Original Article

Analysis of heart rate variability in patients with chronic rheumatoid arthritis

Sheena Ahamed, Riyaz Sheriff[1]

Departments of Physiology and [1]Microbiology, Azeezia Institute of Medical Sciences and Research, Kollam, Kerala, India

Abstract

Background and Aim: Rheumatoid arthritis (RA) is one of the most common debilitating autoimmune disorders associated with morbidity and mortality. Apart from articular causes, the cardiovascular system plays an important role in untoward incidents of the disease. The cardiac risk in them can be estimated by analyzing the autonomic nervous system. Heart rate variability (HRV) analysis is reliable for testing the cardiac autonomic function. In the present study, we have planned to assess the HRV in RA patients and to compare it with the HRV of normal healthy individuals without RA.

Methods: The study group (Group 1) comprised 50 patients of established RA (12 males and 38 females). The control group (Group 2) comprised 50 healthy age- and sex-matched individuals (9 males and 41 females). Short-term HRV recordings of 5 min were done using Multichannel Physiopac PP-8 machine. Normalized low-frequency power (LFnu), normalized high-frequency power (HFnu), and low frequency/high frequency (LF/HF) ratio were analyzed using Kubios HRV software. Statistical analysis was done using Student's *t*-test. $P < 0.05$ was considered statistically significant.

Results: When compared to control group, LFnu and LF/HF ratio increased significantly and HFnu decreased significantly in RA patients. Increase in LFnu shows predominant sympathetic activity, and decrease in HFnu shows parasympathetic attenuation.

Conclusion: RA is associated with sympathovagal imbalance in the form of sympathetic overactivity and vagal withdrawal.

Key words: Autonomic nervous system, heart rate variability, rheumatoid arthritis, sympathovagal balance

Received: 19th October, 2016; *Revised:* 30th November, 2016; *Accepted:* 20th December, 2016

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease primarily affecting the joints, leading to severe disability and premature mortality.[1] Global prevalence is approximately 0.5%–1%.[2] Prevalence of RA in India is 0.19% in men and 1.24% in women.[3,4] Onset of the disease is predominantly in the third to fifth decades of life. Higher incidence is seen in first-degree relatives. RA is related to lifestyle and socioeconomic class.[5] RA has predominant articular manifestations. Extra-articular manifestations are also seen in 40% of patients.[6] Patients with high titers of rheumatoid factor usually exhibit extra-articular manifestations, namely, rheumatoid nodules, rheumatoid vasculitis, pleuropulmonary, gastrointestinal, neurological, cardiovascular, cutaneous, hematologic, and ocular complications.[7] Cardiovascular morbidity in RA is more common and may be up to 40%.[6] The most common cause of cardiovascular disease in RA is coronary artery disease, followed by pericarditis.[8] Others include pericardial effusion, cardiomyopathy, myocarditis, coronary vasculitis, arrhythmia, valvular heart disease, and ischemic heart disease.[9] Higher incidence of congestive cardiac failure, unrecognized myocardial infarction, and sudden death is also seen. About 49.5% of deaths in RA patients are due to cardiovascular causes.[8] Earlier the risk associated with cardiac autonomic nervous system (ANS) dysfunction

Address for correspondence: Dr. Sheena Ahamed, MINAR, NRA-43, Navarangam Lane, Medical College P.O., Thiruvananthapuram - 695 011, Kerala, India.
E-mail: drsheenariyaz@gmail.com

Access this article online

Quick Response Code:

Website: www.ijcep.org

DOI: 10.4103/2348-8832.196914

How to cite this article: Ahamed S, Sheriff R. Analysis of heart rate variability in patients with chronic rheumatoid arthritis. Int J Clin Exp Physiol 2016;3:204-8.

was seldom studied. With the advent of technology and better understanding of the mechanisms regulating the nervous system, research has turned towards the etiopathogenesis of cardiac events in RA. Heart rate variability (HRV) is defined as variations in normal R-R intervals. These are due to modulation of sinus node function by cardiac ANS activity.[10]

The HRV analysis is an easily reproducible noninvasive cardiac autonomic function test.[11,12] It is an electrocardiographic marker reflecting the autonomic activity of the sinus node. It detects the variation in instantaneous heart rate and R-R intervals. A highly variable heart rate is a good sign of adaptability indicating a healthy individual with a well-functioning ANS. Decreased HRV indicates impending cardiovascular pathology.[13-18] Therefore, the aim of the present study is to assess the nature of autonomic dysfunction in chronic RA patients.

