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A Prospective Cross-Sectional Study

Relationship between Heart Rate Variability and Major Depressive Disorder in Young Adults

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Abstract

Objectives: Heart rate variability (HRV) is a cost-effective and convenient tool to assess autonomic dysfunction, which has been sparsely studied in patients with major depressive disorder (MDD) in India. Primary objective is to study the relationship between HRV measures and MDD in young adults with standard normal values. Secondary objective is to evaluate the changes in HRV measure with symptom severity.

Methods: A total of 80 drug-naïve MDD patients, aged 18–45 years, without any major psychiatric or cardiovascular comorbidities, were enrolled in the study. Severity was determined using the Hamilton Depression Rating Scale. Time and frequency domain variables of HRV were analysed from electrocardiogram recordings. The time and frequency domain variables were compared with that of standard normal values using unpaired Student's t-test. These variables were also compared between mild, moderate, and severe MDD using analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

Results: Highly significant differences between patients and standard values were observed in mean interbeat interval (RR) of time domain variable ($p < 0.0001$) and in low frequency (LF) power ($p < 0.0001$), high frequency (HF) power ($p < 0.0001$) and LF/HF ratio ($p < 0.0001$) of frequency domain variables. Significant associations of HRV measures were also found in mean RR interval ($F = 19.96$, $p < 0.000$), LF ($F = 7.53$, $p < 0.001$), HF ($F = 4.62$, $p < 0.0126$), and LF/HF ratio ($F = 140.21$, $p < 0.000$) among different symptom severity groups.

Conclusion: This study provides evidence to implicate HRV as a cost-effective and convenient tool to assess autonomic dysfunction in MDD in young adults.

Keywords: Major depressive disorder; depression; autonomic nervous system; autonomic dysfunction; heart rate variability

Introduction

Depression is a common mood disorder with a global prevalence of 5.0% among adults, making it a major contributor to the overall global burden of disease. Depressive disorders accounted for 279.6 million estimated cases in 2019 [1]. The prevalence of major depressive disorder (MDD) amongst young adults has increased over the years [2].

In MDD, autonomic dysfunction is characterised by a parasympathetic withdrawal and sympathetic overactivity [3]. Heart rate variability (HRV) measures beat to beat interval changes in heart rate which reflects modulation of the autonomic nervous system (ANS). Simple electrocardiogram (ECG) recordings are used to obtain HRV and is used to determine the sympathovagal modulation at the cardiac sinoatrial node [3, 4], An association between cardiovascular disease and depression has prompted to consider depression as a cardiovascular risk factor and an altered ANS functioning, as determined by reduced heart rate variability (HRV), serves as an important candidate to account for this association. HRV is a non-invasive method to evaluate cardiac autonomic functions and a reduced HRV is an established prognostic factor for cardiovascular adverse events [4].

Recent studies have confirmed a reduction in HRV in MDD and other psychiatric disorders, with or without cardiovascular comorbidity, opposed to high HRV in resting condition, which was known to be associated with positive psychological aspects, such as social engagement and self-regulation [3, 5]. The association of ANS function with depression severity has been inconsistent [4].

Studies assessing the role of HRV to evaluate autonomic dysfunction in MDD patients are sparsely studied in young adults in India [6–8], hence this study aims to study the relationship between short-term HRV measures and MDD in drug-naïve patients without any cardiovascular comorbidities, with standard

normal values of HRV parameters. Standard values of HRV parameters were obtained from a systematic review of normative data of short-term HRV recordings in healthy adults [9]. This study also evaluates the effect of severity of depression on HRV.

Methods

This was a prospective study conducted in PSG Institute of Medicals Sciences and Research after obtaining clearance from the Institutional Human Ethics Committee (IHEC) (Project no. 18/311) between December 2018 and February 2020.

The patients who came to the psychiatry outpatient department with symptoms suggesting a depression were examined by the psychiatrist. Those patients who were diagnosed with a MDD were considered for the study after applying the inclusion and exclusion criteria.

