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A pilot study on short term heart rate variability & its correlation with disease activity in Indian patients with rheumatoid arthritis

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***Background & objectives*: Cardiovascular complications may lead to mortality in patients with rheumatoid arthritis (RA). We assessed heart rate variability (HRV), an important autonomic function, to quantify the risk for cardiovascular complications in Indian patients with RA.**

***Methods*: The study was carried out in RA patients (n=45) diagnosed as per American College of Rheumatology criteria and healthy controls. HRV recording and analysis was done using Nevrokard software using time and frequency domain analyses. The overall autonomic tone, parasympathetic drive, sympathetic drive and sympatho-vagal ratio were quantified by using various parameters. It included standard deviation of all R-R intervals (SDNN), standard deviation of successive differences between adjoining normal cycles (SDSD), root-mean square of successive differences (RMSSD), and number of R-R intervals differing by >50 ms from adjacent intervals (NN50) in the time domain analysis. In frequency domain analysis, low frequency (LF) and high frequency (HF), LF/HF and total power were assessed.**

***Results*: Demographic profile was comparable between groups; however, systolic BP was higher in patients with RA. SDNN, SDSD, RMSSD, NN50, LF and HF power and total power (ms x ms) were significantly lower in patients with RA *versus* healthy controls ($P<0.001$). Disease activity score at 28 joints indicating severity of the disease was significantly and positively correlated with SDSD (r=0.375, $R^2=14.06$; $P=0.045$) while LF and HF power (ms × ms) were significantly and inversely correlated with rheumatoid factor (r=-0.438 and -0.445; $R^2=19.1$ and 19.8; $P=0.017$ and 0.016, respectively).**

***Interpretation & conclusions*: HRV was significantly altered in patients with RA and independently associated with disease activity. Hence autonomic function testing, using HRV, may be useful as part of cardiovascular risk assessment in these patients.**

Key words Cardiovascular status - rheumatoid arthritis - short term heart rate variability

Rheumatoid arthritis (RA) affects approximately 0.5 to 1 per cent of the population, and is associated with significant morbidity, premature mortality and decline in functional status[1,2]. Characterized by chronic joint inflammation, RA may lead to bony erosions, deformity, joint destruction and disability. Cardiovascular autonomic dysfunction is the most common complication of RA, and is associated with high mortality[3,4], resulting from arrhythmia and myocardial infarction. Several studies have shown an increased incidence of cardiovascular events in patients with RA[5-7], however, studies evaluating autonomic nervous system imbalance in patients with RA are scanty, and the data available are conflicting[8,9].

Heart rate variability (HRV) is a measurement (quantification) of central autonomic drive (activity) to the myocardium. It depends on a balance between sympathetic and parasympathetic drives to myocardium. In contrast to many conventional tests to evaluate autonomic nervous system, HRV analysis stands as a non invasive method of detecting an early autonomic impairment of heart[10]. A high HRV indicates a good cardiac adaptability while a lower HRV often indicates an abnormal and insufficient adaptability of the autonomic nervous system and is associated with a high risk of cardiovascular events[11]. HRV is also a good predictor for risk incidence and progression of focal coronary atherosclerosis[12]. Evrengul *et al*[13] showed a decreased HRV in patients with RA. Therefore, assessment of HRV has an important role in identifying the patients with RA who are at high risk of life threatening cardiac events[14,15]. The utility of HRV assessment can be extended to a timely diagnosis of altered autonomic function status associated with increased mortality in patients with RA. The available literature shows no study that has presented HRV data in Indian patients with rheumatoid arthritis and its correlation with disease activity. Though there are data available from Western populations, but ethnically and geographically different populations are known to be different with respect to disease and its clinical presentation. Therefore, this study was planned to assess HRV in patients with RA in Indian population and its correlation with disease activity.

