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Comparative cross sectional study on heart rate variability in female patients with rheumatoid arthritis

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Abstract

Rheumatoid Arthritis (RA) is a chronic debilitating disorder affecting the synovial joints with higher prevalence in females. Extra articular manifestations are seen in around 40% of patients with RA. The nervous system faces the brunt of RA. The autonomic nervous system imbalance leads to RA associated cardiac morbidity and mortality. Cardiac dysfunction is due to reduction in heart rate variability (HRV). HRV testing assesses sympathovagal balance and is an easily reproducible method of testing the cardiac autonomic system.

Materials and Methods: A cross sectional study was conducted using 30 female patients and compared to 30 age & sex matched healthy volunteers. The participants were subjected to short term HRV recording using Multichannel Physiopac- PP8. Data was transferred to Kubios HRV version 2.0. The time domain variables including SDNN, RMSSD, mean RR and pNN50 were derived. Frequency domain variables corresponding to the parasympathetic and sympathetic activity were also assessed. Statistical analysis carried out using SPSS software 18.0. p values < 0.05 was considered statistically significant.

Results: The statistical analysis show significance of NN50 and pNN50 among the time domain variables. The frequency domain variables VLF power %, LF power n.u, HF power ms^2, HF power %, HF power n.u and LF/HF ratio were significant.

Conclusion: HRV analysis proves to be an easy, non-invasive, cost effective, reproducible and reliable tool for prediction of cardiac events. This tool will help the clinician to predict and fine tune treatment protocols for RA.

Keywords: Frequency domain, Short term heart rate variability, Spectral analysis, Sympathovagal balance, Time domain.

Introduction

Rheumatoid Arthritis (RA) is a chronic debilitating disorder mainly affecting the synovial joints.[1] Like most of the autoimmune disorders Female gender is affected predominantly by RA. The disease manifests at an early age in women compared to men. Females are affected three times more than their male counterparts.[2] Progression of RA leads to chronic inflammation and joint destruction resulting in significant functional impairment. Etiology of Rheumatoid arthritis is not fully understood and it is said to be enigmatic. 80% of the Rheumatoid arthritis is associated with HLA-DR1 or HLA-DR4 subtypes. This leads to the presence of a specific arthrogenic peptide on CD4+ T cells.[3] The effect of RA goes beyond the joints.[4] It has been postulated that people with high titre of rheumatoid factor tend to develop cardiac complications. It is said that cardiac death is six times common in patients with elevated rheumatoid factor as compared to normal population.[5] The rheumatoid factor containing immune complexes are also said to be responsible for development of extra articular manifestations.[6] The nervous system faces the brunt of RA. The autonomic nervous system imbalance leads to RA associated cardiac morbidity and mortality.[8] The controversy of sympathetic or parasympathetic derangement leading to cardiac dysfunction remains unsolved.[9-12] One of the underlying factors of cardiac dysfunction is the reduction in heart rate variability. In a normal individual, the heart rate is highly variable.[9] A highly variable heart rate is a good sign of adaptability. In general females have a higher heart rate variability.[13] In Rheumatoid arthritis the variability is said to be low. This could be due to a cardiac autonomic dysfunction. Cardiac autonomic dysfunction can be assessed by various methods like Heart rate response to standing, blood pressure response to standing, Heart rate response to passive tilting, assessment of baroreceptor sensitivity, Valsalva ratio, cold pressure test, nor epinephrine spillage technique and standing to lying ratio.[14] These techniques can be cumbersome and difficult to perform in Indian female population. Heart rate variability testing assesses sympathovagal balance and is an easily reproducible method of testing the cardiac autonomic system. HRV analysis proves to be an easy, non-invasive, cost effective and reliable tool for prediction of possibility of cardiac events[15]. HRV data in Indian female population is lacking and hence this study. HRV is mainly assessed using time domain and frequency domain.[16] The parameters of time domain & frequency domain are listed in Table 1 & 2.[14]

Table 1: Time domain parameters

Variable	Units	Description
SDNN	ms	Standard deviation of all NN intervals.
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN Intervals.
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording
SDSD	ms	Standard deviation of differences between adjacent NN intervals
NN50 count		Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. Three variants are possible counting all such NN intervals pairs or only pairs in which the first or The second interval is longer.
pNN50	%	NN50 count divided by the total number of all NN intervals.

