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Original research article

To study heart rate variability and biomarker analysis in rheumatoid arthritis

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Abstract

Introduction: Rheumatoid arthritis is the most common form of chronic systemic inflammatory arthritis. Research participants with a recent diagnosis of RA will have their cardiovascular autonomic functioning assessed by measuring their resting heart rate variability.

Materials & Methods: The present study was a case-control investigation undertaken at the Neurophysiology laboratory, specifically within the Department of Physiology, GMC Siddipet, Telangana, India. The study was conducted from June 2022 to May 2023. A total of 20 individuals who had just received a diagnosis of rheumatoid arthritis were selected for participation in this study. These individuals were recruited from the Rheumatology outpatient department at the GMC Siddipet, Telangana, India.

Result: In RA patients, the heart rate and systolic blood pressure were higher. Patients with RA had significantly lower SDNN, SDSD, RMSSD, NN50, LF and HF power in nu and total power than healthy controls. Seropositive patients had higher LF power in the normalized unit than seronegative individuals. When compared to seronegative patients, the LF/HF ratio rose in seropositive patients. Seropositive participants had lower HF power in the normalized unit than seronegative subjects did. We also noticed that the study group had higher RF, CRP, and platelet counts, which were related to higher sympathovagal imbalance. This shows how significant these factors are in the development of cardiovascular risk in RA patients.

Conclusion: The standard basic investigation of RA can include the straightforward, noninvasive resting HRV analysis. Regular evaluation of the biomarker's platelet count, CRP and RF may aid in the early detection of cardiovascular complications in RA patients.

Keywords: Heart rate variability, biomarkers, rheumatoid arthritis patients

Introduction

Rheumatoid arthritis (RA) is widely recognized as the prevailing form of chronic systemic inflammatory arthritis. The condition is distinguished by the presence of symmetrical polyarthritis, which causes deformation and can vary in both extent and severity [1]. This is accompanied by synovitis of the joint and tendon sheaths, as well as the loss of articular cartilage and erosion of the bone near the affected joints. Cardiovascular system involvement is a significant complication in the context of extra-articular symptoms of rheumatoid arthritis (RA), and it has the potential to result in sudden cardiac death. The median life expectancy of men is reduced by an average of 7 years, while for women it is shortened by 3 years in comparison to the control population [2, 3].

Arrhythmia and myocardial infarction are two factors in why rheumatoid arthritis (RA) patients sometimes experience sudden cardiac mortality. When the autonomic nervous system's normal operations are disturbed, cardiovascular events can occur. Autoantibodies that attack nerve growth factor also damage the superior cervical ganglion and the vagus nerve, leading to arrhythmia and myocardial infarction [4]. When inflammatory mediators and immunological complexes are present, ischemia develops. The hypothalamic-pituitary-adrenal (HPA) axis is less sensitive in patients with chronic inflammatory diseases like rheumatoid arthritis (RA). Because of this impaired sensitivity, not enough cortisol is produced in response to inflammation [5]. As a result, estrogen receptor expression is upregulated in synovial cells and sympathetic activity is increased, circulating cytokines are increased, sympathetic innervation of the local synovium is decreased. Neuroendocrine disorders in RA patients are exacerbated by the aforementioned variables. Therefore, inflammatory mediators, endocrine abnormalities and autoantibodies all have a role in the development of autonomic dysfunction in rheumatoid arthritis (RA) [6].

Heart rate variability (HRV) is a straightforward and noninvasive method used to evaluate cardiovascular

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autonomic function. The task can be easily executed. The quantification measurement pertains to the variability of sinus rhythm. The extent to which the heart is influenced by sympathetic and parasympathetic activity determines the outcome. The device is capable of identifying the initial dysregulation of autonomic equilibrium. The reduction in variability of biological signals serves as an indicator of potential loss in homeostatic self-regulation [7, 8].

Numerous research pertaining to cardiovascular events in rheumatoid arthritis (RA) have been conducted in Western countries. However, there is a lack of sufficient studies analyzing autonomic imbalance in the Indian population, and the existing evidence shows inconsistencies [8, 9]. The variability in abnormality may be attributed to the incorporation of different quantities of tests. The objective of our study was to evaluate the autonomic function in individuals with rheumatoid arthritis (RA) by the utilization of resting heart rate variability (HRV) analysis. In this investigation, we hope to learn more about how HRV indices relate to inflammatory biomarkers such rheumatoid factor, C-reactive protein, and platelet count.

Materials and Methods

The present study was a case-control investigation undertaken at the Neurophysiology laboratory, specifically within the Department of Physiology, at GMC Siddipet, Telangana, India. The study was conducted from June 2022 to May 2023. A total of 20 individuals who had just received a diagnosis of rheumatoid arthritis were selected for participation in this study. These individuals were recruited from the Rheumatology outpatient department at the GMC Siddipet, Telangana, India.

