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Heart Rate Variability as an Indicator of Autonomic Nervous System Dysfunction in Rheumatoid Arthritis (RA)

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Abstract **Original Research Article**

Rheumatoid arthritis (RA) is one of the most common debilitating autoimmune disorders associated with morbidity and mortality. Cardiovascular complications are main extra articular complications. The cardiac risk in them can be estimated by analyzing the autonomic nervous system which can be assessed easily and non-invasively by Heart rate variability (HRV). Assessment of autonomic dysfunction in RA patients by measuring heart rate variability and its correlation with various factors.45 RA patients (40 females and 5 males; age group 18-45 years) along with 45 age and BMI matched controls were evaluated by Frequency domain HRV parameters: LF nu. (%); HF nu. (%) and LF/HF ratio recorded by Polyrite D based on EKG. The mean heart rate, standard deviation of all R-R intervals (SDNN), rootmeansquare 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. Statistical analysis was performed using SPSS software version 20 and t-test was used to derive the level of significance. LFnu and LF/HF ratio increased significantly ($P < 0.001$) whereas HFnu decreased significantly ($P < 0.001$) in RA patients. There is a significant decrease in heart rate ($P < 0.001$) and significant increase in SBP ($P < 0.001$) and DBP show significant difference between both the groups. There is no correlation with disease severity but has significant negative correlation of all time domain parameters and LFnu with duration of illness. All time domain parameters are significantly low in RA patients compared with control subjects. Decreased Heart rate variability indicates deranged cardiovascular autonomic functions in RA patients and significantly associated with duration of illness.

Keywords: Rheumatoid arthritis (RA), Heart rate variability (HRV), rootmeansquare of successive differences (RMSSD).

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology primarily affecting the joints, leading to severe disability and premature mortality [1]. The prevalence of RA is around 0.5 -1% worldwide with women suffering 2-3 times more than men [2]. RA has predominant articular manifestations while extra-articular manifestations are also seen in 40% of patients [3, 4]. Cardiovascular morbidity in RA is more common and may be up to 40% [3]. The most common cardiovascular manifestation in RA is coronary artery disease, followed by pericarditis [5]. Others include pericardial effusion, cardiomyopathy, myocarditis, coronary vasculitis, arrhythmia, valvular heart disease, and ischemic heart disease [6]. Higher incidence of congestive cardiac failure, unrecognized myocardial infarction, and sudden death are also seen. About 49.5% of deaths in RA patients are due to cardiovascular causes [5]. Analysis of heart rate variability (HRV) nowadays has become one of the popular tools for the detection of early sympathetic-parasympathetic imbalance in the autonomic nervous system dysfunction [7]. Low variability in HR implies poor or inhibited ability to maintain internal homeostasis. Generally sympathetic influence increases HR (tachycardia response) and lowers variability of the heart rate, while parasympathetic input slows the HR (bradycardia response) and increases the variability [8]. Low HRV is a known predictor of mortality in many clinical populations and it is associated with several cardiovascular risk factors [9]. HRV analysis is 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].

MATERIAL AND METHODS

The present study was conducted in the Department of Medicine in collaboration with the Department of Physiology, S.M.S. Medical College and Hospital, Jaipur, Rajasthan from 1 June 2015 to 31 May 2016 on 45 RA patients between the age group of 18-45 years taken from the Department of Medicine, S.M.S. Hospital, Jaipur along with 45(40 female, 5 male), age and BMI matched healthy 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: 18-45 yrs. aged newly diagnosed Rheumatoid Arthritis patients, as per the 2010 ACR-EULAR CLASSIFICATION CRITERIA and Age and BMI matched healthy controls subjects in study.

Exclusion Criteria: Pregnancy, smoker, chronic diseases affecting autonomic functions like 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 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. The assessment of Heart Rate Variability was done by recording with Polygraph (RMS Polyrite D, version 1.0) based on the principle of EKG. For short term analysis of HRV ECG was recorded in the supine posture for 5 minute after 15 minutes of supine rest in a quiet environment. The mean heart rate, standard deviation of all R-R intervals (SDNN), rootmeansquare 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. The analogue ECG signals were converted to digital signal and stored in the computer for offline Frequency Domain Analysis. In the Frequency Domain analysis, the power spectrum for HRV was calculated with the Fast Fourier Transformation (FFT) based method [13].

