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Evaluation of autonomic imbalance in irritable bowel syndrome and functional dyspepsia

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ABSTRACT

Introduction and Aim. Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are functional gastrointestinal disorders that may involve autonomic imbalance. This study assessed autonomic nervous system activity using short-term heart rate variability (HRV). To our knowledge, this is the first study in an Indian population to directly compare autonomic modulation across IBS subtypes and FD using a unified HRV protocol, demonstrating subtype-specific alterations – particularly reduced LF/HF in IBS-diarrhea (IBS-D).

Material and methods. Thirty IBS patients and thirty FD patients diagnosed using the Rome IV criteria, along with thirty healthy controls, were enrolled. Short-term HRV analysis was performed following ECG acquisition using the LABCHART platform.

Results. Mean low-frequency/high-frequency (LF/HF) ratio was 1.26±0.83 in IBS, 1.40±1.171 in FD, and 1.60±1.196 in controls. High-frequency (HF) power values (ms^2) were 733.9±1661.16 (IBS), 534.18±778.28 (FD), and 674.87±1187.16 (controls), with no significant differences among the three groups ($p>0.05$). Subgroup analysis revealed significantly lower LF/HF values in IBS-D compared to controls (0.98±0.69 vs. 1.60±1.196; $p=0.038$), while HF values did not differ ($p>0.05$). No significant differences were found between IBS-constipation (IBS-C) patients and controls.

Conclusion. IBS-D patients exhibited decreased LF/HF and increased HF values, indicating enhanced parasympathetic modulation, which may contribute to diarrhea-predominant symptoms. IBS-C patients showed a trend toward higher LF/HF and lower HF values, compatible with increased sympathetic modulation, although results were not statistically significant. FD patients showed no autonomic differences relative to controls. These findings highlight subtype-specific autonomic patterns in IBS and provide novel HRV-based insights from an Indian cohort.

Keywords. autonomic imbalance, autonomic nervous system, constipation, dyspepsia, gastrointestinal diseases, irritable bowel syndrome

Introduction

Functional gastrointestinal disorders (FGIDs) arise as a result of the interaction between the gut and the brain. It is a group of disorders characterized by motility disturbance, visceral hypersensitivity, altered gut microbiota, and altered central nervous system processing.[1] Two major functional GI disorders affecting the population are – irritable bowel syndrome (IBS) and functional dyspepsia (FD). IBS is a chronic gastrointestinal disease characterized largely by abdominal pain and changes in stool consistency and frequency. Global prevalence of IBS was found to be 11.2%.[2] Its prevalence in India varies from 4.2 to 14%.[3] Functional dyspepsia is characterized by epigastric pain, discomfort, early satiety, and burning. Global prevalence of FD has been demonstrated to be varying between 11–29.2%.[4] The pathophysiology of IBS and FD is yet to be clearly worked out. Various mechanisms have been proposed for IBS ranging from alteration in the gut microbiome (dysbiosis) and neurotransmitter imbalance [5] to dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. [6] Loss of vagal tone and receptive relaxation of the stomach to food has been implicated to contribute to the pathogenesis of FD.[7] Abnormal gastric emptying has also been implicated in FD pathogenesis.[8] Psychological stress and presence of other psychiatric co-morbidities has been shown to affect the etiopathogenesis of both IBS and FD.[9,10]

Recently, working out the mechanisms producing underlying differences between the IBS subtypes i.e., IBS-Diarrhea predominant (IBS-D) and IBS-Constipation predominant (IBS-C) together with understanding the role of the vagus nerve in IBS is being encouraged as a research priority.[11] HRV (Heart-rate variability) analysis is a well-validated method that can be used to non-invasively assess autonomic functioning. It is based on the principle of beat-to-beat variation i.e., changes in the RR intervals (time between successive R waves of an ECG) between heart beats.[12,13] As discussed above, IBS and FD significantly overlap in pathophysiology. However, there is a lack of studies investigating HRV patterns in IBS and FD in the same setting. Additionally, previous studies comparing the HRV patterns of IBS subtypes are few and utilize the older ROME III criteria for diagnosis [14]. Further, there exists a gap in autonomic research in the Indian population. The Indian population has shown several variations in comparison to other Asian populations such as a higher prevalence of the IBS-Diarrhea subtype, higher prevalence in older age groups etc[15].

