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Original Research Article

A Cross-Sectional Study of Cardiac Autonomic Functions and Inflammatory Parameters in Patients with Fibromyalgia

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Abstract:

Background: Cardiovascular autonomic nervous system dysfunction (CAD) is a common observation in fibromyalgia patients. This study is intended to investigate the cardiac autonomic function status in patients with fibromyalgia and their level of inflammatory markers and disease severity, as there aren't many studies available on the subject.

Objectives: To investigate inflammatory markers, heart rate variability (HRV), and controls in fibromyalgia. To evaluate the correlation between heart rate variability (HRV) and inflammatory markers patients with fibromyalgia

Material and Methods: Thirty controls and thirty diagnosed cases of fibromyalgia participated in the study. The short-term variability of heart rate was used to measure autonomic function. Inflammatory markers, namely TNF-α and IL-10, were measured from 3 millilitres of overnight fasting serum. The degree of fibromyalgia was evaluated by IL-1 and TNF-alpha.

Results: Patients with fibromyalgia disease showed a substantial reduction in HRV frequency domain parameters, such as LF ($p = 0.00^*$), HF ($p = 0.00^*$), LF/HF ratio ($p = 0.00^*$), and time domain parameters, namely RMSSD ($p = 0.00^*$), SDNN ($p = 0.00^*$), NN50 ($p = 0.00^*$), and total power ($p = 0.00^*$). They had higher levels of TNF-α. TNF-α and the LF/HF ratio have a have a significantly positive correlation.

Conclusions: In patients with fibromyalgia, there is a significant correlation between HRV and both inflammations. The use of HRV as a reliable screening tool for autonomic disturbance in fibromyalgia patients may significantly lower their future morbidity and death risk.

Keywords: Fibromyalgia, Autonomic Dysfunction, HRV, Inflammatory Markers, Sympathetic Tone, Parasympathetic Tone.

Introduction

Low back pain is a common source of disability that affects different parts of the body all over the world. [1]. Research indicates that fibromyalgia, a non-inflammatory condition, may be influenced by elevated inflammatory mediators and cytokines.[2,3] Cytokines, such as interleukin-1, IL-2, IL-6, and IL-8, regulate inflammation through paracrine and autocrine mechanisms. [4]

Changes in the neurological system, which includes the brain, spinal cord, and peripheral receptors, are associated with persistent pain. [2,3]. Low heart rate variability (HRV) is indicative of inadequate autonomic nerve system adaptability and is associated with an increased risk of cardiovascular events. A high HRV suggests that the heart is quite flexible.[5-mohan babu] According to the neurovisceral integration theory, a complex brain system that integrates information from the body and externally controls changes in sensory perception, motor behaviour, physiological cognitive responses, and behavioral responses. [6]. Risk and uncertainty are impacted by the amygdala, which regulates the prefrontal cortex and sends signals to the autonomic nervous system (ANS). [7].

Heart rate variability (HRV) measurement is a non-invasive method for characterizing oscillations across successive ECG, RR periods and assessing ANS control of the cardiac sinus node. [8] Despite

the fact that FMS is a non-inflammatory illness, a growing body of research indicates that elevated inflammatory mediator and cytokine levels may be pathogenic elements. [9] Both autocrine and paracrine mechanisms are used by non-structural proteins and cytokines to control inflammation. [9] Since research on the relationship between HRV and inflammatory markers in Indian patients is inadequate, this study attempts to evaluate inflammatory markers and HRV in fibromyalgia patients.

This study aims to measure HRV and inflammatory markers in fibromyalgia patients

Aims and Objectives

1. The study aims to assess cardiac autonomic functions in patients with fibromyalgia utilising heart rate variability (HRV) and inflammatory markers.
2. In fibromyalgia patients, the study's objective was to assess the association between inflammatory markers and the severity of the illness utilising HRV.

Material and Methods

In cooperation with the Departments of Medicine and Biochemistry, the Department of Physiology designed the current study as a cross-sectional study.

Government Medical College and Super Facility Hospital, Azamgarh, conducted a study on 60 patients, 30 of whom were age- and sex-matched healthy controls and 30 of whom were diagnosed with fibromyalgia. The patients were recruited voluntarily between 2023 and 2023 at the medicine's outpatient clinics.

Every participant had their medical history questioned, and they were all subjected to general physical and anthropometric examinations. In order to record and analyse HRV [10] the A.D. Instruments 870B80 Exercise Physiology System was employed. Every recording was made between the hours of 8 am and 10 am; two hours of complete fasting, devoid of all liquids, were followed before testing. Throughout the recordings, both the patients and the healthy controls were at ease and stayed in a recumbent position.