Material & Methods

Patients: Consecutive patients (n=45, 39 female and 6 male) with RA as diagnosed by 1987 American Rheumatism Association criteria for RA[16] visiting Rheumatology Clinic, All India Institute of Medical Sciences, New Delhi, India, between 2004 and 2005, were included in the study. All patients were tested for autoantibodies and rheumatoid factor was detected in serum samples using the RA latex test. All patients underwent physical examination and investigations including 12-lead electrocardiography, routine biochemistry including differential leukocyte count, erythrocyte sedimentation rate (ESR), total serum cholesterol, fasting serum glucose as a routine diagnostic procedure.

Patients with diabetes mellitus, previous myocardial infarction, congestive heart failure and peripheral neuropathy were excluded from the study. Patients using any medications which may affect autonomic functions like antihypertensive, diuretics, *etc*. were also excluded from the study. All patients were treated as per the guidelines of the American Association of Rheumatoid Arthritis criteria[17]. Healthy controls (n=45, 39 female and 6 male) were recruited from amongst doctors and other hospital staff (housewives, security guards, laboratory technicians, *etc.*). Written informed consent was obtained from all the subjects. The institute's ethics committee approved the study protocol.

Recording of autonomic tone: For the HRV recording and analysis Nevrokard software (version 6.4.0), manufactured by Medistar, Solvenia, was used. All recordings were obtained between 1100 and 1600 h; a 2 h fasting was ensured prior to testing including all beverages. Patients and healthy controls remained in recumbent position during the recordings, were awake and relaxed. The blood pressures (BP), heart rate (HR), respiratory rate (RR) were recorded for each subject after 10-15 min of rest. The ECG records with normal sinus rhythm were used for analysis. A careful visual analysis was performed on all records to exclude intervals between ectopic beats, between normal and ectopic beats, and artifacts. Following a recording of continuous ECG for 5 min in standard test conditions, heart rate variability was assessed by time domain and frequency domain analyses. The mean heart rate, standard deviation of all R-R intervals (SDNN), root-mean square of successive differences (RMSSD), and number of R-R intervals differing by >50 m sec from adjacent intervals (NN50) were measured in the time domain analysis. Spectral measures were obtained by the fast-Fourier transform method[18]. The recording and analysis were done as described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[9]. The power in the heart rate spectrum between 0.003

and 0.40 Hz was defined as total power (ms×ms), and was specified as low frequency [LF, (0.04-0.15 Hz), predominantly marker of sympathetic activity] and high frequency [HF, (0.16-0.4 Hz), marker of parasympathetic activity]. Also the ratio of low-to-high frequency power (LF/HF), reflecting the sympathovagal balance was measured, where a high value of this ratio indicated sympathetic dominance of cardiac autonomic drive[19]. Our methodology of autonomic function testing has been described previously[20].

Statistical analysis: To compare the results, independent 't' test and non parametric tests (Mann-Whitney) were applied as applicable for the analysis of autonomic function tests in the patients and healthy controls. To correlate, Spearmen correlations was used. SPSS 11.5 (Illinois, Chicago, USA) was used for the statistical analysis.

Results

The mean age of patients with RA was 40.62 ± 13.95 yr and that of healthy controls was 36.78 ± 6 yr. The systolic BP was significantly higher in patients with RA as compared to healthy controls (119.82 ± 20.57 *vs.* 109.69 ± 11 mmHg, *P*=0.005). Other baseline clinical characteristics, like diastolic blood pressure, heart rate and respiratory rate remained comparable in the two groups (Table I).

Regarding short term HRV, it was observed that all the time domain parameters were significantly lower in patients with RA as compared to that of healthy controls (Table II). Patients showed a significantly lower standard deviation, and root mean square of their difference of all R-R intervals (patients with RA *vs.* healthy controls, SDNN, SDSD, RMSSD, NN50, *P*<0.001). In frequency domain analysis in the RA group, HF power, indicating parasympathetic activity and LF power, indicating mainly sympathetic activity, both were decreased (*P*<0.001). However, LF and HF power in normalized unit remained comparable in patients with RA and the healthy controls. Also, the ratio of LF and HF remained comparable in the two groups. Consequently the total power (ms×ms) was significantly lower in the patients with RA (*P*<0.001), while total power in the normalized unit (nu) was comparable in the two groups.