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As already discussed, functional GI disorders are disorders of interaction between the gut and brain whose effects manifest as abnormalities in gastric emptying time, abnormal receptive relaxation of the stomach, and altered intestinal motility and secretions. Gastrointestinal motility and secretions are mainly controlled by the intrinsic enteric nervous system whose functions are modulated externally by the autonomic system via the vagus and sympathetic nerves, which are in turn, are controlled by the brain. Thus, it can be hypothesized that autonomic dysfunction might be the cause of disease in these patients.

In the current study, we aim to use the short-term 5-minute HRV recording to assess the autonomic functioning in two functional GI disorders - IBD and FD in the Indian population. We also aim to investigate if there is a difference in HRV patterns in IBS subtypes- IBS-D and IBS-C. We will be employing the ROME IV criteria for the diagnosis of our patients.

Aim

This study aims to determine whether patients with IBS, its clinical subtypes, and FD exhibit autonomic dysfunction, and to characterize their sympathetic and parasympathetic modulation using short-term HRV analysis. Importantly, this work provides one of the first comparative assessments of autonomic activity across IBS subtypes and FD within a single standardized HRV protocol, highlighting potential subtype-specific autonomic patterns – particularly in IBS-diarrhea.

Material and methods

Study design and setting

This is a cross-sectional study set in a tertiary health center in urban India. The sample size was determined using an appropriate formula-

Using reference article [16],

$$n=\frac{2(z\alpha + z1-\beta)^2\sigma^2}{d^2}$$

Where, $z\alpha$=Standard table value for 95 percent Confidence Interval=1.96

$z1-\beta$=Standard table value for 80 percent power=0.9

σ=Standard deviation=14.1

d=10.6=effect size

$$n=\frac{2(1.96+0.9)^2(14.1)^2}{(10.6)^2}$$

n=28.9

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Hence, 30 IBS, 30 FD and 30 controls were chosen as the sample size. Due clearance from the Institutional ethics committee was received before initiating the study.

Materials used and participants

PowerLab 26T (4 channel, 16-bit resolution polygraph) *(AD Instruments, Colorado Springs, USA)*, LABCHART 8 (*AD Instruments, Colorado Springs, USA)*, HRV 2.0 module *(AD Instruments, Colorado Springs, USA)*, and 3M™ Red Dot™ monitoring electrodes (*3M, Maplewood, USA*) were used in our study. Consecutive patients belonging to the age group of 18-80 years who presented to the outpatient gastroenterology clinic were included. Subjects were recruited between August 2023 and July 2024. IBS or FD was diagnosed based on the ROME IV criteria by an experienced gastroenterologist.[17] Controls were volunteers recruited on the basis of age and socioeconomic matching. Each patient and control underwent abdominal ultrasound, routine blood tests, as well as thyroid function tests. FD patients underwent upper GI endoscopy to rule out structural disease. IBS patients were classified based on Bristol stool scale and ROME IV criteria for various IBS subtypes. IBS patients were divided into two subsets - IBS-D and IBS-C.[18]

Patients with IBS-M (Mixed) and those diagnosed with both IBS and FD were excluded. Patients or controls with other gastrointestinal diseases, psychiatric illness, thyroid disease, diabetes mellitus, cardiac arrhythmias and those on medications such as NSAIDs, prokinetic drugs, antidiarrheal, laxatives, antispasmodic agents, tricyclic antidepressants, and SSRIs were excluded. Participants who had a history of caffeine intake or smoking within the last 24 hours were also excluded.

HRV recording

Readings were taken in the autonomic function test (AFT) lab. The readings were taken at the same time (11 AM –1 PM) every day to minimize error caused by diurnal variation of HRV.

Patients were given 15 minutes of rest to stabilize their respiratory and heart rates. Blood pressure, heart rate and respiratory rates were noted. ECG was recorded in the lead I configuration (negative electrode – right wrist, positive electrode – left wrist, and ground electrode – right ankle). ECG wires were connected to a bio amp which was connected to the PowerLab 26T machine. Patients were instructed to breathe according to the metronome set at 12 breaths/minute.