MATERIALS AND METHODS

This study was conducted in the Department of Physiology, SRM Medical College Hospital and Research Centre, Chennai. Ethical Committee clearance was obtained. Fifty confirmed RA patients of the age group 30–65 years attending the Rheumatology Department were selected for the study. RA factor and C-reactive protein were estimated to know the disease activity. Rhelax–CRP kit and Rhelax–RF kit from Tulip Diagnostics, India, were used for the assessment. The 2010 American College of Rheumatology/European League Against Rheumatism Classification criteria was used to select the patients.[1] Study group (Group 1) comprised 38 females and 12 males. Fifty age- and sex-matched healthy volunteers without RA were selected as the control group (Group 2). Subjects with other forms of arthritis, symptomatic cardiac illness, ischemic heart disease, respiratory illness, hypertension, pregnancy, patients in severe pain, males and females of age <30 years and >66 years were excluded from the study.

The test was performed between 8 AM and 11 AM. The subjects were asked to refrain from tobacco and strenuous exercise on the day of the test. Two-hour fasting was recommended before the test. The electrophysiology laboratory was maintained at normal room temperature. They were given a period of 15 min to get accustomed to the surroundings. Test procedure was explained, and written informed consent was obtained before starting the recording. They were instructed not to sleep, talk, or move during the recording. Vital signs, height, weight, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded. The subject was then asked to lie supine for 15 min. HRV recording was done using Multichannel Physiopac-PP8 machine having 8 channels, electrocardiogram box, four limb leads, and one chest lead. Continuous sinus rhythm without artifacts was recorded for 5 min using lead II. The data were then transferred to Kubios HRV Software (version 2.0) from Biosignal analysis and Medical Imaging group, Department of Physics, University of Kuopio, Finland, for further analysis. The frequency domain variables are low-frequency (LF) waves of 0.04–0.15 Hz, high-frequency (HF) waves of 0.15–0.4 Hz, very LF (VLF) waves of ≤0.04 Hz. The ratio between the LF and HF waves (LF/HF ratio) indicates the sympathovagal balance. VLF measurement is dubious and hence avoided in short-term recordings.[11] LF waves are considered as a marker of sympathetic activity.[19-21] HF waves indicate vagal activity.[22,23] The power components can be measured as absolute values or in normalized units.[19] Normalization explains the balanced behavior of the ANS. It also reduces the effect in the frequency values when there is a change in the total power.[11] The variables considered here are normalized low-frequency power (LFnu), normalized high-frequency power (HFnu), and LF/HF ratio.

Statistical analysis of data

The data were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as mean ± standard deviation. Analysis was done by Student's *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the general characteristics of both study group and control group subjects. There is no significant

Table 1: Comparison of general characteristics among the study group (Group 1) and control group (Group 2) subjects

Parameter	Group	*n*	Mean±SD	*P*
Age	Group 1	50	48.28±1.646	0.007
	Group 2	50	42.92±1.024	
Body weight	Group 1	50	67.77±1.118	0.933
	Group 2	50	67.94±1.67	
BMI	Group 1	50	25.4916±0.3176	0.502
	Group 2	50	24.9506±0.736	
Heart rate	Group 1	50	75.76±0.617	0.012
	Group 2	50	78.8±1.014	
SBP	Group 1	50	121.52±1.373	0.005
	Group 2	50	116.16±1.248	
DBP	Group 1	50	78.08±0.996	0.199
	Group 2	50	76.36±0.881	
MAP	Group 1	50	92.5±1.0175	0.0028
	Group 2	50	89.46±0.8904	

Data expressed are mean±SD. Analysis of data was done by Student's *t*-test. *P*<0.05 was considered statistically significant. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, SD: Standard deviation

difference in the BMI between Group 1 and Group 2. There is a significant decrease in heart rate ($P < 0.05$) and significant increase in SBP ($P < 0.01$) and mean arterial pressure ($P < 0.01$) in Group 2 whereas DBP did not show any significant difference between both the groups [Table 1].

Table 2 shows the frequency domain indices between study and control group of subjects. LFnu and LF/HF ratio increased significantly ($P < 0.001$) whereas HFnu decreased significantly ($P < 0.001$) in Group 1 when compared to Group 2.

Table 3 shows the time domain parameters such as the square root of the mean of the sum of the squares of differences between adjacent NN Intervals (RMSSD), standard deviation of all NN intervals (SDNN), number of pairs of adjacent NN intervals differing by >50 ms in the entire recording (NN50), and NN50 count divided by the total number of all NN intervals (pNN50) between the two groups. RMSSD and SDNN did not show any significant difference between the two groups. NN50 ($P = 0.01$) and pNN50 ($P < 0.05$) were significantly less in Group 1 when compared to Group 2 subjects.