It was observed that patients' age correlated significantly and inversely with SDSD (Spearmen's rho, *r*=-0.392, R^2=15.36, *P*=0.008), SDNN (*r*=-0.422, R^2=17.8, *P*=0.004), NN50 (*r*=-0.382, R^2=14.59, *P*=0.01), LF power m sec (*r*=-0.341, R^2=11.6, *P*=0.02),

Table I. Baseline demographic and clinical characteristics

	Patients with rheumatoid arthritis (*N*=45)	Healthy controls (*N*=45)
Age (yr)	40.62 ± 13.95	36.78 ± 6
Gender		
Male	6	6
Female	39	39
SBP	119.82 ± 20.57*	109.69 ± 11*
DBP	74.71 ± 12.26	71.29 ± 9.02
HR	79.96 ± 13.92	75.07 ± 10.69
RR	18.42 ± 3.87	17.33 ± 4.12

Values are mean ± SD
SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate
*P=0.005 compared to healthy controls

Table II. Heart rate variability parameters in patients with rheumatoid arthritis and healthy controls

	Patients with rheumatoid arthritis (*N*=45)	Healthy controls (*N*=45)
Coefficient of variance	4.0 (1.5-8.9)*	5.9 (2.1-17.1)
SDNN	30 (9.9-73.5)*	47.3 (16.1-145.9)
SDSD	23.6 (2.9-86)*	35.9 (10.3-188)
RMSSD	23.6 (2.9-85.7)*	35.8 (10.4-187.7)
NN50	4 (0-88)*	22 (0-117)
LF power, ms×ms	174.8 (17.2-3047)*	537.3 (55.1-2634)
LF power, nu	41.1 (8.3-90.4)	44 (11.8-86.4)
HF power, ms×ms	228 (2.6-2464)*	460 (37-18704)
HF power, nu	49.5 (4.9-90)	46 (10-84.6)
LF/HF	0.9 (0.1-18.5)	1 (0.1-8.7)
Total power, ms×ms	796.9 (54.5-5742)*	1765 (208-21902)
Total power, nu	141.7 (92.2-550)	137.5 (69.6-444)

All values expressed as median (range)
SDNN, standard deviation of all R-R intervals; SDSD, standard deviation of successive differences between adjoining normal cycles; RMSSD, root mean square successive difference; NN50, number of R-R interval differences equal or more than 50 milliseconds; LF, low frequency heart rate; HF, high frequency heart rate; LF (nu), LF in normalized unit; HF (nu) - HF in normalized unit; LF/HF - Ratio between LF and HF
*P<0.001 compared to healthy controls

Table III. Spearmen correlations between heart rate variability and clinical parameters in patients with rheumatoid arthritis

	SDSD	SDNN	NN50 m sec	LF power ms × ms	HF power ms × ms
Age	-0.392[a]	-0.422[b]	-0.382[c]	-0.341[d]	-0.445[e]
Duration of illness	0.124	0.278	0.07	0.313	0.173
DAS28	0.375[f]	0.025	0.273	-0.029	0.343
RF-IgA	0.001	-0.095	0.053	-0.065	-0.035
RF-IgG	0.1	0.130	0.153	0.111	0.092
Anti-CCP	-0.058	0.129	0.007	0.091	-0.106
Physician's global assessment	0.293	0.114	0.151	-0.088	0.121
Swollen joint count	0.351	0.136	0.216	0.068	0.283
Tender joint count	0.216	0.045	0.140	0.061	0.201
Rheumatoid factor	-0.36	-0.281	-0.306	-0.438[g]	-0.445[h]
Rheumatoid factor latex	0.095	-0.177	0.014	-0.340	0.014

[a]P=0.008, R^2=15.36; [b]P=0.004, R^2=17.8; [c]P=0.01, R^2=14.59; [d]P=0.02, R^2=11.6; [e]P=0.002, R^2=19.8; [f]P=0.045, R^2=14.06; [g]P=0.017, R^2=19.1; [h]P=0.016, R^2=19.8