Each participant's heart rate (HR) and blood pressure (BP) were measured following a 10- to 15-minute rest period. After five minutes of continuous electrocardiogram (ECG) recording under standard test conditions, the built-in HRV module evaluated short-term HRV offline. The analysis covered both the time and frequency domains. TNF-α and IL-10, in that order. The same day, serum was separated, and it was promptly frozen at -20 °C until analysis. The levels of TNF-α and IL-10 were examined using the standard sandwich-type enzyme-linked immunosorbent assay (Thermo Fischer Scientific, Austria) or two-step capture method. [11]

Data Analysis

SPSS, Inc., Chicago, IL, USA, version 21, was used for statistical analysis. Continuous variables were presented as median with interquartile range or as mean ± standard deviation. Prior to statistical analysis, the Shapiro-Wilk and Kolmogorov-Smirnov tests were used to ensure that the data were normal. The Mann-Whitney test was utilized for variables that were not normally distributed, and the unpaired t-test was employed to compare parameters that were normally distributed. Using Pearson's and Spearman's correlations, correlation analysis was performed to ascertain the relationship between HRV and inflammatory markers.

$P < 0.05$ was deemed statistically significant for all statistical tests.

Results

The average age of the patients with fibromyalgia was 37.32 ± 8.14 years, while the healthy controls had an average age of 34.43 ± 9.58years. The anthropometric measures of patients with fibromyalgia and healthy controls differ significantly in BMI (25.49 ± 1.30 vs. 24.98 ± 1.13, $P < 0.03$*), as Table 1 illustrates.

The significant differences between the Fibromyalgia patients and the control group in the time domain parameters of HRV, SDNN ($p = 0.00$*), RMSSD ($p = 0.00$*), NN50 ($p = 0.00$*), and total power ($p = 0.00$*) are displayed in Table 2.

Our study found that, as compared to controls, individuals with fibromyalgia exhibited significantly lower overall HRV in the context of short-term HRV. Table 3 indicates that compared to healthy controls, patients with fibromyalgia had substantially reduced LF ($p = 0.00$*), HF ($p = 0.00$), and LF/HF ratio of the frequency domain parameter ($p = 0.00$).

There was an evidently positive association between TNF-α and the HRV indices HF, NN50, and RMSSD. Table 4 demonstrates that while there was an association between IL-10 and HRV, pro-inflammatory markers such as TNF-α and IL-10 also manifested a significantly positive correlation with the LF/HF ratio.

Table 1: Basal characteristics and Cardiovascular Parameters in Fibromyalgia patients and Healthy Controls

Parameters	Fibromyalgia patients (Mean ± SD)	Healthy Controls (Mean ± SD)	p-value
Age	37.32 ± 8.14	34.43 ± 9.58	NS
BMI	25.49 ± 1.30	24.98 ± 1.13	0.03*
Heart Rate (bpm)	81.55 ± 13.58	82.23 ± 12.48	0.763
Systoloc BP	120.17 ± 4.27	114.5 3 ± 3.91	0.00*
Diastolic BP	74.66± 6.51	73.95 ± 7.92	0.624

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

Table 2: Time Domain Parameters in Fibromyalgia patients and Healthy Controls

Parameters	Fibromyalgia patients (Mean ± SD)	Healthy Controls (Mean ± SD)	p-value
RMSSD (ms)	25.43 ± 10.53	36.71± 11.97	0.00*
SDNN (ms)	32.11 ± 19.07	41.16 ± 17.31	0.03*
pNN50	9.42 ± 2.63	36.97 ± 4.63	0.00*
Total power	881.34 ± 76.93	1972.92 ± 86.44	0.00*

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

Table 3: Frequency Domain Parameters in Fibromyalgia patients and Healthy Controls

Parameters	Fibromyalgia patients (Mean ± SD)	Healthy Controls (Mean ± SD)	p-value
LF (ms^2)	228.38 ± 23.23	533.12 ± 29.31	0.00*
HF (ms^2)	219.13 ± 41.43	501.23 ± 54.53	0.00*
LF/HF ratio	1.13 ± 0.189	1.43 ± 0.781	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: Pearsons correlation of inflammatory markers with heart rate variability parameters in Fibromyalgia patients

	TNF- α		IL-10	
	R	p	r	p
SDNN	-0.289	0.196	-0.236	0.255
RMSSD	-0.168	0.237	-0.178	0.358
NN50	-0.95	0.474	-0.119	0.571
LF/HF ratio	0.491	0.001*	0.499	0.004*
LF	-0.256	0.148	-0.168	0.374
HF	0.373	0.028*	-0.172	0.351
Total power	-0.170	0.331	0.223	0.225

***p<0.05 statistically significant**

Discussion

The primary conclusions of this study indicate that, when compared to healthy individuals, patients with persistent low back pain had higher levels of sympathetic nervous system activity as determined by HRV parameters. In individuals with fibromyalgia, we observed a preponderance of sympathetic tone with a reduced activation of parasympathetic tone, as seen by decreased time domain or frequency domain indices. This may indicate low vagal tone or even enhanced sympathetic flow in pain sufferers.