Table 2: Frequency domain variables between study and control group of subject

Parameter	Group	*n*	Mean value	*P*
LFnu	Group 1	50	76.32±1.37	<0.0001
	Group 2	50	65.84±1.06	
HFnu	Group 1	50	23.68±1.37	<0.0001
	Group 2	50	33.62±0.91	
LF/HF ratio	Group 1	50	3.67±0.18	<0.0001
	Group 2	50	2.08±0.10	

Data expressed are mean±SD. Analysis of data was done by Student's *t*-test. *P*<0.05 was considered significant. LFnu: Normalized low-frequency power, HF: Normalized high-frequency power, nu: Normalized units, LF/HF ratio: Low frequency/high frequency ratio, SD: Standard deviation

Table 3: Time domain variables between study and control group of subjects

Parameter	Group	*n*	Mean value	*P*
RMSSD	Group 1	50	15.8±2.8146	0.839
	Group 2	50	15.188±1.0745	
SDNN	Group 1	50	22.34±2.647	0.168
	Group 2	50	26.76±1.768	
NN50	Group 1	50	2.34±0.565	0.01
	Group 2	50	4.92±0.811	
pNN50	Group 1	50	1.088±0.2478	0.04
	Group 2	50	1.824±0.2527	

Data expressed are mean±SD. Analysis of data was done by Student's *t*-test. *P*<0.05 was considered significant. RMSSD: The square root of the mean of the sum of the squares of differences between adjacent NN Intervals, SDNN: Standard deviation of all NN intervals, NN50: Number of pairs of adjacent NN intervals differing by >50 ms in the entire recording, pNN50: NN50 count divided by the total number of all NN intervals, SD: Standard deviation

DISCUSSION

The HRV changes in RA are due to subclinical inflammation.[24,25] Autonomic neuropathy may be present in any kind of connective tissue disorder even in preclinical stage. This is related to the presence of autoantibodies against ANS and may play a role in the pathogenesis of autonomic dysfunction.[26] Research in RA to detect the presence and type of cardiac autonomic dysfunction has led to various theories. Few support sympathetic overactivity as a reason for alteration of HRV.[13,27,28] An equal number of studies support parasympathetic predominance as well.[29,30] Bekkelund *et al*., Tumiati *et al*., and Piha and Voipio-Pulkki concluded that there is no autonomic dysfunction in patients with RA.[31-34] However, in the present study, we found that the HRV parameters, namely, LF power and LF/HF ratio representing sympathetic activity were significantly more in RA patients whereas HF power representing the cardiac vagal modulation was significantly less in RA patients when compared to the control group subjects. The results clearly indicate that there is sympathetic overactivity in RA patients. This increased sympathetic activity could be due to increased inflammatory markers and immunological cytokines in RA patients as inflammatory markers if chronically elevated are known to stimulate the sympathetic activity.

In the present study, SBP was higher in patients with RA compared to the control group. It was predicted that sympathetic predominance would increase the heart rate, but conversely, the heart rate was lesser compared to the comparison group. The reason for this aberration from the normal is not clearly understood.

RA is one of the most disabling conditions known to humankind. Its severe morbidity associated with the articular manifestations is well known. Now, the nonarticular manifestations of RA also gain importance because of their contribution to the morbidity and mortality. The life expectancy of RA patients is found to be decreased by 5–10 years. The economic burden of the patients has increased due to the increasing cost of investigations to detect or predict the development of complications associated with RA. HRV analysis proves to be an easy, noninvasive, cost-effective, reproducible, and reliable tool for detection of upcoming cardiac events. It will help the clinician to foresee the possible cardiac event, thereby providing a better treatment protocol for RA patients. In turn, it helps in decreasing the disease burden and improves the quality of their life.

Limitations of the study

The major limitation is that we have not done the correlation and regression analysis for assessing the duration of the disease with the degree of sympathovagal

imbalance. Another limitation is that the study was carried out only in patients from a single geographical area. Changes in HRV based on race and ethnicity have not been assessed.