The age criteria for the subjects was between 18 and 45 years, because above 45 years, diabetes mellitus and hypertension are more common, which can have an influence on the heart rate variability.

DSM-IV (Diagnostic and Statistical Manual of Mental Health) criteria were applied to diagnose MDD. The Hamilton Depression Rating Scale was used to grade the severity of depression as mild, moderate or severe.

Consumption of alcohol and nicotine was not considered before including the subjects in the study.

Drug-naïve patients aged between 18–45 years, diagnosed with MDD according to DSM-IV criteria and those who consented to participate, were enrolled in the study [10]. According to DSM-IV criteria, patients who had a major depressive episode, including depressed mood and loss of interest or pleasure in all activities for a period of at least two weeks and additional symptoms of changes in appetite, weight or sleep, feelings of worthlessness, recurrent thoughts of death or suicidal ideation, etc., were diagnosed with MDD [10].

Patients with a history of psychiatric illness, previous history of or current cardiac illness, systemic hypertension, diabetes mellitus or thyroid disorders were excluded from the study.

Sample size was calculated using OpenEpi software Version 3.01 with 95% confidence interval, based on prevalence of MDD in young adults which was found to be 5.25% as per National Mental Health Survey 2015-16 [11]. A sample size of 80 was confirmed.

All MDD patients enrolled in the study were assessed for the severity of depression using the 17-item Hamilton Depression Rating Scale [12]. Scores ranging between 8-16 were considered as mild, 17-23 as moderate and a score of 24 and above was indicative of severe depression, with the maximum score being 52 [13].

ECG was recorded for each patient diagnosed with MDD. The patients were instructed to abstain from caffeine at least 24 hours before recording. ECG was recorded in a silent room maintained at a temperature of 22-26 °C. ECG and HRV were recorded between 9 am and 12 pm to avoid any diurnal influences.

Short-term HRV was recorded following guidelines by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [14]. Lead II ECG was recorded after the patient was asked to lie down in supine position. Baseline recording was done after five minutes of supine rest. ECG was recorded for five minutes and ECG signals were acquired at the rate of 100 samples/second using data acquisition system BIOPAC MP100 (BIOPAC Inc., USA) (minimum 250 Hz sampling rate). The raw ECG signals and RR intervals were acquired on a moving time base. Ectopic heartbeats and artifacts were removed from the recording before analysis. RR tachogram was extracted from the edited 256 second ECG using R wave detector. HRV was analysed using Kubios HRV software.

The HRV parameters included time and frequency domain variables. Time domain variables included mean RR interval (ms), standard deviation of normal-to-normal intervals (SDNN) (ms), root mean square of SDNN (RMSSD) (ms), number of pairs of adjacent NN interval differing by more than 50 ms in the entire recording (NN50) and NN50 divided by total NN intervals (pNN50) (%). Frequency domain variables included low frequency power (LF) (relative power of low frequency band between 0.04-0.15Hz) (ms2), high frequency power (HF) (relative power of high frequency band between 0.15-0.4Hz) (ms2) and LF/HF ratio.

Statistical Analysis

Statistical analysis was done using SPSS software version 19. The time and frequency domain variables of HRV of patients with MDD were compared with that of standard normal population values [9] using unpaired Student's t-test, by mean and standard deviation. These variables were also compared between mild, moderate, and severe MDD using analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

Results

The study comprised of 80 drug-naïve patients ranging between 18–45 years of age (mean-42.75 years), diagnosed with MDD. Among the patients, the majority of them had a mild depression (57.5%, n = 46), followed by

Table 4: Comparison of heart rate variability parameters from patients with standard normal values [9]