Real-time ECG signals appearing on the screen were refined to acquire clean signals. A high pass filter of 0.5 Hz and a low pass filter of 50 Hz was applied and a range of 5 mV was set. Data was acquired continuously for 5 minutes in supine posture at a rate of 500 Hz. The R wave peaks were automatically detected by the software. Ectopic beats (<5), noise, spikes and artifacts were automatically excluded from analysis by using Labchart's beat classifier view and also by manual screening of the recording. Any

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recording which had more than 5 ectopic beats or more than 5 seconds of aberrant ECG signal was completely repeated. Eleven recordings were repeated due to the above reasons.

HRV analysis

In the frequency-domain analysis of HRV, the spectral analysis was applied in our study, which decomposes the R-R interval time series into its fundamental oscillatory components. Very low frequency (VLF) oscillations were set between 0-0.04 Hz. High frequency (HF) was set between 0.15–0.40 Hz; low frequency variations (LF) were between 0.04-0.15 Hz. LF/HF ratio (LF/HF) was calculated to derive the sympatho-vagal balance.[19, 20]

The time domain parameters of HRV consist of SDNN (Standard Deviation of Normal-to-Normal Intervals), RMSSD (Root Mean Square of Successive Differences) and pNN50 (Percentage of NN50), where, normal to normal interval (NN), is the time period between two consecutive heartbeats originating from the sinus node. SDNN (standard deviation of all NN intervals) offers a global measure of overall HRV, while pNN50 and RMSSD are specific markers of parasympathetic (vagal) activity.[19,20] These parameters are relevant for the long-term heart rate variability and were not considered in the current analysis.

The HRV recording from our subjects was analyzed automatically by Labchart's HRV 2.0 module. The frequency domain outcome parameters (HF, LF/HF) were obtained. The report of each patient was saved in a database.

Statistical analysis

Analysis was done by exporting the data to SPSS software version 25.0 (*IBM, Armonk, NY, USA*). Mean age and standard deviation were calculated. Normality assessment was done using visual assessment of the histogram. One-way ANOVA was used to compare the age differences of the three groups. Chi-square test was used to compare the gender profile between the three groups. Non-parametric tests were used for HF and LF/HF analysis as the data was non-normally distributed. Statistical significance for HF and LF/HF was analyzed using the Kruskal Wallis test. Analysis between the IBS subtypes was done using Mann Whitney U test. Rank biserial correlation was used as a measure of effect size. P values <0.05 were taken to be statistically significant.

Results

The study involved a total of 90 participants broken down into three groups namely, 30 controls, 30 IBS patients and 30 FD patients. Sub-groups within the IBS cohort included 19 participants with IBS-D and 11 with IBS-C. The mean age of the participants did not vary significantly between the groups (39.07±15.935 for controls, 41.57±15.476 for IBS and 41.17±11.341 for FD patients) (Table 1). There was no significant

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statistical difference in the gender profile between controls and FD patients although the IBS group had a greater proportion of males (Table 1).

Table 1. Age profile of the three groups

Group	Control	IBS	FD	p
Sample size	30	30	30	–
Mean age in years (SD)	39.07 (15.935)	41.57 (15.476)	41.17 (11.341)	0.771
Gender (Male/Female)	17/13	24/6	18/12	0.121

Heart rate of IBS patients was higher (78.78±16.44) and that of FD patients was lower (76.14±12.03) in comparison to controls (77.96±13.62) but the heart rate did not vary significantly between IBS, FD and controls. (Table 2).

Table 2. Heart rate and spectral domain measures of HRV*

Group	HR	HF (ms^2)	LF/HF
IBS	78.79	733.9±1661	1.26±0.839
IBS-D subgroup	77.10	934.63±2043	0.98±0.69*
IBS-C subgroup	80.50	387.18±524.9	1.75±0.88
FD	76.14	534.18±778	1.4±1.171
Healthy controls	77.96	674.87±1187	1.6±1.196

* p=0.038 compared to controls, all other values – p>0.05 compared to controls

The mean LF/HF value for IBS patients was 1.26±0.839 for IBS, 1.4±1.171 for FD and 1.6±1.196 for controls. HF values (in ms^2) were 733.9±1661.16 for IBS, 534.18±778.28 for FD and 674.87±1187.16 for controls. A comparison of HF and LF/HF values between the three groups using statistical tools showed no statistically significant difference (p=0.36) (Table 2).