CONCLUSION

HRV is altered in the form of sympathetic overactivity and vagal inhibition. Future studies may be conducted to assess the role of autonomic imbalance in the causation of cardiovascular morbidities and mortalities in RA.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Aletaha D, Neogi T, Silman A, Funovits J, Felson D. 2010 rheumatoid arthritis classification criteria. Arthritis Rheumatol 2010;62:2569-81.
2. Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender- and age-related differences in heart rate dynamics: Are women more complex than men? J Am Coll Cardiol 1994;24:1700-7.
3. Akhter E, Bilal S, Kiani A, Haque U. Prevalence of arthritis in India and Pakistan: A review. Rheumatol Int 2011;31:849-55.
4. Joshi VL, Chopra A. Is there an urban-rural divide? Population surveys of rheumatic musculoskeletal disorders in the Pune region of India using the COPCORD Bhigwan model. J Rheumatol 2009;36:614-22.
5. Bengtsson C, Nordmark B, Klareskog L, Lundberg I, Alfredsson L; EIRA Study Group. Socioeconomic status and the risk of developing rheumatoid arthritis: Results from the Swedish EIRA study. Ann Rheum Dis 2005;64:1588-94.
6. Limmino MA, Salvarani C, Macchioni P, Montecucco C, Fossaluzza V, Mascia MT, *et al*. Extra-articular manifestations in 587 Italian patients with rheumatoid arthritis. Rheumatol Int 2000;19:213-7.
7. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, *et al*. Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. Arthritis Rheum 2003;48:54-8.
8. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: A population-based study. Arthritis Rheum 2005;52:722-32.
9. Voskuyl AE. The heart and cardiovascular manifestations in rheumatoid arthritis. Rheumatology (Oxford) 2006;45 Suppl 4:iv4-7.
10. Herald MS. Physiological mechanisms of heart rate variability. Rev Bras Hipertans 2007;14:8-15.
11. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.
12. Malik M, Camm AJ. Components of heart rate variability – What they really mean and what we really measure. Am J Cardiol 1993;72:821-2.
13. Evrengül H, Dursunoglu D, Cobankara V, Polat B, Seleci D, Kabukçu S, *et al*. Heart rate variability in patients with rheumatoid arthritis. Rheumatol Int 2004;24:198-202.
14. Hon EH, Lee ST. Electronic evaluation of the fetal heart rate. VIII. Patterns preceding fetal death, further observations. Am J Obstet Gynecol 1963;87:814-26.
15. Jahan K, Begum N, Ferdousi S. Power spectral analysis of heart rate variability in female rheumatoid arthritis patients. J Bangladesh Soc Physiol 2012;7:8-12.
16. Stys A, Stys T. Current clinical applications of heart rate variability. Clin Cardiol 1998;21:719-24.
17. Mansier P, Clairambault J, Charlotte N, Médigue C, Vermeiren C, LePape G, *et al*. Linear and non-linear analyses of heart rate variability: A minireview. Cardiovasc Res 1996;31:371-9.
18. da Silva E, Rebelo AC, Tamburús NY, Salviati MR, Santos MC, Zuttin RS. Spectral Analysis of Heart Rate Variability in Women, Fourier Transform Applications, Dr Salih Salih (Ed.) ISBN: 978-953-51-0518-3. InTech, DOI: 10.5772/36709. Available from: http://www.intechopen.com/books/fourier-transform-applications/spectral-analysis-of-heart-rate-variability-in-women.
19. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:482-92.
20. Kamath MV, Fallen EL. Power spectral analysis of heart rate variability: A noninvasive signature of cardiac autonomic function. Crit Rev Biomed Eng 1993;21:245-311.
21. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 1994;90:1826-31.
22. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220-2.
23. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, *et al*. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248 (1 Pt 2):H151-3.
24. Louthrenoo W, Ruttanaumpawan P, Aramrattana A, Sukitawut W. Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus. QJM 1999;92:97-102.
25. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. Eur Heart J 2004;25:363-70.
26. 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. Clin Exp Immunol 1997;110:423-7.
27. Yadav RK, Gupta R, Deepak KK. A pilot study on short term heart rate variability & its correlation with disease activity in Indian patients with rheumatoid arthritis. Indian J Med Res 2012;136:593-8.
28. Kawser J, Noorzahan B, Sultana F. Power spectral analysis of heart rate variability in female rheumatoid arthritis patients. J Soc Physiol 2012;1:8-12.
29. Leden I, Eriksson A, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J Rheumatol 1983;12:166-70.
30. Saraswathi PV, Neelambikai N, Mahesh A, Govindarajan K. Cardiovascular parasympathetic nervous system dysfunction in female rheumatoid arthritis patients. Indian J Physiol Pharmacol 2013;57:23-30.
31. Bekkelund SI, Jorde R, Husby G, Mellgren SI. Autonomic nervous system function in rheumatoid arthritis. A controlled study. J Rheumatol 1996;23:1710-4.
32. Tumiati B, Perazzoli F, Negro A, Pantaleoni M, Regolisti G.

Heart rate variability in patients with Sjögren's syndrome. Clin Rheumatol 2000;19:477-80.
33. Piha SJ, Voipio-Pulkki LM. Elevated resting heart rate in rheumatoid arthritis: Possible role of physical deconditioning. Br J Rheumatol 1993;32:212-5.
34. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. Cardiovasc Res 1996;32:208-16.