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A cross-sectional study on cardiac autonomic functions and inflammatory markers in chronic fatigue syndrome

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ABSTRACT

Background: Chronic fatigue syndrome (CFS) is a complex multisystem disease that affects around 1 million of the Indian population every year and is characterized by persistent fatigue. CFS is related to cardiovascular illness, and cardiovascular autonomic nervous system dysfunction is often seen. We investigated the state of cardiac autonomic function in CFS and associated it with their level of inflammatory markers and disease severity since there is not much research on the subject. **Aims and Objectives:** The objective of this study is to evaluate cardiac autonomic functions by using heart rate variability (HRV) in patients with CFS and in healthy controls. The study aimed to evaluate the correlation between HRV and inflammatory markers in patients with CFS and in healthy controls. **Materials and Methods:** Thirty controls and 30 diagnosed cases of CFS were used in the research. The short-term variability of heart rate was used to measure autonomic function. We measured tumor necrosis factor-alpha (TNF-α) and interleukin (IL-10) in 3 mL of overnight fasting serum. TNF-α and IL-10 were used to evaluate the severity of CFS. **Results:** Patients with CFS showed a substantial reduction in low frequency (LF) (P = 0.00*), high frequency (HF) (P = 0.00*), LF/HF ratio (P = 0.00*), and time domain parameters of HRV, namely RMSSD (P = 0.03*), SDNN (P = 0.00*), NN50 (P = 0.00*) and total power (P = 0.00*). Patients with CFS had considerably higher levels of TNF-α. TNF-α and LF/HF ratio and RMSSD, NN50, and HF were shown to have a substantially favorable correlation. **Conclusions:** Our research indicates a substantial correlation between autonomic dysfunction and inflammatory activity, as well as the severity of CFS. Therefore, we suggest that HRV might be a useful technique for accurately screening CFS patients for autonomic disruption symptoms early on, which can significantly lower morbidity and death in the future.

Key words: Chronic fatigue syndrome; Autonomic dysfunction; Heart rate variability; Inflammatory markers; Sympathetic tone; Parasympathetic tone

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INTRODUCTION

A multisystem condition with an uncertain etiology, chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis (ME), is very incapacitating. It is characterized by intense and unexplainable tiredness, for which rest is ineffective. Among the many main CFS/ME symptoms are incapacitating tiredness; other essential ones include autonomic dysfunction, sleep difficulties, cognitive impairment (commonly known as "brain fog"), post-exertional malaise, and myalgias, or aching muscles.[1] Patho physiologically, post-COVID-19 condition (PCC) patients' objective abnormalities of orthostatic intolerance and symptoms of neuroinflammation are shockingly similar to those of ME/CFS patients.[2] In medical research, heart rate variability (HRV) analysis (HRV analysis) is a non-invasive method used to track changes in autonomic function, predict patient outcomes, and characterize autonomic

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dysfunction in cardiovascular diseases (CFS/ME). It tracks dynamic changes in cardiac autonomic control right away. Recent time- and frequency-domain studies have enhanced HRV's capacity to track active changes; this might be used as a surrogate end-point marker in therapy trials and the next CFS/ME diagnostic guidelines.[3] Strong evidence for the involvement of the autonomic nervous system (ANS) in CFS/ME patients has been established by earlier research involving magnetic resonance imaging-detected anomalies in brain structure and function.[4-6] The research looks at the overall association between ANS symptoms and HRV in CFS/ME sufferers. It gauges the components and relative intensities of the HR signal as well as the dispersion of cardiac cycle length using time- and frequency-domain research. For some of these individuals, the results might aggravate ANS symptoms further.[7] Regarding the behavior of the HRV variables in people with CFS/ME, the studies provide some contradictory results. Yamamoto et al.,[8] noted a reduction in time- and frequency-domain characteristics after head-up tilt in CFS/ME patients but no anomalies in the baseline supine posture when compared to healthy controls. Little studies on the relationship between HRV and inflammatory markers tumor necrosis factor-alpha and interleukin-10 (TNF-α and IL-10) in Indian CFS patients exist. We recognize the variations in diseases and their clinical manifestations across geographically and ethnically varied groups, even if Western civilizations have readily available data. Therefore, the objective of this work was to investigate in Indian participants the correlation between inflammatory indicators and cardiovascular autonomic dysfunction.