DAS 28, 28 joint disease activity severity, Rheumatoid factor immunoglobulin A, rheumatoid factor immunoglobulin G; anti-CCP, anti-cyclic citrullinated peptide antibody; SDSD, standard deviation of successive differences between adjoining normal cycles; SDNN, standard deviation of all R-R intervals; NN50, number of R-R interval differences equal or more than 50 milliseconds; LF, low frequency heart rate; HF, high frequency heart rate

and HF power m sec (r=-0.445, R^2=19.8, P=0.002). Also disease activity score at 28 joints (DAS28) correlated significantly and positively with SDSD (r=0.375, R^2=14.06, P=0.002). Rheumatoid factor displayed an inverse significant correlation with LF and HF power ms (r=-0.438, R^2=19.1, P=0.017 and r=-0.445, R^2=19.8, P=0.016, respectively) (Table III).

Discussion

The morbidity and mortality in patients with RA is attributed more to its cardiovascular complications rather than the disease itself[3-5,19]. A timely diagnosis and management of the disease not only improves prognosis but also improves the quality of life. HRV stands as a non-invasive yet valid technique to assess autonomic nervous system fluctuations in normal healthy individuals and patients with various cardiovascular and non-cardiovascular disorders[10]. The present results demonstrated that patients with RA had an impaired autonomic nervous system.

RA, a progressive autoimmune inflammatory disease, follows the same suit of altered autonomic functions as in other autoimmune diseases[21]. Earlier, we have shown that there was a significant reduction in HRV in patients with systemic sclerosis[20], which is consistent with findings from previous studies[22,23]. In the present study, the systolic BP was significantly higher in patients with rheumatoid arthritis than controls at baseline. The other baseline parameters were statistically comparable between the two groups. In HRV, all the measures of time domain and HF, LF and total power (ms×ms), were significantly lower from that of the healthy controls, which is similar to results from previous studies[13,21,24]. A reduced HRV is suggestive of a relative increase in sympathetic and reduced vagal modulation of sinus node[19]. An altered HRV is also known to be related to a sub-clinical inflammation in subjects who were apparently healthy with no evidence of heart disease[25]. An altered balance between HRV and sympathovagal imbalance, *i.e.* an increased sympathetic or a reduced vagal activity, is known to be a strong and independent predictor of post-infarction mortality and holds a good prognostic value in patients with heart failure and diabetic neuropathy, and vagal predominance, on the other hand possibly exert protective and antifibrillatory effects[26]. Regarding the LF/HF ratio, we did not find any significant difference between healthy controls and patients, while a previous study[13] showed a significant decrease in HF and increase in LF and LF/HF ratio in patients with RA, suggesting predominance of the sympathetic modulation of the heart. However, in our study we found a decrease in both HF (ms×ms) and LF (ms×ms)

in patients with RA as compared to the healthy control group. An interesting observation was the VLF in RA patients which was approximately 50 per cent whereas it was approximately 44 per cent in the controls. The physiological importance of VLF is not clear, and this is the reason usually LFnu, HF nu and the ratio LF/HF are preferred for autonomic analysis. However, no significant difference was seen in LF power (nu), HF power (nu), LF/HF ratio and total power (nu) between the two groups, which might be due to small sample size.

Previous studies that assessed a correlation between the disease characteristics and HRV showed variable and conflicting results. Anichkov *et al*[27] showed significant correlations of SDNN and SDANN with swollen joints count, Ritchie Articular Index, DAS28 and disease duration. In the same study, SDNN also correlated with leucocyte count and smoking while SD1 significantly correlated only with the disease duration. However, another study found no correlation of HRV with disease activity or duration of the disease, number of swollen joints, ESR, or rheumatoid factor in the RA group[24]. Regarding correlation of age with HRV in the patients with RA, it has been shown that HRV is significantly related to the age, gender and 24 h heart rate (or mean NN)[28,29]. Anichkov *et al*[27] did not find any correlation of long-term HRV indices with age in RA patients. In our study, short term HRV parameters such as SDSD, SDNN, NN50, LF and HF power decreased significantly with increasing age in patients with RA. LF and HF power both decreased significantly with increasing rheumatoid factor values, and SDSD increased significantly with increasing disease activity (DAS28). We have also used coefficient of determination (R^2) to see this correlation. The significant correlations had coefficient of determination approximately 16 per cent, which is considered to be fair level of significance between the two variables. The R^2 value of LF power and HF power with rheumatoid factor was approximately 20 per cent. The relationship between HRV and disease characteristics cannot be explained completely in view of scanty data available till date. Our study demonstrated an increased sympathetic control of heart and blood pressure, as has been observed in other autoimmune diseases.