Variable		Group	Mean	SD	p-value
Time domain	Mean RR interval (ms)	Normal	926	90	**<0.0001****
		Depression	664	125.4	
	SDNN (ms)	Normal	50	16	0.1341
		Depression	51.76	10.1	
	RMSSD (ms)	Normal	42	15	0.0893
		Depression	44	8.7	
	pNN50 (%)	Normal	20	16	0.1256
		Depression	21.8	10.4	
Frequency domain	LF (ms2)	Normal	519	291	**<0.0001****
		Depression	888.7	285.1	
	wHF (ms2)	Normal	657	777	**<0.0001****
		Depression	482.8	205.1	
	LF/HF	Normal	2.8	2.6	**< 0.0001****
		Depression	3.91	0.3	

** highly significant; SDNN: Standard deviation of normal-to-normal interval; RMSSD: Square root of the mean squared differences of successive normal-to-normal intervals of HRV; pNN50: Number of pairs of adjacent NN interval differing by more than 50 ms in the entire recording (NN50) divided by the total number of all NN intervals; LF: Power in low frequency range (0.04-0.15 Hz); HF: Power in high frequency range (0.15-0.4 Hz); LF/HF – Ratio of low frequency power to high frequency power.

moderate (22.5%, n = 18) and severe MDD (20%, n = 16).

The time and frequency domain variables of HRV of patients, when compared with standard normal values [9], revealed significant difference in mean RR interval (p <0.0001), LF (p <0.0001) and HF (p <0.0001) components and LF/HF ratio (p <0.0001). Remaining time domain variables did not show any difference from the standard values (table 4).

Between group comparison of time and frequency domain variables of HRV by severity of MDD (mild, moderate and severe), again revealed significant difference across the three groups in mean RR interval (F = 19.96, p <0.000), LF (F = 7.53, p <0.001) and HF (F = 4.62, p <0.0126) components and LF/HF ratio (F = 140.21, p <0.000). Other time domain variables of HRV did not show any significant difference between mild, moderate, and severe MDD (table 5).

Table 5: Comparison of heart rate variability parameters of patients with mild, moderate and severe depression using one-way ANOVA

Variable	Mild	Moderate	Severe	F-value	p-value
Mean RR interval (ms)	754.2	627	543	19.96	**0.0000****
SDNN (ms)	51.9	52.4	53.2	0.0809	0.9224
RMSSD (ms)	42.8	43.7	44.3	0.1982	0.8206
pNN50 (%)	20.6	21.4	22.7	0.3880	0.6797
LF (ms2)	711.11	834.7	1054	7.5277	**0.0010***
HF (ms2)	596	487	365	4.6226	**0.0126***
LF/HF	3.15	4.67	6.98	140.21	**0.0000****

* significant; ** highly significant; SDNN: Standard deviation of normal-to-normal interval; RMSSD: Square root of the mean squared differences of successive normal-to-normal intervals of HRV; pNN50: Number of pairs of adjacent NN interval differing by more than 50 ms in the entire recording (NN50) divided by the total number of all NN intervals; LF: Power in low frequency range (0.04-0.15 Hz); HF: Power in high frequency range (0.15-0.4 Hz); LF/HF: Ratio of low frequency power to high frequency power.

Discussion

The prevalence of MDD among young adults and adolescents has increased over time, which necessitates tools that predict depression among a susceptible population. A study conducted in a large sample of young adults saw a rising trend from 8.8% to 9.6% between 2005-2014 and a further increase in prevalence has been projected [2]. Young adults with depression often are not aware of their symptoms and do not seek medical help. Low self-esteem levels, lack of social support and social isolation have been quoted as risk factors in young adults with mild depressive symptoms [15]. In the context where young adults believe their symptoms to be situational, depressive symptoms can manifest as mild rather than moderate or severe. Our study saw a predominance of mild MDD patients (58%) compared to moderate (23%) and severe (19%) MDD.

HRV is a non-invasive method to identify ANS functions. We employed the short-term HRV recording method, which can be done within several minutes and with less time for data processing providing dynamic changes in autonomic function within minutes. Confounding factors such as temperature, respiration, physical activity, etc. can be controlled while recording short-term HRV as opposed to long-term methods [16].