Subgroup analysis in the IBS group showed that the mean of the LF/HF values of the IBS-D group was the least (0.98±0.69), followed by controls (1.6±1.19), and IBS-C (1.75±0.88). The HF values (in ms^2), on the

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other hand, were found to be least in the IBS-C (387.18±524.9) followed by controls (674.87±1187.16), and IBS-D (934.63±2043.71). A statistically significant difference was found ($p=0.038$) in the LF/HF values between IBS-D patients and healthy controls, with a moderate effect (rank-biserial correlation=0.353, 95% CI [0.035, 0.608]). On the other hand, there was no difference in the HF values between the 2 groups ($p>0.05$). IBS-C showed no difference in either parameter compared to controls ($p>0.05$) (Fig. 1 and Table 2).

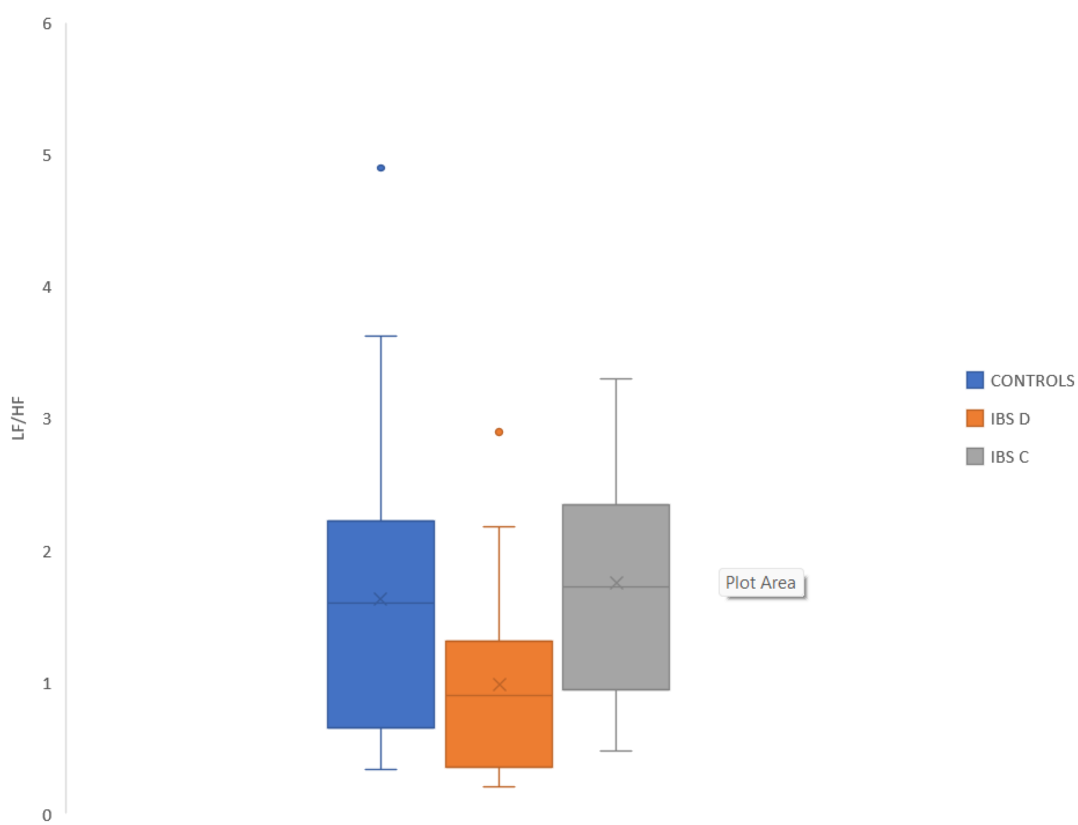

Fig. 1. Box-and-whisker plot showing distribution, outliers, and mean of the LF/HF values of IBS subtypes and controls

Figures 2 and 3 show representative HRV power spectrum plots and Poincaré plots of a healthy control and an IBS-D patient.