Aims and objectives

The aim of the study is to evaluate cardiac autonomic functions using HRV and inflammatory markers in patients with CFS.

The objective of the study was to evaluate the relationship between illness severity and inflammatory markers using HRV in patients with CFS.

MATERIALS AND METHODS

The current study was planned as a cross-sectional study in the Department of Physiology, jointly conducted with the Departments of Medicine and Biochemistry at Naraina Medical College, Kanpur. It involved 60 patients, 30 of whom were age- and sex-matched healthy controls and 30 of whom were diagnosed cases of CFS who voluntarily consented to be recruited at the medicine's outpatient clinics in a sequential manner between 2021 and 2022. The institutional ethics committee with ethical clearance number NMCRC/IEC/2021/009 granted permission to carry out the research on January 5th, 2021. Every participant had a general physical examination, an anthropometric assessment, and a question regarding their medical history.[9]

A 2-h fast, including all liquids, was guaranteed before testing; all recordings were made between 8 and 10 am. It was directed to the individuals to lay down in the supine position on the day of testing. After placing the electrodes in lead II and letting the individuals rest for 10–15 min, the electrocardiogram (ECG) was recorded for 5 min. Throughout the process, the subjects were told to keep their eyes closed and to refrain from talking, moving their bodies, coughing, and sleeping. Each participant's HR and blood pressure (BP) were measured after a 10–15-min rest period. After 5 min of continuous ECG recording under typical test settings, the built-in HRV module evaluated short-term HRV offline. Parameters in the time and frequency domains were identified.[9]

Time domain parameters

The SDNN index (ms) measures the standard deviation of all NN intervals during 24 h, while RMSSD (ms) indicates the square root of the mean of the sum of squares of differences between consecutive NN intervals. The NN50 count is the number of pairs of consecutive NN intervals that vary by more than 50 ms over the whole recording. The proportion of adjacent NN that deviates by more than 50 ms across a 24-h ECG recording is indicated by pNN50.

Parameters in the frequency domain

The frequency domain characteristics include total power, high frequency (HF), low frequency (LF), and very low frequency (VLF) power. Sympathovagal balance is represented by the LF: HF ratio.[9] A 3-mL blood specimen was collected to test pro- and anti-inflammatory markers, including IL-10 and TNF-α. The serum was separated and refrigerated for examination. TNF-α and IL-10 levels were evaluated using a conventional two-step capture or sandwich-type enzyme-linked immunosorbent assay.[10] The licensed statistical program SPSS version 21.0 was used to prepare, input, and analyse the data. The data were presented in the form of mean±SD. Nonparametric testing or paired Student's t-tests were used to determine the statistical significance of the changes between the pre- and post-interventions. Regression analysis and Pearson's correlation coefficient were used in multivariate studies. A significance threshold of $P<0.05$ was used.

RESULTS

The mean age of the CFS patients was 39.12±7.14 years; the mean age of the healthy controls was 36.43±6.78 years.

Table 1 shows clear variations in body mass index between the anthropometric measurements of patients with CFS and healthy controls (24.39±1.30 vs. 23.58±1.503, P<0.03*). Table 2 shows the notable change in the time domain parameters of HRV, SDNN (P=0.00*), RMSSD (P=0.00*), NN50 (P=0.00*), and total power (P=0.00*) between the CFS patients and the control group. In the framework of short-term HRV, our study revealed that patients with CFS had noticeably reduced total HRV compared to controls. Patients with CFS had a significantly lower LF (P=0.00*), HF (P=0.00), and LF/HF ratio of the frequency domain parameter (P=0.00%) than healthy controls, as shown in Table 3. TNF-α clearly showed a significant positive correlation with the HRV indices HF, NN50, and RMSSD. Table 4 shows that although IL-10 and HRV showed a correlation, pro-inflammatory markers such as TNF-α and IL-10 also clearly showed a very positive correlation with the LF/HF ratio.

