



A Case Control Study of Autonomic Function Tests in female Rheumatoid Arthritis patients

KEYWORDS

Rheumatoid Arthritis (RA), sustained handgrip (SHG)

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ABSTRACT *Background – In Rheumatoid Arthritis (RA) patients' involvement of autonomic nervous system has rarely been studied¹.*

Objective – Evaluation of cardiovascular autonomic neuropathy (CAN) in RA patients.

Material and methods – 45 RA female patients (age group 35-45 years) along with 45 age and BMI matched female controls were evaluated by: 30:15 ratio; E: I ratio; BP response to standing; BP Response to sustained handgrip (SHG) by CAN Win analysis system (window based). Statistical analysis was performed using SPSS software version 20 and Z-test was used to derive the level of significance.

Results – The mean 30:15 ratio, E/I ratio, Rise in diastolic blood pressure on SHG were found lower (p value < 0.001) whereas mean orthostatic fall in systolic blood pressure was found higher (p value < 0.001) in RA patients as compared to control group.

Conclusion – Deranged cardiovascular autonomic functions are found in RA patients.

INTRODUCTION

Rheumatoid Arthritis is a chronic multisystem autoimmune connective tissue disease of unknown aetiology characterized by persistent inflammatory synovitis, usually involving peripheral joints in symmetric distribution and in some cases, extra articular involvement². Rheumatoid arthritis can begin at any age, but has its peak between 35 to 55 years of age³. The prevalence of RA is around 0.5-1% worldwide with women suffering 2-3 times more than men⁴. Among the cases of nervous system involvement in RA, those of the peripheral nervous system are well documented, autonomic nervous system involvement has rarely been studied¹.

Cardiovascular reflex tests proposed by Ewing et al have been most widely used as they are non invasive, results are easy to reproduce and they reflect the state of ANS throughout the body⁵. An inability of the autonomic nervous system to efficiently compensate for internal and external environmental changes may predispose RA patients to arrhythmias, thereby increasing cardiovascular morbidity and mortality by up to 50%⁶. The present study is an attempt to an early understanding of the autonomic nervous system dysfunctions in rheumatoid arthritis patients which can help in diagnosis, prevention and treatment.

Material and Methods

The present study was conducted in the Upgraded department of Physiology in collaboration with the Department of Medicine, S.M.S. Medical College and Hospital, Jaipur, Rajasthan from 1st June 2015 to 31st May 2016 on 45 RA female patients between the age group of 35-45 years taken from the Department of Medicine, S.M.S. Hospital, Jaipur along with 45 age and BMI matched healthy female controls taken from accompanying attendants of the patients.

Ethical Statement: This study was approved by the Institutional Research Review Board of SMS Medical College and Hospital.

All subjects gave informed written consent.

Inclusion Criteria: 35-45 yrs aged newly diagnosed Rheumatoid Arthritis female patients, as per the 2010 ACR-EULAR CLASSIFICATION CRITERIA⁷ and Age and BMI matched healthy female controls subjects in the follicular phase of regular menstrual cycle (28 days) were included in the study.

Exclusion Criteria: Pregnancy, smoker, chronic diseases and drugs affecting autonomic functions were excluded from the study.

All subjects were tested between 11 am to 1.00 pm under similar laboratory conditions and were allowed to adapt themselves to experimental and environmental condition for 30 minutes to make them comfortable, as anxiety and stress can affect autonomic functions. The subjects were asked to avoid coffee, nicotine or alcohol 24 hours prior and food 2 hours prior of autonomic function test. The room ambient temperature was maintained at 24-25°C. A thorough history was taken and general physical examination was done to screen out the subjects.

CANWin - CANWin detect Cardiac Autonomic Neuropathy based on Ewing battery of tests.

For assessment of Parasympathetic functions following tests were performed:-

- Heart rate response to standing or 30:15 R-R ratio

- Heart rate response to deep breathing (Expiration / Inspiration ratio)

For assessment of Sympathetic functions following tests were performed-

- Blood pressure response to standing
- Blood pressure response to sustained handgrip

Statistical Analysis: Statistical analysis was performed using SPSS software version 20 and Z-test was used to derive the level of significance.