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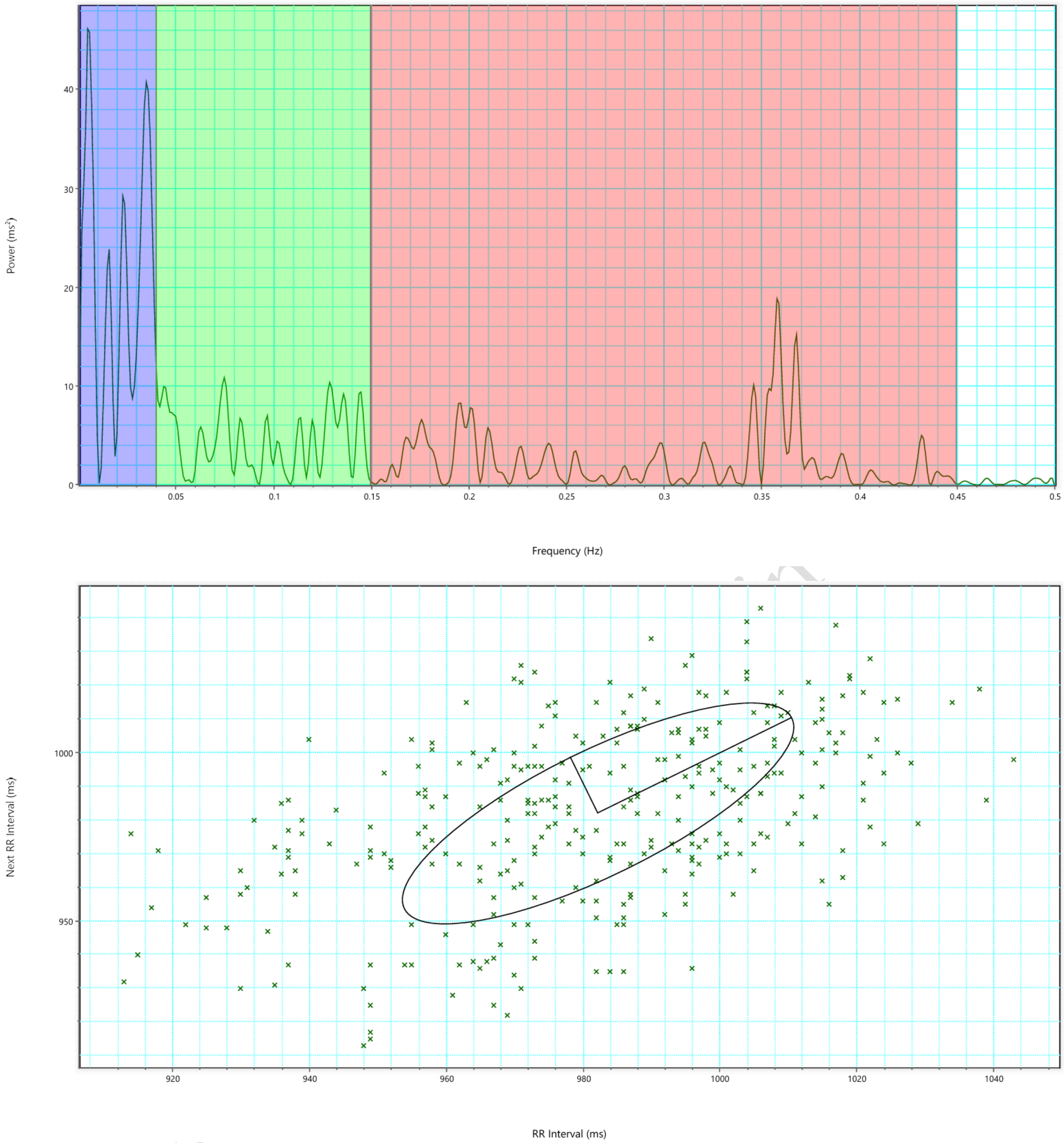
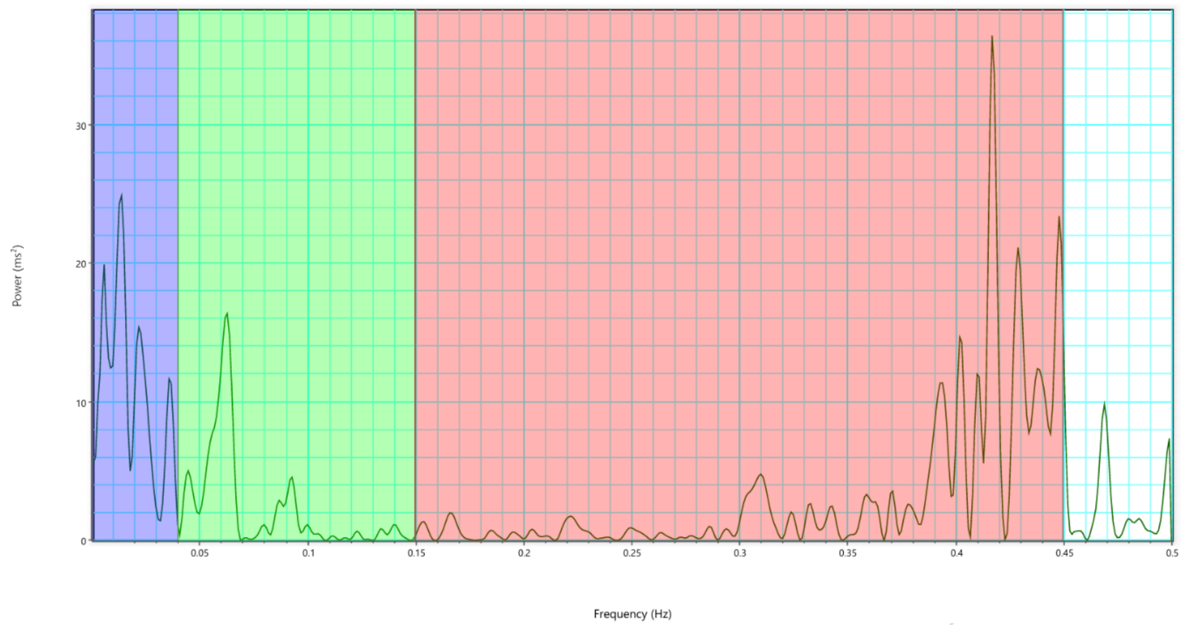