In conclusion, conventional risk factors do not fully explain excessive cardiovascular morbidity and mortality in RA cohorts[7,12,30]. In this scenario, there is a need for new methods for cardiovascular risk factors assessment. In the present study, we have assessed HRV in Indian patients with rheumatoid arthritis and tried to correlate the HRV with disease activity and other clinical parameters of rheumatoid arthritis. As the study was a pilot study, the sample size was based on assumption rather than the formal statistical calculations. Based on these findings a larger study can be planned with more specific outcome measures and an adequate sample size. HRV was significantly altered in these patients with RA and independently associated with disease activity. Hence autonomic function testing, using HRV, may be useful in cardiovascular risk assessment in the patients with RA.

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References

1. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; *26* (Suppl 5): S35-61.
2. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009; *11* : 229-45.
3. Mutru O, Laakso M, Isomaki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. *Br Med J* 1985; *290* : 1797-9.
4. Prior P, Symmons DP, Scott DL, Brown R, Hawkins CF. Cause of death in rheumatoid arthritis. *Br J Rheumatol* 1984; *23* : 92-9.
5. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; *44* : 2737-45.
6. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, *et al*. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003; *107* : 1303-7.
7. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005; *52* : 402-11.
8. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, *et al*. Power spectral analysis of heart rate and arterial pressure variability as a marker of sympato-vagal interaction in man and conscious dog. *Circ Res* 1986; *59* : 178-93.
9. 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.
10. Stein PK, Bosner MS, Kleiger RF, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J* 1994; *127* : 420-4.

11. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, *et al*. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. *Circulation* 1996; *94* : 2850-5.

12. Huikuri HV, Jokinen V, Syvanne M, Nieminen MS, Airaksinen KE, Ikaheimo MJ, *et al*. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999; *19* : 1979-85.

13. Evrengul H, Dursunoglu D, Cobankara V, Polat B, Seleci D, Kabukcu S, *et al*. Heart rate variability in patients with rheumatoid arthritis. *Rheumatol Int* 2004; *24* : 198-202.

14. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; *59* : 256-62.

15. Malliani A, Lombardi F, Pagani M, Cerutti S. Power spectral analysis of cardiovascular variability in patients at risk for sudden cardiac death. *J Cardiovasc Electrophysiol* 1994; *5* : 274-86.

16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; *31* : 315-24.

17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; *62* : 2569-81.

18. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995; *25* : 1276-86.

19. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. *Cardiovasc Res* 1996; *32* : 208-16.

20. Yadav RK, Gupta R, Thabah MM, Poojary G, Madhavan SM, Deepak KK. Autonomic status in systemic sclerosis in India. *Indian J Physiol Pharmacol* 2006; *50* : 397-402.

21. 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.

22. Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich, B, *et al*. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjogren syndrome and other autoimmune diseases. *Lupus* 2007; *16* : 181-5.

23. Aydemir M, Yazisiz V, Basarici I, Avci AB, Erbasan F, Belgi A, *et al*. Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus. *Lupus* 2010; *19* : 255-61.

24. Louthrenoo W, Ruttanaumpawan P, Aramrattana A, Sukitawut W. Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus. *Q J Med* 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. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. *Int J Cardiol* 2002; *84* : 1-14.

27. Anichkov DA, Shostak NA, Ivanov DS. Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients. *Int J Clin Pract* 2007; *61* : 777-83.

28. Ramaekers D, Ector H, Aubert AE, Rubens A, Van de Werf F. Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? *Eur Heart J* 1998; *19* : 1334-41.

29. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol* 1998; *31* : 593-601.

30. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; *44* : 2737-45.

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