Observations and tables:

Table: 1

Comparison of anthropometric and baseline clinical characteristics of case and control

Parameter	Groups (Mean ± SD)		Z- value	p - value	Significance
	Case (n=45)	Control (n=45)			
Age (yrs)	39.82 ± 4.11	38.64 ± 3.06	1.573	>0.05	NS
BMI(Kg/m ²)	24.14 ± 2.42	23.29 ± 1.83	1.89	> 0.05	NS
SBP (mmHg)	119.53 ± 7.78	116.78 ± 8.16	1.637	> 0.05	NS
DBP (mmHg)	81.13 ± 7.16	79.22 ± 7.42	1.242	> 0.05	NS
HR (Beats/min)	79.73 ± 10.43	76.38 ± 12.08	1.408	> 0.05	NS
RR (per min)	11.62 ± 1.68	11.38 ± 1.39	0.738	> 0.05	NS

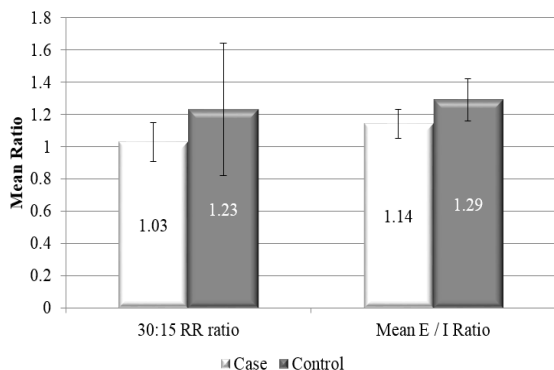
BMI (Body mass index), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), HR (Heart rate), RR (Respiratory rate)
NS (not significant)

Table: 2

Comparison of parasympathetic parameters in RA patients and controls

Parameter	Group (Mean ± SD)		Z- value	p -value	Significance
	Case (n=45)	Control (n=45)			
30:15 RR ratio	1.03 ± 0.12	1.23 ± 0.41	3.175	< 0.001	HS
E/I Ratio	1.14 ± 0.09	1.29 ± 0.13	6.522	< 0.001	HS

HS (Highly significant)



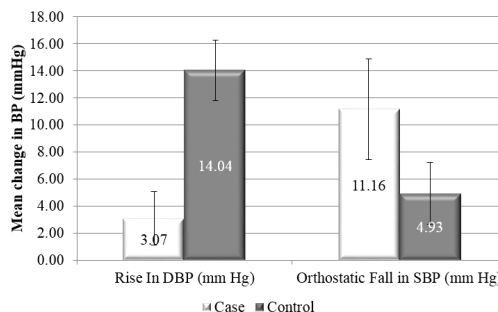
Bar diagram: 1 Comparison of parasympathetic parameters in RA patients and controls

Table: 3

Comparison of sympathetic parameters in RA patients and controls

Parameter	Group (Mean ± SD)		Z- value	p -value	Significance
	Case (n=45)	Control (n=45)			
Orthostatic fall in SBP (mmHg)	11.16 ± 3.72	4.93 ± 2.30	9.555	< 0.001	HS
Rise of DBP (mmHg)	3.07 ± 1.98	14.04 ± 2.23	24.652	< 0.001	HS

SBP (Systolic blood pressure), DBP (Diastolic blood pressure), HS (Highly significant)



Bar diagram: 2 Comparison of sympathetic parameters in RA patients and controls

Results:

- The mean of 30:15 R-R ratio in rheumatoid arthritis patients was 1.03 ± 0.12 and of control subjects was 1.23 ± 0.41. (Table 2) (p-value < 0.001) (Bar diagram 1)
- The mean of E/I ratio in rheumatoid arthritis patients was 1.14 ± 0.09 and of control subjects was 1.29 ± 0.13. (Table 2) (p-value < 0.001) (Bar diagram 1)
- The mean of Orthostatic fall in systolic blood pressure in rheumatoid arthritis patients was 11.16 ± 3.72 mm of Hg and of control subjects was 4.93 ± 2.30 mm of Hg. (Table 3) (p-value < 0.001) (Bar diagram 2)
- The mean of Rise in diastolic blood pressure in response to sustained handgrip in rheumatoid arthritis patients was 3.07 ± 1.98 mm of Hg and of control subjects was 14.04 ± 2.23 mm of Hg. (Table 3) (p-value < 0.001) (Bar diagram 2)

Discussion:

In our study the mean of Immediate heart rate response to standing or 30:15 R-R ratio and mean of heart rate variation in deep breathing or E:I ratio were found to be significantly lower in Rheumatoid Arthritis patients as compared to control subjects. (p value < 0.001) which is similar to the findings of Milovanović B et al. (2010)⁸, Saraswathi P V et al. (2013)⁹

Mean fall in systolic blood pressure in response to standing was found significantly higher in Rheumatoid Arthritis patients compared to control subjects (p-value < 0.001) and mean rise in diastolic blood pressure with sustained handgrip was found significantly lower in Rheumatoid Arthritis patients compared to control subjects (p-value < 0.001). These findings are in agreement with the findings of Bidikar MP et al. (2010)¹⁰ and Bhise RM et al. (2013)¹¹.