Fig. 2. HRV power spectrum plot of a healthy control with LF/HF of 0.7, corresponding Poincaré plot is shown



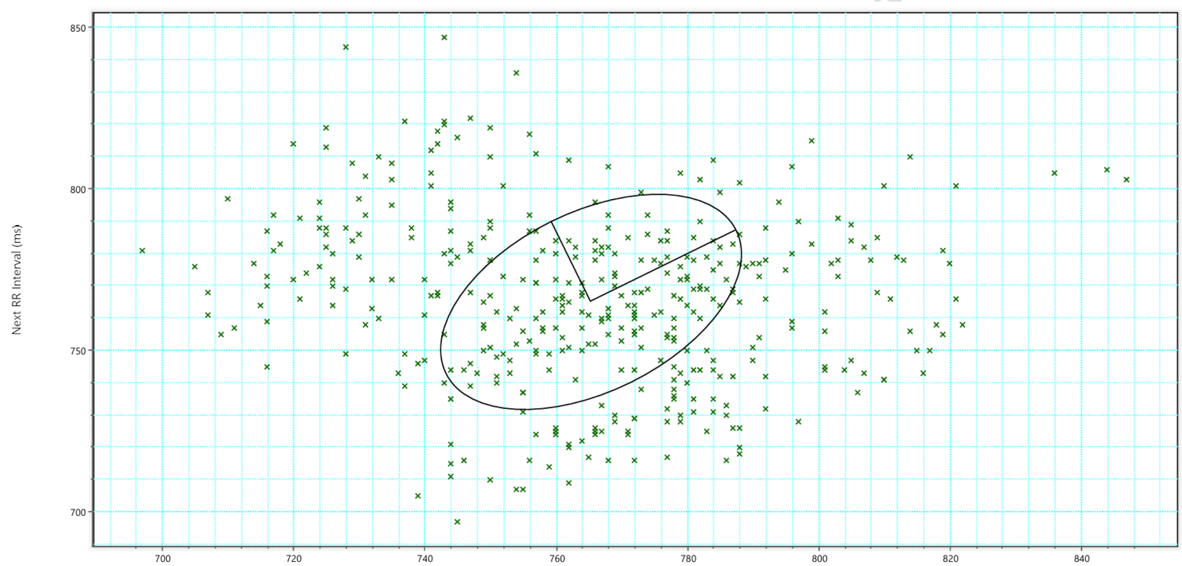


Fig. 3. HRV power spectrum of a patient with IBS-D with LF/HF of 0.26 showing high HF component and parasympathetic dominance (top), the corresponding Poincaré plot shows increased short-term variability with greater scattering of points