Statistical Analysis: Statistical analysis was performed using SPSS software version 20 and t-test was used to derive the level of significance. 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 [14].

RESULTS AND DISCUSSION

Table-1 shows the general characteristics of both study group and control group subjects. There is no significant difference in the BMI between Group 1 and Group 2. There is a significant decrease in heart rate ($P < 0.001$) and significant increase in SBP ($P < 0.001$) and DBP show significant difference between both the groups.

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 indices between study and control group. In this RA(Group1) patients have significant 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, $P<0.001$).

Table-4 shows the correlation of duration of illness (in years) and severity of disease in terms of DAS score. Data shows that there is no correlation with disease severity but has significant negative correlation of all time domain parameters and LFnu with duration of illness.

Among 45 patients 40 were females and 5 were male with mean age of 29.4 years and average duration of illness was 18.5 years.

Table-1: Comparison of General Characteristics among the Study Group (Group 1) and Control Group (Group 2) Subjects

Parameters	Group	N	mean±SD	P value
Age	Group 1	45	39.76±7.88	0.00
	Group 2	45	32.83±3.87	
Body weight	Group 1	45	58.83±11.09	0.35
	Group 2	45	57.17±5.25	
BMI	Group 1	45	23.45±5.25	0.70
	Group 2	45	23.12±2.83	
Heart rate	Group 1	45	77.33±11.69	0.00
	Group 2	45	83.67±5.64	
SBP	Group 1	45	120.04±19.46	0.00
	Group 2	45	108.00±4.81	
DBP	Group 1	45	76.36±12.44	0.00
	Group 2	45	72.00±3.26	

Table-2: Frequency Domain Variables between Study and Control Group of Subject

Parameters	Group	N	mean±SD	P value
LFnu	Group 1	45	58.78±9.30	0.00
	Group 2	45	47.70±17.19	
HFnu	Group 1	45	41.22±9.30	0.00
	Group 2	45	52.30±17.19	
LF:HF	Group 1	45	1.54±0.51	0.003
	Group 2	45	1.14±0.72	

Table-3: Time Domain Variables between Study and Control Group of Subjects

Parameter	Group	N	Mean	P value
SDSD	Group 1	45	25.3	<0.001
	Group 2	45	38.6	
SDNN	Group 1	45	28.7	<0.001
	Group 2	45	43.2	
RMSSD	Group 1	45	25.2	<0.001
	Group 2	45	38.7	
NN50	Group 1	45	5	<0.001
	Group 2	45	21	

Table-4: Spearmen Correlations (R) Of HRV with Disease Activity and Duration of Disease in Patients of Rheumatoid Arthritis

Parameter	DAS28 (P value)	Duration of illness (P value)
SDSD	0.121 (0.343)	-0.451 (<0.001)
SDNN	0.052 (0.112)	-0.351 (<0.001)
NN50 m sec	0.071 (0.573)	-0.558 (<0.001)
LF power ms × ms	0.113 (0.087)	-0.375 (<0.001)
HF power ms × ms	0.187 (0.075)	0.421 (<0.001)

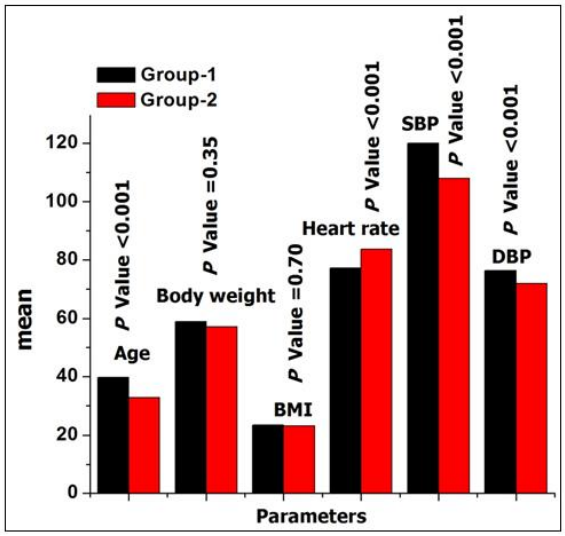

Fig-1: Column diagram showing general characteristics of both groups (I & II)