Time domain variables of HRV quantify the variability of successive heartbeats during interbeat interval and frequency domain variables measure the distribution of heart rate oscillations across different frequency bands [17]. Among the time domain variables, we found a significant decrease in mean RR interval in MDD patients from standard values. No significant difference was observed in other time domain parameters, which was similar to a study conducted in India that failed to show any significant difference in time domain parameters between patients and healthy controls [7]. However, this contrasts with Hartmann et. al.'s study on drug-naïve depressive individuals where there was a significant difference in RMSSD values between healthy controls and depressive patients among time domain variables [18]. A recent meta-analysis of HRV in major depression revealed a significant reduction in SDNN, RMSSD and mean RR interval [19]. Though the time domain variables reflect both sympathetic (SDNN, RMSSD) and parasympathetic (RMSSD) influences on heart rate [7], the physiological interpretation of the effect of time domain variables on depression remains unclear due to such inconsistent findings.

This study showed significant increase in LF power in MDD patients compared to standard values and a decrease in HF power and LF/HF ratio. This was consistent with similar other studies, where significant differences were observed in LF and HF power [7, 18, 19] and LF/HF ratios between cases and controls [7]. However, an increase in LF/HF ratio was found in two of these studies, which included a meta-analysis, that also reported a reduction in LF power [7, 19]. This is contradictory to our findings, where a decrease from standard LF/HF ratio was found, which was indicative of decreased sympathovagal balance and a high LF power, reflecting enhanced sympathetic activity. The low HF power was indicative of lower parasympathetic activity among depressed individuals. While individual HRV measures might not be associated with depression specifically, it could be associated with the general abnormalities in HRV time and frequency domains. Parasympathetic withdrawal and sympathetic overactivity are observed in MDD patients [3], which was also evident in our study.

Relating to association of depression severity with time and frequency domain variables of HRV in MDD patients, we found no significant association in time domain measures except for a high mean RR interval in mild MDD compared to moderate and severe MDD. However, significant differences were found in LF, HF and LF/HF ratio across mild, moderate, and severe MDD. We found that LF and LF/HF ratio increased with severity, which indicates an increased autonomic imbalance in severe MDD. HF reduced with severity indicating a decreasing vagal activity. This was similar to another study conducted on drug-naïve young adults, which showed a negative relationship between HF and depression severity. However, they did not study the association of depression severity with other frequency domain measures [20]. A meta-analysis conducted in adolescent depressive patients did not show any significant association of HF with depressive symptoms [21]. It could be argued that the significance in HRV measures observed across depression severity could be a result of unknown confounding factor, except we observed a very high significance in LF/HF ratio (p <0.0000). Hence, future studies should explore the role of LF/HF ratio on symptom

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severity. Our study findings can probably help design studies to further understand the effect of antidepressants over time on symptom severity, since antidepressants themselves manifest changes in HRV.

Limitations

Apart from the small sample size of the study, this study lacked a control group consisting of healthy individuals from an Indian cohort. This could have provided determinative values to compare with the patients HRV measures. While the study's strengths lie in recruitment of drug-naïve patients without any confounding comorbidity, assessing effect of antidepressants on HRV measures could have been a valuable addition to confirm the potential of HRV to determine autonomic imbalance in MDD.

Conclusion

An overall reduction in HRV was observed in MDD patients. Changes in frequency domain measures were more prominent than changes in time domain measures and were also associated with symptom severity. Despite the limitations mentioned above, this study does provide evidence to implicate HRV as a cost-effective and convenient tool to assess autonomic dysfunction in MDD in young adults.

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Disclosure Statement

There is no conflict of interest in our study. The authors have no affiliation with any organization with a direct or indirect financial interest.

Author Contribution

VS conceived and designed the study, selected and recruited study participants, collected and monitored data, interpreted data, did statistical analysis, drafted the final report and handled publication.
RN conceived and designed the study, drafted the final data and handled publication.
All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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