Discussion

Various studies have employed a wide array of tools, designs and parameters to assess autonomic function in patients. A lack of standardization exists, with studies using different methods for collecting data, taking varied lengths of readings, applying different software for analysis of HRV, and considering various outcome measures for physiological interpretation of results. In the current study, we have used short-term recording of HRV with ECG for recording. Short-term, 5-minute recording was chosen as it is convenient to replicate in clinical practice in the future and represents the dynamic relationship between the sympathetic and parasympathetic branches of the autonomic nervous system. The vagus nerve is inhibited on inspiration, and consequently, the heart rate increases. On expiration, the heart rate decreases due to relatively higher vagal tone. This constant fluctuation results in respiratory sinus arrhythmia, which along with the baroreceptor reflex, contributes to short term HRV. [19] Only the frequency domain parameters were considered for analysis as they are deemed to be a better metric in the short-term recording.[19] Hence, we cannot compare time-domain parameters of other studies with our results.

HRV analysis showed no statistical difference between the parameters selected for analysis, namely, LF/HF and HF between each group - IBS, FD, and controls. Studies comparing IBS and controls have shown results similar to our study, where the HRV patterns did not differ significantly from controls.[16, 21] These insignificant results in the IBS subgroup may have arisen as we combined patients of IBS-C and IBS-D under the same group. The opposing pathophysiological mechanisms in IBS-D and IBS-C may have contributed to the results being insignificant. Previous studies on IBS have emphasized on categorizing patients separately based on bowel patterns – evaluating IBS-D and IBS-C separately.[22] Another possible explanation for the insignificant results may be that changes in the autonomic nervous system (ANS) only in certain IBS patients, such as those who have suffered childhood trauma or life stressors. IBS is considered a heterogeneous disorder with different pathophysiological mechanisms leading to similar symptoms. Other studies demonstrated results divergent from our study and showed increased sympathetic dominance.[23-25]

In patients with FD, our results differed from previous research. Previous studies have hypothesized that delayed gastric emptying is due to reduced antral tone, which is affected by the vagus.[26] Studies have found a decreased vagal tone and sympathetic dominance in FD patients, indicated by increased LF/HF and decreased HF.[27, 28] It must be noted that these studies made use of the long-term method of HRV recording. Other studies showed a decreased vagal response after a meal only in patients with delayed gastric emptying.[29] Hence, our results, which showed no difference between FD and controls could be due to the accentuation of ANS abnormalities during meals in these patients.

Subgroup analysis of IBS showed that the LF/HF in IBS-D was significantly lower compared to controls. LF/HF values in IBS-C were higher compared to healthy controls but the difference was not found to be significant. As we already know, the parasympathetic nervous system increases colonic transit time and the sympathetic nervous system decreases gut motility. As LF/HF signifies sympatho-vagal balance, our results showing higher LF/HF in IBS-C and lower LF/HF in IBS-D compared to controls shows that there is a relative sympathetic dominance in IBS-C patients and a relative parasympathetic dominance in IBS-D patients. This could also possibly explain the diarrhea-predominant symptoms seen in IBS-D. This conclusion remains speculative considering the low sample size and cross-sectional design of our study. However, similar conclusions were drawn by a study assessing autonomic function using postural adjustment ratio and colon transit time in IBS subtypes by Aggarwal et al.[30] However, the authors did not include HRV analysis in their study. Jarrett et al.[31] on the other hand concluded that IBS-C patients

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diagnosed using ROME III had lower HF and significantly higher LF/HF than in controls. However, unlike our results, the IBS-D patients did not differ with controls. The authors used long-term HRV recordings for their analysis and this might have caused the conflicting results. Similar results were also obtained in a study confined to IBS-C patients diagnosed using the ROME III criteria where the authors found that LF/HF was higher and HF was lower in the IBS-C group in comparison to controls.[14] Hence, our study is the was able to find a difference in frequency-domain HRV parameters between IBS-D and controls. It is also important to note that the majority of the studies discussed above either used the long-term recording of HRV or used ROME III to diagnose patients. Our study differed from these studies by using the ROME IV criteria for diagnosis and the 5-minute recording of HRV. Additionally, our study provides one of the first IBS subtype-specific HRV comparisons within the Indian population.