Table 2: Frequency domain parameters

Analysis of short term recordings			
Variable	**Units**	**Description**	**Frequency range**
5 min total power	ms^2	The variance of NN intervals over the temporal segment	approximately ≤ 0·4 Hz
VLF	ms^2	Power in very low frequency range	≤ 0·04 Hz
LF	ms^2	Power in low frequency range	0·04–0·15 Hz
LF norm	n.u	LF power in normalised units	LF/(Total Power–VLF) x 100
HF	ms^2	Power in high frequency range	0·15–0·4 Hz
HF norm	n.u.	HF power in normalised units	HF/(Total Power–VLF)x100
LF/HF		Ratio between LF and HF	LF [ms^2]/HF [ms^2]

Materials and Methods

A comparative analytical cross sectional study was conducted using 30 female patients (Group 1) presenting to the Rheumatology clinic to confirm seropositive rheumatoid arthritis. 30 age & sex matched healthy volunteers (Group 2) were selected as a comparison group. This study was carried out at SRM Medical College Hospital, Kattankulathur, Kancheepuram district of Tamil Nadu. Institutional Ethics Committee clearance was obtained for the same vide Ref No 302/IEC/2012. The study period was between November 2012-November 2013. Patients and volunteers who were less than 30 years or more than 65 years were excluded from the study. The heart rate variability analysis was carried out in the Department of Physiology after obtaining a written informed consent from all the participants. After initial assessment basic parameters like height, weight, and blood pressure were assessed. The participants were subjected to Heart rate variability recording using Multichannel Physiopac- PP8 from Medicaid systems. The recordings were transferred to Kubios HRV software version 2.0 for analysis. The participants were allowed to rest in supine position for fifteen min before fixing the chest and limb leads. The sinus rhythm recording was scrutinized for artefacts. A short term recording of 5 minutes without artefacts was recorded and the data was transferred to Kubios HRV version 2.0. The software uses Fast Fourier Transformation to obtain the time domain and frequency domain variables. The time domain variables including SDNN, RMSSD, mean RR NN50 and pNN50 were derived. Frequency domain variables which look at the high frequency & low frequency variables corresponding to the parasympathetic and sympathetic activity were also assessed. The data sheet was prepared using MS Excel and statistical analysis was carried out using SPSS software 18.0. Independent t test, Mann Whitney U test was performed and p values < 0.05 was considered statistically significant.

Results

30 female patients with confirmed rheumatoid arthritis underwent Heart rate variability analysis using Multichannel Physiopac – PP8. As comparative group, 30 age matched

female volunteers were selected. Among the time domain parameters Standard heart rate, NN50, PNN50 were statistically significant (Table 3). Among the frequency domain parameters VLF Power %, LF Power n.u, HF Power %, HF Power n.u and LF/HF ratio showed statistical significance (Table 4). SDNN is a marker of overall heart rate variability.

Discussion

Rheumatoid arthritis is an autoimmune connective tissue disorder which is more prevalent in female population. The exact reason for this gender affiliation has not been clearly understood. Indian prevalence is approximately 0.19-2.5%.[17] Prevalence in female population is estimated to be around 1.24%.[18] Clinically patient presents with symptoms related to small joint involvement. As time progresses even the bigger joints are involved. In developing country like India the symptoms are ignored especially in the female population. By the time they seek medical help the cartilaginous changes have already set it. Although Rheumatoid arthritis is mainly the disease of the joints, it also affects the other major systems of the body because of its autoimmune nature. Apart from all these, the maximum brunt of the disease is seen in the cardiovascular system.