Table 1: Basal characteristics and cardiovascular parameters in chronic fatigue syndrome patients and healthy controls

Parameters	Chronic fatigue syndrome patients Mean±SD	Healthy controls Mean±SD	P-value
Age	39.12±7.14	36.43±6.78	NS
BMI	24.39±1.30	23.58±1.503	0.03*
Heart rate (bpm)	80.45±12.48	81.13±11.38	0.893
Systoloc BP	119.87±3.07	113.13±4.87	0.00*
Diastolic BP	73.46±5.41	72.85±8.61	0.624

*P<0.05 statistically significant. BMI: Body mass index, BP: Blood pressure, SD: Standard deviation

Table 2: Time domain parameters in chronic fatigue syndrome patients and healthy controls

Parameters	Chronic fatigue syndrome patients Mean±SD	Healthy controls Mean±SD	P-value
RMSSD (ms)	22.67±11.97	34.94±10.53	0.00*
SDNN (ms)	31.69±18.24	42.16±14.87	0.03*
pNN50	7.21±1.33	37.67±3.52	0.00*
Total power	721.81±46.23	1692.12±56.14	0.00*

*P<0.05 statistically significant. Values are expressed as mean±SD, SD: Standard deviation

Table 3: Frequency domain parameters in chronic fatigue syndrome patients and healthy controls

Parameters	Chronic fatigue syndrome patients Mean±SD	Healthy controls Mean±SD	P-value
LF (ms^2)	231.48±27.08	561.43±36.24	0.00*
HF (ms^2)	201.52±32.16	498.38±43.77	0.00*
LF/HF ratio	0,97±0.201	1.41±0.844	0.00*

*P<0.05 statistically significant, LF: Low frequency; HF-high frequency; LF/HF ratio (low frequency to high-frequency ratio), SD: Standard deviation

Table 4: Pearson's correlation of inflammatory markers with heart rate variability parameters in chronic fatigue syndrome patients

HRV parameters	TNF-α		IL-10	
	r	P	R	P
SDNN	−0.219	0.186	−0.256	0.214
RMSSD	−0.159	0.228	−0.169	0.348
NN50	−0.85	0.464	−0.109	0.561
LF/HF ratio	0.498	0.001*	0.481	0.004*
LF	−0.246	0.138	−0.159	0.368
HF	0.369	0.031*	−0.163	0.341
Total power	−0.169	0.319	0.214	0.210

*P<0.05 statistically significant, LF: Low frequency; HF-high frequency, TNF-α: Tumour necrosis factor alpha

DISCUSSION

This study is the first to show a relationship between HRV and inflammatory markers in CFS/ME. The study's goal was to discover plausible indices generated from HRV analysis that may be linked to self-reported measurements. This suggests that, as would be predicted, high levels of inflammatory markers are linked to low HRV. The study concludes by showing a relationship between two HRV indices (HFnu and RMSSD) and inflammatory markers. Specifically, low values of HF (obtained from frequency domain analysis) and low values of RMSSD (obtained from time domain HRV analysis) are linked to high TNF-α and IL-10 in CFS/ME patients but not in healthy controls. This study assessed autonomic function in PCC and ME/CFS patients, focusing on the correlation of HRV and blood pressure variability (BPV) indices with clinical features. Similar to our results, a study showed that patients with PCC and ME/CFS were significantly more anxious and depressed than healthy subjects, with the median level of anxiety and depression in both groups corresponding to the subclinical level.[11] The study also found that patients with PCC were more physically active than those with ME/CFS. The absolute values of LF and HF HRV in ME/CFS and PCC patients were lower than in healthy subjects, indicating reduced sympathetic and parasympathetic activity.[11] The study also found that slow breathing (6 breaths/min) had therapeutic potential for PCC, as the HRV parameters increased to the same level as healthy subjects. The most optimal model for predicting ME/CFS diagnosis was based on HF HRV during spontaneous breathing, showing a sensitivity of 81.3% and a specificity of 79.4%. The findings may aid in understanding the pathogenesis of orthostatic intolerance in both PCC and ME/CFS.[11]

Our research confirmed previous findings that decreased parasympathetic tone in CFS patients caused autonomic

dysfunction. The study analyzed the correlation between HRV and BP variability (BPV) in patients with heart failure (ME/CFS) and peripheral vascular disease (PCC). It found that fatigue was not related to depression or anxiety in these patients, indicating that fatigue is related to dysautonomia rather than depression.[11] The study also found that some HRV and SBPV parameters were correlated with age, suggesting age-related autonomic dysfunction. The study also found that baroreflex sensitivity in patients was affected by dysautonomia, which could contribute to the reduction in cerebral blood flow.[11] Thus, our study confirmed previous findings, which have proven that decreased parasympathetic tone and sympathetic hyperactivity were the causes of autonomic dysfunction in CFS patients.