Our study also showed that the HF band was higher in the IBS-D subtype and lower in the IBS-C subtype in comparison to controls, thus indicating higher vagal modulation in IBS-D and lower vagal activity in IBS-C. These results comply with the interpretation of our results for the LF/HF parameter in our study. This further suggests a higher parasympathetic modulation in IBS-D and higher sympathetic modulation in IBS-C. These results also suggest that sympathetic dominance in IBS-C could be due to vagal withdrawal instead of relative sympathetic dominance. Further, the parasympathetic dominance in IBS-D could be from vagal hyperactivity rather than sympathetic withdrawal.

Stress is thought to play a major role in initiating functional GI disease and patients also report a flare up of symptoms during periods of stress.[32, 33] Centers of the brain influencing stress might have an influence on the ANS. A review of case report forms of patients involved in our study showed presence of symptoms such as palpitations, fibromyalgia, and increased perspiration in many patients. These symptoms could further suggest the presence of autonomic imbalance in patients with functional GI disease.

Our findings have two significant clinical implications. Firstly, our findings show that patients with IBS-D and IBS-C differ in their autonomic profile using the short-term recording of HRV. This paves the way for the potential use of short-term HRV as a biomarker in IBS. Secondly, our findings support the premise of augmenting the ANS for potential therapeutic benefit in IBS and FD. In fact, studies which have attempted to do so have already shown promising results. A study exploring the effect of taVNS (Transcutaneous Auricular Vagal Nerve Stimulation) in FD showed patients reported reduced symptoms of dyspepsia, decreased the scores of anxiety, depression, and improved gastric accommodation.[34] Another study on the therapeutic effect of auricular acupressure in IBS showed that participants had a lower frequency of diarrhea, abdominal pain and discomfort at the end of the trial.[35] Additionally, CBT and hypnosis are also being used as complementary treatment options for IBS and FD and likely work by increasing vagal tone.[36] Further studies are required on ANS abnormalities in FGIDs which would add to the understanding of the disease process and to the development of effective treatment strategies.

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Study limitations

Our study has a few limitations. The major limitation of our study is the small sample size of the main (IBS, FD, HC) and subtype disease groups (IBS-D, IBS-C). It may have affected the strength and reliability of our results. The sample size may not have been sufficient to detect subtle differences in autonomic function in our patients. Additionally, the study's cross-sectional design limits the possibility to comment on causality and pathophysiological associations. This could have caused an error in HRV recordings by causing a bias in the HF values. We did not perform any autonomic testing additional to HRV to assess our subjects. Furthermore, we did not assess any changes prior to and following food intake. HRV analysis brings its own set of possibilities for errors. Gender could not be matched across the groups and might have changed our findings. Depression and anxiety levels/subclinical disease are also known to affect HRV results,[37] and were not taken into account, although patients with a known diagnosis of either of the two were excluded.

Conclusion

In conclusion, this study identified distinct autonomic patterns among IBS subtypes using short-term HRV analysis. Patients with IBS-diarrhea demonstrated significantly reduced LF/HF ratios, consistent with enhanced parasympathetic modulation, whereas IBS-constipation patients showed a trend toward higher LF/HF and lower HF values, suggesting relative sympathetic predominance. However, these differences were not statistically significant. No autonomic abnormalities were observed in patients with functional dyspepsia compared with healthy controls. Additionally, this study provides one of the first subtype-specific HRV comparisons within an Indian cohort using a standardized protocol, highlighting autonomic heterogeneity within IBS. Given the small sample size, particularly in the IBS-C subgroup, and the cross-sectional design, these findings should be interpreted cautiously. Larger, longitudinal studies are warranted to confirm these observations and to further explore whether autonomic modulation contributes to symptom expression or could serve as a therapeutic target in functional gastrointestinal disorders.

Declarations

Funding

No funding was received to conduct this study. The authors have no financial interests to disclose.

Author contributions

Conceptualization, L.D.; Methodology, L.D; Software, L.D.; Validation, L.D., P.K.S. and P.C.B.; Formal Analysis, L.D.; Investigation, L.D.; Resources, L.D.; Data Curation, L.D.; Writing – Original Draft Preparation, L.D. and P.K.S.; Writing – Review & Editing, L.D. and M.S.; Visualization, L.D. and M.S.; Supervision, P.C.B.; Project Administration, P.K.S. and P.C.B.

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Conflicts of interests

The authors declare no competing interests.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved on 16/6/2023 by the BMCRI Institutional Ethics Committee, Bangalore Medical College and Research Institute, Bangalore (No: BMCRI/PS/85/2022-23).

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