Hence it can be presumed that there is derangement of autonomic function in RA patients. 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 Ra¹².

In an another study of the outflow of the sympathetic nervous system

(SNS) and the hypothalamic pituitary adrenal (HPA) axis tone, in rheumatoid arthritis (RA), a low levels of cortisol and ACTH in relation to serum neuropeptide Y (NPY) were found which may be proinflammatory because cooperative anti-inflammatory coupling of the two endogenous response axes is missing. In addition, disease related factors such as depression, chronic pain, weight gain, and others may add to the uncoupling phenomenon¹³.

Thus regular assessment of autonomic functions can be used as a biomarker for early detection and subsequent management of cardiovascular morbidity and mortality in female RA patients.

Conclusion: It is concluded that Rheumatoid Arthritis patients have sympathetic hyperactivity and reduced parasympathetic activity, when compared with the normal subject. Thus regular assessment of autonomic functions by CAN Win can be used as biomarker to prevent cardiovascular morbidity and mortality as it is easy to perform, non-invasive and cost effective.

Strength, Limitations and Recommendations:

Certainly, the strength of our study is the careful selection of the subjects and an effort to rule out all possible confounding factors which can affect the results.

The study was conducted in a limited time period on a small sample size. Better results may be obtained with a large sample size over a longer time period.

References:

1. Straub RH, Zeuner M, Lock G, Rath H, Hein R, Schölmerich J et al. Autonomic and sensorimotor neuropathy in patients with systemic lupus erythematosus and systemic sclerosis. *The Journal of rheumatology*. 1996 Jan;23(1):87-92.
2. Fauci AS. *Harrison's principles of internal medicine*. McGraw-Hill, Medical Publishing Division; 2008;2:2083-2092.
3. Deal CL, Meenan RF, Goldenberg DL, Anderson JJ, Sack B, Pastan RS, et al. The clinical features of elderly - onset rheumatoid arthritis. A comparison with younger - onset disease of similar duration. *Arthritis & Rheumatism*. 1985 Sep 1;28(9):987-94.
4. Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. *Pharmacoeconomics*. 2004 Sep 1;22(1):1-2.
5. Ewing DJ. Cardiovascular reflexes and autonomic neuropathy. *Clinical Science*. 1978 Oct 1;55(4):321-7.
6. Coumel P. Autonomic influences in atrial tachyarrhythmias. *Journal of cardiovascular electrophysiology*. 1996 Oct 1;7(10):999-1007.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatism*. 2010 Sep 1;62(9):2569-81.
8. Milovanović B, Stojanović L, Milićević N, Vasić K, Bjelaković B, Krotin M. Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk. *Srp Arh Celok Lek*. 2010 Feb;138(1-2):26-32.
9. Saraswathi PV, Neelambikai N, Mahesh A, Govindarajan K. Cardiovascular parasympathetic nervous system dysfunction in female rheumatoid arthritis patients. *Indian J Physiol Pharmacol*. 2013;57(1):23-30.
10. Bidikar MP, Ichaporia RB. Autonomic (sympathetic) nervous system involvement in rheumatoid arthritis patients. *Indian J. Physiol. Pharmacol*. 2010 Jan-Mar; 54(1): 73-79.
11. Bhise RM, Hatekar AD, Kaundinya SD. Blood pressure and pulse rate responses to sustained handgrip dynamometer test in rheumatoid arthritis patients. *Indian Journal of Applied Basic Medical Sciences*. 2013;15(20):39-47.
12. Maule S, Quadri R, Mirante D, Pellerito RA, Marucco E, Marinone C et al. Autonomic nervous dysfunction in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA): possible pathogenic role of autoantibodies to autonomic nervous structures. *Clinical & Experimental Immunology*. 1997 Dec 1;110(3):423-7.
13. HÄRLE P, STRAUB RH, Wiest R, Meier A, Scholmerich J, Atenzi F et al. Increase of sympathetic outflow measured by NPY and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with SLE and RA - Another example of uncoupling of response systems. *Ann Rheum Dis* 2005; 65: 51-6.