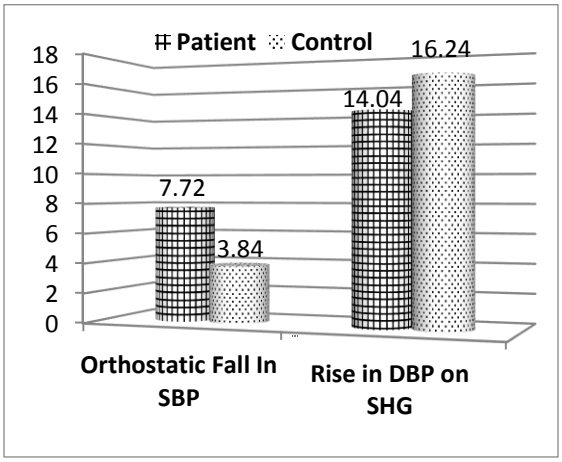


Table: 2 Comparison of sympathetic parameters in RA patients and controls

Parameter	Group		p-value##
	Patient# (Mean±SD)	Control# (Mean±SD)	
Orthostatic Fall in SBP	7.72 ± 8.57	14.04 ± 4.01	0.037 (S)
Rise in DBP on SHG	14.04 ± 4.01	16.24 ± 2.92	0.045 (S)
# mmHg ##p value significant <0.05 S- significant			

Graph: 2 Comparison of sympathetic parameters in RA patients and controls



The significant findings are being enumerated briefly. Mean resting heart rate of subjects was 79.32 ± 11.38 and that of control was 74.08 ± 10.67 with a p-value of 0.059, which is found to be non-significant, but resting heart rate is higher in patient group than that of control group. Mean basal systolic blood pressures in supine resting condition was higher in patients as compared to that of control which is 119.10 ± 7.53 for patients and that for control is 114.52 ± 6.81 with a p-value of 0.012, which is significant ($p<0.05$). Mean basal diastolic blood pressure of patients in supine resting condition was 80.18 ± 6.10 and that of control was 77.32 ± 5.08 with a p-value of 0.047, which is significant ($p<0.05$). Out of 50 patients, 10% of RA patients had significant orthostatic fall in systolic BP by more than 20 mm Hg on standing from supine position.

Discussion:

The comparative study, between our series of patients and the controls, showed significant difference for both sympathetic & parasympathetic autonomic function tests. In the present study, heart rate variation to deep breathing (E:I), 30:15 ratio, Valsalva ratio were found to be low in patients as compared to control group and the 'p' values were found to be very significant, which is similar to the findings of Toussirot et al[16], Geenen et al and in contrast, studies of Bekkelund et al[17], and Piha et al found no CVS ANS abnormality.

As far as sympathetic tests results are concerned, out of the 50 patients, 10% of the RA patients had significant orthostatic hypotension with fall in BP by more than 20 mmHg on standing from supine position. The BP response to sustained handgrip was abnormal in 32% RA patients. These findings are almost similar to findings by Bidikar et al and Bhise et al. Bidikar et al observed that the resting HR and BP were significantly higher in RA patients as compared to controls[18]. Bhise et al observed that the rise in diastolic blood pressure was very highly significant in RA patients than control group on sustained hand grip[19].

Thus, autonomic testing indicates involvement of the sympathetic and parasympathetic pathways in patients of RA. This suggests that clinical sensory neuropathy in RA is usually accompanied by an autonomic neuropathy also. The actual mechanism is not clear. The pathogenesis of the ANS dysfunction in patients with RA is not clearly understood. An involvement of humoral and cellular immune component has been suggested to play a role in severe autonomic neuropathy. The cross-talk between the brain and immune system in inflammatory arthritis is exerted mainly through the activation or down-regulation of the hypothalamic–ANS, hypothalamic– pituitary–adrenal and hypothalamic–pituitary–gonadal axes[20]. The contribution of a direct immunological damage to components of neural pathways can be postulated which is supported by the demonstration of circulating complement fixing autoantibodies directed against sympathetic and parasympathetic nervous structures, represented by superior cervical ganglia and vagus nerve, respectively, in patients with SLE and RA[21]. There was a significant positive association between AFTs score and the presence of these antibodies.

The concept of treating patients with asymptomatic CAN may not appeal to some physicians, particularly in light of the fact that there are no outcome data from clinical trials yet[22]. Anti-oxidants may ameliorate CAN. Endurance training is a non-pharmacological intervention of CAN that induces a high parasympathetic tone[23]. One should be cautious in prescribing drugs that have effects on the cardiovascular ANS in patients with RA with possible autonomic dysfunction. Asymptomatic patients may be closely followed up clinically and the AFTs may be repeated every 6 months for detection of progression.

Conclusion:

In summary, cardiovascular ANS dysfunction occurs in RA. The abnormal cardiovascular autonomic function tests observed in our study suggest that these patients are prone to develop a subclinical form of autonomic neuropathy. It is usually not evident, unless one specifically tests for it, by using the standard cardiovascular reflex tests, before overt symptoms of ANS dysfunction occur. Hence, 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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