Inclusion Criteria

- 20 to 60 years of age, encompassing both sexes.
- Rheumatoid arthritis was determined to exist using the EULAR classification criteria-2010.
- Patients who have just received a diagnosis but have not yet begun treatment.

Exclusion Criteria

- Alcoholic and a smoker.
- Neurological conditions and bronchial asthma.
- Pregnant women's.

Methodology

The research was carried out in the neurophysiology lab from 10 AM to 1 PM. The facility was kept serene with little lighting and a temperature range of 25 to 280 C. Prior to recording, a 2-hour fast without beverages was made sure of. The subjects were instructed to urinate. The participant received thorough guidance on the material and had all of their questions answered. The subjects were then asked for their free, written consent. The individuals underwent a quick preliminary general and clinical evaluation. The test volunteers were given comfort and space to unwind. Blood samples of 2ml were taken for the RF and CRP assays and 1.8ml were taken in an EDTA-coated test tube for the platelet count. It was measured in centimeters of height and kilograms of weight. After the individuals had rested for 10-15 minutes in the supine posture, the blood pressure, heart rate, and respiration rate were all recorded. Following spirit cleaning, the electrodes were attached in the following locations:

Statistical analysis

The data that was obtained was subjected to analysis using SPSS version 17. Descriptive statistics, specifically the mean and standard deviation, were employed to elucidate the properties of the data.

Results

Table 1: Study baseline and control group characteristics

	Group	No.	Mean
Age in years	Cases	10	10.51
	Control	10	10.20
BMI	Cases	10	12.24
	Control	10	12.53

There is no statistically significant difference observed in the age and BMI between the study group and the control group. Therefore, both the research and control groups exhibit comparability.

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Table 2: Comparison of study and control group mean HR, SBP and DBP

Sr. No.		Group	N
1.	Mean HR (bpm)	Cases	10
		Control	05
2.	SBP (mmHg)	Cases	10
		Control	05
3.	DBP (mmHg)	Cases	10
		Control	00

The study group exhibited a statistically significant increase in the mean heart rate compared to the control group. The study group exhibited a statistically significant increase in systolic blood pressure compared to the control group. There was no statistically significant variation observed in the diastolic blood pressure.

Table 3: Study and control groups

Parameter	Study		Control	
	Mean	SD	Mean	SD
LF n.u.	65.25	21.87	53.01	15.51
HF n.u.	35.27	18.14	46.87	15.41
LF/HF	3.81	3.24	2.00	0.77

The study group exhibited higher levels of LF power in normalized units (n.u.) and a higher LF/HF ratio compared to the control group. The study group exhibited a decrease in HF power in normalized units compared to the control group.

Table 4: Comparing time domain metrics between seropositive and seronegative study group participants

	Sero-positive		Sero-negative	
	Mean	SD	Mean	SD
HR (bpm)	78.12	8.9	78.12	8.6
RR (ms)	760.51	84.24	640	339.9
SDNN (ms)	25.1	9.81	25.32	8.14
RMSSD (ms)	21.27	10.14	32.7	16.98

The RR interval, SDNN and RMSSD exhibited a decrease in the seropositive subjects compared to the seronegative individuals.

Table 5: Comparison of frequency domain metrics in research group CRP positive and negative patients

	CRP-positive		CRP-negative	
	Mean	SD	Mean	SD
LF nu	64.78	21.28	62.19	22.7
HF nu	34.77	18.15	34.49	21.14
LF/HF	3.14	3.1	3.87	3.31

The participants who tested positive for C-reactive protein (CRP) exhibited higher levels of low frequency (LF) power in normalized units and an elevated LF/HF ratio. The patients who tested positive for C-reactive protein (CRP) exhibited a reduction in normalized unit of high-frequency (HF) power. However, such results did not demonstrate statistical significance.

Discussion

The most common extra-articular effect of RA is cardiovascular system involvement. The pathogenesis relies heavily on inflammatory mediators and autoantibodies. Early detection and treatment of the cardiovascular issue in RA improves prognosis and quality of life. In both healthy and ill individuals, HRV can be used as a noninvasive indicator of autonomic nervous system function. What follows is the examination of supine resting short-term heart rate variability.

The average SBP was controlled at 118.37.06 among the participants in the research. The study group had significantly higher SBP than the control group. These findings provide more evidence that sympathetic overactivity is present in RA patients. Consistent with the findings of Laden *et al*. and Piha *et al*. Parasympathetic efferent vagal damage may be to blame for the increased heart rate, as suggested by the research of Ewing *et al*. HRV [10, 11] is a helpful, non-invasive method for assessing autonomic nerve function.