The cardiovascular events are mostly silent in Rheumatoid arthritis. There needs to be an effective method to assess and predict the upcoming cardiac events. Among the numerous Autonomic Function Tests, Heart Rate Variability Analysis is the easiest, reproducible and non-invasive technique. Heart Rate Variability analysis is an index of cardiac autonomic function of an individual.[14]

This study was conducted in 30 diagnosed RA patients and was compared with age and sex matched controls. The parameters considered for analysis were Mean RR, SDNN, Mean Heart Rate, Standard heart rate, RMSSD, NN50, pNN50, VLF, LF, HF and LF/HF ratio. Out of the various parameters in this study, Mean RR, Standard heart rate, VLF power %, LF power (n.u), HF power %, HF (n.u) and the LF/HF ratio showed a significant result.

This study showed that there was sympathetically predominant heart rate variability in female patients with Rheumatoid arthritis. 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. The LF frequency which indicates sympathetic activity was more and HF which is an indicator of parasympathetic activity was diminished in relation to the comparison group. The LF/HF ratio was elevated indicating sympathetic predominance in patients of Rheumatoid arthritis.

Table 3: Time domain variables

Parameters	Group	Mean	p Value
SDNN STDN	Group 1	24.06±19.39	0.955
	Group 2	24.28±8.78	
MEAN HR	Group 1	78.25±4.47	0.137
	Group 2	80.89±8.49	
STD HR	Group 1	1.96±1.02	0.007
	Group 2	2.66±0.91	
RMSSD	Group 1	14.39±15.67	0.888
	Group 2	14.82±6.54	
NN50	Group 1	2.50±4.24	0.04
	Group 2	4.53±4.71	
PNN50	Group 1	1.04±1.67	0.04
	Group 2	1.81±1.82	
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			

Table 4: Frequency domain variables

Parameters	Group	Mean	p Value
VLF.PEAK (Hz)	Group 1	0.02±0.01	0.6
	Group 2	0.03±0.06	
VLF.POWER (ms^2)	Group 1	207.33±266.34	0.5
	Group 2	180.93±173.92	
VLF.POWER (%)	Group 1	56.46±15.52	0.001
	Group 2	41.15±18.04	
LF.PEAK (Hz)	Group 1	0.07±0.03	0.242
	Group 2	0.08±0.03	
LF.POWER (ms^2)	Group 1	148.40±221.22	0.3

	Group 2	130.80±102.20	
LF., POWER (%)	Group 1	33.45±12.65	0.08
	Group 2	181.43±779.50	
LF.POWER (n.u)	Group 1	76.80±6.59	0.0001
	Group 2	65.29±7.76	
HF.PEAK (Hz)	Group 1	0.19±0.03	0.2
	Group 2	0.71±2.93	
HF.POWER (ms^2)	Group 1	42.00±60.84	0.03
	Group 2	70.43±63.33	
HF.POWER (%)	Group 1	10.10±4.97	0.0001
	Group 2	19.87±6.10	
HF.POWER (n.u)	Group 1	23.20±6.59	0.0001
	Group 2	33.81±5.97	
LF/HF	Group 1	3.58±1.06	0.0001
	Group 2	2.01±0.55	
LF power ms^2: Power in low frequency range, VLF power ms^2: Power in very low frequency range, HF ms^2 Power in the high frequency range, LF/HF Ratio between LF and HF			

Conclusion

RA is one of the most disabling conditions known to mankind. The non-articular manifestations of RA gain importance because of their contribution to morbidity and mortality. The life expectancy of RA patients is decreased by 5-10 years. The unpredictable natures of cardiac events play an important role in cardiovascular mortality. In this scenario, HRV analysis proves to be an easy, non-invasive, cost effective, reproducible and reliable tool for prediction of cardiac events. This analysis will help the clinician to fore see the possible cardiac event, thereby providing a better detection and treatment protocol for Rheumatoid arthritis patients.

Conflict of Interest: None.

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