Compared to healthy controls at baseline, Reyes del Paso et al. [12] found lower mean values in all domains of HRV frequency, indicating a general decrease in HRV in research involving fibromyalgia patients. In a study of fifty-five individuals with persistent neck and shoulder discomfort, Hallman and Lyskov [13] examined daily stress perception, physical activity, and autonomic nervous system regulation. Comparing the authors' findings to the control group, they discovered reduced HRV and shorter RR intervals. These results show that the group with persistent pain had less parasympathetic tone activation. Our findings also revealed a significant reduction in time domain and frequency domain indices, indicating a decrease in parasympathetic tone and sympathetic predominance in fibromyalgia patients.

The study by Tracy and others [14] investigated changes in heart rate variability (HRV) in chronic pain illnesses such as fibromyalgia, temporomandibular disorders, persistent neck and shoulder pain, and persistent low back pain. They found a correlation between chronic pain disorders and a decrease in HRV, particularly in data related to the HF domain. Comparing patients with chronic pain to healthy controls, the investigators found a mod-

erate decrease in HF cases. The most widely used HRV measurements in the time domain are parameters like SDNN (standard deviation of the average NN intervals) and RMSSD (root mean square of successive RR interval differences).

Additionally, a noteworthy decline in the time domain and frequency domain indices was found in our data, suggesting that patients with fibromyalgia had a less parasympathetic tone and a more sympathetic predominance. Telles et al. discovered a predominance of the LF-HRV parameter (sympathetic activity) in their subjects after studying 62 individuals with chronic low back pain. [15] Zhang et al. found that LF predominated over HF, but these studies lacked a control group of healthy participants. [16] Measuring HRV during rest may be a crucial clinical tool for treating chronic pain disorders. Gockel et al. found a correlation between higher pain intensity and high levels of disability, lower HRV, and those with intermediate disability as opposed to those with minimum disability. [17] When compared to healthy controls, Koenig et al. found that those with persistent neck pain reported higher levels of catastrophizing and had lower HF. [18] Additionally, compared to the healthy control group, our data showed a substantial decrease in LF and HF, which indicates a decrease in parasympathetic tone and a preponderance of sympathetic tone in fibromyalgia patients.

Fibromyalgia is characterised by dysregulation of pro- and anti-inflammatory cytokines, with a preference for pro-inflammatory cytokines. This imbalance is linked to several genes, including TNF, IL-1, IL-6, and IL-8, which may be linked to comorbidities. This study was intended to measure serum IL-6 levels in patients with Fibromyalgia Syndrome (FMS) and investigates potential relationships with illness burden indicators such as fatigue, sleep quality, and quality of life. The study found 95% of patients were female, with the gender gap in FMS likely due to hormonal factors and tender spots for diagnosis. [19,20,21]. In comparison to healthy control groups, we observed a significant rise in IL-1 and TNF in patients with fibromyalgia.

The Fibromyalgia group showed a significant decline in all-time domain HRV measures, indicating lower total sympathovagal modulation compared to the healthy control group. The LF/HF ratio was higher in the fibromyalgia group, suggesting a more active sympathetic nervous system. Elevated TNF-α and IL-1 levels were observed, indicating higher inflammation in Fibromyalgia patients.

The study's limitations

Given the limitations of this study, we recommend conducting further longitudinal research with larger samples in order to obtain more solid results. In the trial, there weren't many patients. It is essential that we perform a study with only guys because most of our participants were women.

Conclusion

Based on our research results, we were able to link elevated inflammatory markers to sympathetic overdrive, which reduces HRV, based on the results of our experiment. Our findings provide medical practitioners with encouraging and beneficial information on how to assess inflammatory marker levels and an unfavourable autonomic profile as practical tools to improve fibromyalgia therapy effectiveness. The results of these tests may provide important new information on the long-term risk factors influencing cardiovascular morbidity and mortality in fibromyalgia patients. Moreover, these tests may serve as a non-invasive screening method to determine the presence and severity of autonomic dysfunction in fibromyalgia.

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