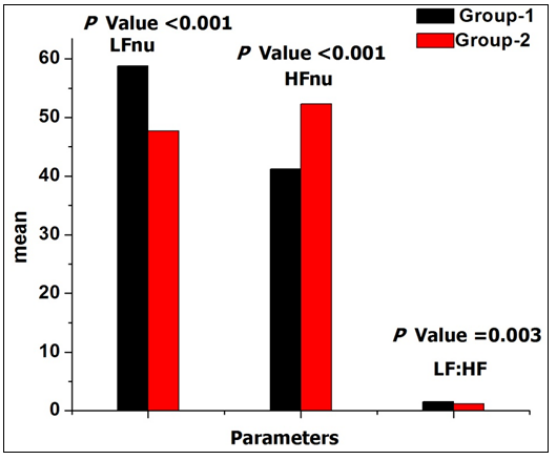

Fig-2: Column Diagram Showing Frequency Domain Variables between Study and Control Group of Subject

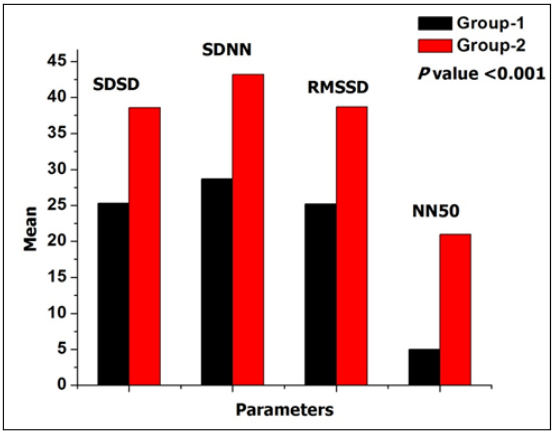

Fig-3: Column Diagram Showing Time Domain Variables between Study and Control Group of Subjects

The HRV changes in RA are due to subclinical inflammation [15, 16]. Autonomic neuropathy may be found in any kind of connective tissue disorder even in preclinical stage and is related to the presence of auto antibodies against ANS and may play a role in the pathogenesis of autonomic dysfunction [17]. Research in RA to detect the presence and type of cardiac autonomic dysfunction has led to various theories. Few consider sympathetic overactivity as a reason for alteration of HRV [18, 19]. An equal number of studies support parasympathetic predominance as well [20, 21]. Bekkelund *et al.*, Tumiati et al., and Piha and Voipio-Pulkki concluded that there is no autonomic dysfunction in patients with RA [22-25]. 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. Previous studies that assessed a correlation between the disease characteristics and HRV showed variable and conflicting results. Anichkov *et al*., [26] 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. Yadav *et al.*, also found that the LF and HF power both decreased significantly with increasing rheumatoid factor values, and SDSD increased significantly with increasing disease activity (DAS28). 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 [27]. 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]. In the present study, SBP and HR were higher in patients with RA compared to the control group. HRV decreases significantly with increasing age. In our study HRV is statistically significantly decreases with duration of illness and no association was found with disease severity a point. This may be due to that at any point of time disease may be active or may be in quiescent stage. So overall exposure of ANS to autoimmune insult is more important than duration. 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 supposed 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.

CONCLUSIONS

HRV could be is valuable, easy, cost-effective, reproducible, and reliable non invasive tool for the early detection of ANS involvement in RA patients. As the duration of illness increases, the HRV decreases and probability of cardiovascular complications increases, so it can be used as a useful tool for cardiovascular risk assessment in rheumatoid arthritis patients. 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.

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