The cause of dysautonomia in ME/CFS and PCC is unclear, but it may be a potential link between microglia and cardiovascular diseases. The ANS innervates vascular walls and regulates contractility and tension, potentially affecting endothelial and vascular tissues. The study also found that reduced HRV predicted the severity, extent, and progression of human coronary atherosclerosis, even in asymptomatic subjects.[11]

This uniformity across the various HRV indices is demonstrated for the 1st time in this study. Our findings somewhat support those of earlier research. In the baseline supine position, Yamamoto et al.,[8] found that CFS/ME patients had a decreased mean RR but not SDNN compared to matched healthy controls. We also found similar results in our research. On the other hand, Yataco et al.,[12] had previously documented no variations in LF, HF, or LF/HF between healthy controls and CFS/ME patients in the baseline supine posture. Boneva et al.,[13] observed shorter mean RR and decreased LF during sleep, along with greater plasma levels of nor-epinephrine and lower levels of aldosterone. According to the authors, this indicates neuroendocrine disruptions and a predominant sympathetic ANS. Rahman et al.,[14] monitored HR during nocturnal sleep in CFS/ME patients and found that these patients had lower RMSSD, HF, and LF/HF ratios than those of the healthy controls. This finding is consistent with the review by Meeus et al.,[15] which found that HRV was exclusively lowered in ME/CFS patients at rest. We also found similar results in our research. Frequency domain analysis was employed by Lewis et al.,[6] to examine the variations in autonomic dysfunction between the POTS and non-POTS CFS/ME subgroups. It is intriguing to note that the POTS cases had decreased LF, HF, and VLF. The authors suggested these frequency indices as potential biomarkers for differentiating between these two CFS/ME symptoms, but they omitted HRV time domain characteristics. One measure of HRV is the cardiac autonomic modulation index. While both vagal and sympathetic activity contributes to LF fluctuation, vagal (parasympathetic) function is the primary source of HF variability in the frequency domain. The ratio of LF to HF is regarded as a measure of sympathovagal balance. For time domain indices, vagal (parasympathetic) activity is the primary source of pNN50 and RMSSD, while SDNN is a measure of overall variability, similar to the total power index in the frequency domain.[16] Sympathetic hyperactivity and parasympathetic hypoactivity are observed in autonomic function in CFS/ME patients, and this autonomic imbalance may be related to changes in the central control pathomechanisms. Previous research employing HF power in the frequency domain approach and RMSSD in the HRV time domain method to study parasympathetic activity has demonstrated that changes occur in the HF component following electrical vagal stimulation, muscarinic receptor inhibition, and vagotomy.[16] In the HRV time domain study of RR intervals, we discovered decreased mean RR, SDNN, RMSSD, and pNN50 in CFS/ME patients compared with healthy controls. In the frequency domain analysis, we found decreased LF and HF and an increased LF/HF index in CFS/ME patients. It had not before been documented that these HRV indices from various domains concurred.

Limitations of the study

Given the limitations of this study, we suggest conducting comprehensive longitudinal research with a larger sample size to obtain more conclusive results. There were not many patients in the study. Because the majority of our participants were women, it is imperative that we conduct a study that only includes men.

CONCLUSION

Based on our research, patients with CFS had higher sympathetic activity and lower parasympathetic tone causing autonomic dysfunction. We found a correlation between inflammatory markers to sympathetic overdrive, which lowers HRV in patients with CFS. This study provides valuable insights for medical professionals to examine the levels of inflammatory markers and an unfavorable autonomic profile as a tool for investigation as well as supportive treatment in CFS.

HRV can be used as a non-invasive screening technique for disease progression, and severity and further to rule out morbidity and mortality of cardiovascular complications in patients with CFS.

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Authors' Contributions:
AN- Definition of intellectual content, literature survey, prepared the first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **AT-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **WA-** Design of study, statistical analysis, and interpretation; **PR-** Review manuscript; literature survey and preparation of figures, coordination, and manuscript revision.

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