Any fluctuation in resting HRV increases the likelihood of adverse cardiac events. The following are the results of an HRV analysis using HRV analysis software version 2.2 on 5-minute recordings from the study and control groups. This demonstrated, with high statistical certainty, that RA patients exhibited

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elevated levels of sympathetic activity. The normalized HF power was significantly lower in the study group compared to the healthy controls. This was a statistically significant finding. This demonstrates that RA patients no longer experience parasympathetic emotions. Although there was a general decline in power in the study group, it was not statistically significant when compared to the control group. This demonstrates the decreased state of the cardiovascular autonomic nerve system in RA patients. The LF/HF ratio was significantly higher in the research group than in the controls [12, 13].

This is evidence of the dysfunction of the sympathetic nervous system, which characterizes RA patients. Our study's overall frequency domain parameters demonstrate that RA patients have a condition of depressed vagal tone on the heart and an altered sympathovagal balance. Our findings matched those of the Everngul *et al*. study exactly. He noticed a significant drop in HF and an increase in LF and the LF/HF ratio, both of which are indicative of a predominance of the sympathetic activity of the heart. In contrast, Yadav *et al*. [14, 15] studied the Indian population and discovered that HRV is reduced in RA patients due to a drop in both LFms2 and HFms2.

An increase in sympathetic activity and a decrease in parasympathetic vagal tone may contribute to an elevated heart rate, as proposed by Sandhuetal. This diminished parasympathetic tone may lead to an increase in heart rate. Eighty percent of our study participants tested positive for RF, whereas twenty percent tested negative for the virus. This could be due to the fact that the participants were all referred to the rheumatology clinic as outpatients. According to the research conducted by Kuriya, Boultry and Machold, 80% of people with RA will have a positive rheumatoid factor test at some point. However, only 40% are positive at the onset of clinical symptoms [16, 17].

From August of 1981 through August of 2010, Sune F. Nielsen *et al*. conducted a prospective cohort research. The total population was calculated to be 9,712 persons. According to the study's findings, people with elevated rheumatoid factor in the general population had a 26-fold increased risk of developing rheumatoid arthritis in the road. In the frequency domain, normalized measures of LF power were greater in seropositive patients than in seronegative people. Seropositive patients had a higher LF/HF ratio compared to their seronegative counterparts [18-20]. These results demonstrate that seropositive patients exhibit elevated sympathetic activity. The normalized HF power of seropositive participants was lower than that of seronegative persons. In statistical terms, it was a big deal. Seropositive patients' levels of parasympathetic inhibition are revealed [21-23].

Sixty-two percent of the participants' serum tested positive for CRP. C-reactive protein and rheumatoid factor values were negative in all of the healthy controls. In frequency domain measurements, the CRP positive patients had more LF power than the CRP negative patients, as expressed in normalized units. These results demonstrate a sympathetic predominance in CRP-positive patients. Subjects with elevated C-reactive protein had reduced HF power in the normalized unit compared to those without the protein. Positive CRP tests reveal how much the parasympathetic system is being shut down in a patient. No statistical evidence existed to suggest its relevance. This may be due to insufficient data [24, 25].

The study group's platelet count increased significantly when compared to that of the control group. In statistical terms, it was a big deal. There was a strong positive correlation between platelet count and the LF nu LF/HF ratio. According to these results, there is a link between having a high platelet count and having an imbalance in your sympathovagal response. Our research shows that the biomarkers RF, CRP, and an elevated platelet count contribute to the reduced HRV and sympathovagal imbalance seen in rheumatoid arthritis patients, characterized by parasympathetic withdrawal and sympathetic overactivity [24-26].

We looked at how RF, C-reactive protein, and platelet count relate to the autonomic balance of the cardiovascular system. There was no association between HRV features and clinical indicators such the Disability Assessment Scoring System-28, fatigue, joint involvement, or joint discomfort. More information about the importance of biochemical indicators including RF, CRP, and platelet count, among others, may be gleaned via future patient recruitment attempts and study expansion.

Conclusion

Patients with rheumatoid arthritis showed signs of increased sympathetic activity, including a higher resting heart rate and systolic blood pressure. Patients with RA have a clear sympathovagal imbalance, manifesting as sympathetic overactivity and parasympathetic retreat in their resting HRV. Significant decreases in the RR interval, SDNN, and RMSSD of the study group indicate parasympathetic withdrawal. The increased sympathetic activity caused by the absence of parasympathetic activity is reflected in the increased LF power and decreased HF power of the study group. Increases in both the LF and HF ratios indicate an imbalance between the sympathetic and vagal nervous systems. HRV was lower in RA patients with elevated serum RF and CRP levels compared to those with normal serum RF and CRP levels. Autonomic dysregulation was positively linked with patients' reports of an increase in platelet count due to RA. Positive RF, CRP, and an elevated platelet count were all associated with an increased risk of cardiovascular problems in RA patients, as demonstrated by these results. Thus, it may be possible to detect cardiovascular issues in RA patients earlier with routine screening of these signs and evaluation of cardiovascular state using HRV analysis.

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