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LONGITUDINAL ASSESSMENT OF HEART RATE VARIABILITY IN BIPOLAR DISORDER: TRACKING CHANGES FROM MANIA TO EUTHYMIA AT TERTIARY CARE HOSPITAL, SALEM, TAMILNADU

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Abstract

Introduction: Autonomic nervous system dysregulation is seen to be associated with behavioral disinhibition and increased impulsivity. Impulsivity is considered to be an important component throughout the course and presentation of symptoms of bipolar disorder and has been proposed to represent a core feature of the illness. Heart rate variability is a useful tool to assess autonomic dysfunction. Thus, patients with low overall heart rate variability may demonstrate reduced cardiac regulatory capacity and thus increased likelihood of myocardial infarction. **Aims:** The aim of the present study is to investigate the impact of Bipolar disorder on the autonomic nervous system, as indicated by heart rate variability in Indian population. **Methods:** A longitudinal observational study with twelve patients diagnosed as bipolar affective disorder who presented with episode of mania, as confirmed using Mini International Neuropsychiatric Interview (MINI) 5.0.0 were assessed for severity using Bech - Rafaelsen Mania Scale. Patients who were eligible for study were assessed for heart rate variability measurements at the time of mania and euthymia, which later was analyzed statistically to derive conclusion. **Results:** Comparison of calculated mean of different variables measured in two different phases of bipolar effective disorder, have shown heart rate variability stayed low in mania phase when compared to euthymia, which was not significant statistically. **Conclusions:** Patients with bipolar affective disorder may have risk of cardiovascular comorbidity as they have low heart rate variability during mania phase in comparison to state of euthymia.

Keywords: Bipolar Affective Disorder, Heart Rate Variability, Mania, Euthymia.

INTRODUCTION

As per ICD 11, bipolar affective disorder is defined as episodic mood disorders characterized by the occurrence of manic, hypo-manic or mixed episodes or symptoms which typically alternate with depressive episodes or periods of depressive symptoms over the course.[1]

Bipolar type I disorder is an episodic mood disorder which is characterized by the typical occurrence of one or more manic or mixed episodes.1 A manic episode is an extreme mood state which stays for at least one week unless shortened by a treatment intervention.

It is identified by clusters of symptoms including euphoria, irritability, or expansiveness, and also by increased activity or a subjective experience of increased energy, accompanied by other characteristic symptoms such as, decreased need for sleep, increased self-esteem or grandiosity, rapid or pressured speech, flight of ideas, distractibility, impulsive or reckless behaviour, and rapid changes among different mood states (i.e., mood lability).[1]

In 1990 worldwide prevalence (in millions) of bipolar affective disorder was found to be 24.8, which later increased to 39.5 in 2019.[2]

Dysregulation of autonomic nervous system is found to be associated with a variety of psychiatric disorders, including major depression, schizophrenia, and post-traumatic stress disorder.[3]

It appears that heart rate variability is influenced through vagal nerve and thus represent as an index of self-regulatory control, in a way that any individuals who appears to have a greater resting heart rate variability may perform better when tested for executive functions, whereas individuals with reduced heart rate variability may appear to correlate with disease and mortality as it reflects heart's ability to adapt and respond to events similar to exercise or stressors, thus showing its regulatory capacity being compromised. Thus patients with low overall heart rate variability may demonstrate reduced cardiac regulatory capacity and thus increased likelihood of myocardial infarction.[4]

The aim of the present study is to investigate the impact of Bipolar disorder on the autonomic nervous system, as indicated by heart rate variability in Indian population.

Objectives

1. To investigate trend of heart rate variability in bipolar disorder patient from state of mania to euthymia.
2. To find comorbidity association between affective disorders and cardiovascular disease (CVD).
3. To evaluate non-linear measurements to quantify the unpredictability of a time series.

METHODOLOGY

This longitudinal observational study was approved by the institutional human ethics committee, Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Vinayaka Missions Research Foundation (DU),Salem. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study.

Participants:

Twelve patients, including both male and female who reported at Department of Psychiatry of Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, were taken into consideration for the study. Patients were then evaluated for diagnostic assessment using Mini International Neuropsychiatric Interview (MINI) 5.0.0 and World Health Organization (WHO) authorized International Classification of Diseases 10th Revision (ICD 10). When patients were diagnosed as Bipolar affective disorder with mania episode, they were then taken for severity assessment using Bech

- Rafaelsen Mania Scale at the time of necessary admission. The socio-demographic details of the patients were recorded, which included patient's name, age, residence, socioeconomic status and along with these details patient's height and weight. Patient's past history including details related to age of onset, previous episodes of all three polarity and previous history of hospitalization with recovery from the episodes were also noted.

Inclusion Criteria

Inclusion criteria for this study is first, individuals must have a confirmed clinical diagnosis of bipolar affective disorder (BD) and be currently experiencing a manic state. Secondly, participants must fall within the age range of 18 to 65 years old.

Inclusion Criteria

Participants who meet certain exclusion criteria will be ineligible for inclusion in the study. Firstly, individuals with additional psychiatric illnesses that meet Axis I or II criteria, apart from the primary diagnosis of bipolar affective disorder, will not be considered. Secondly, individuals with a past medical history of myocardial infarction, stroke, or any other cardiac disease will be excluded from participation. Thirdly, those who have a history of drug abuse or dependence within the past six months will not be included.

Additionally, individuals with known morbidity of diabetes mellitus will be excluded. Furthermore, participants who have undergone prior Electro-Convulsive therapy will not be eligible. Finally, individuals displaying psycho-motor agitation that prevents the acquisition of a 20-minute resting heart rate variability recording will also be excluded from the study. These exclusion criteria are crucial for ensuring the homogeneity and integrity of the participant pool, thereby enhancing the validity and reliability of the study results.

Measurements of Heart Rate Variability:

It was taken care of before the start of assessment patients stayed without last twelve hours of caffeinated beverages consumption, prior to assessment for heart rate variability readings.Measurements were taken during daytime, ranging from 11am to 3pm. During assessment patient were made into supine position and had spontaneous breathing for 20 minutes of heart rate variability assessment. Patient were made into resting position with minimal movement to ensure good quality of measurements being recorded.

Heart rate variability measurements were recorded using Polar H 10 chest strap (Polar Electro Oy, Kempele, Finland). Patient were then fitted with Polar heart chest strap in which central machine was placed just above the xiphi-sternum and the soft strap with recording electrodes surrounded the chest.

The live measurement recorded by Polar heart chest strap was directly transmitted to Elite HRV software through live Bluetooth connection. Real time recordings of all RR intervals were taken and saved for further analysis.

All collected data of heart rate variability measurements were then forwarded to Kubios HRV standard software version 3.5.0 (Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuopio, Finland). Values for time domain, frequency domain and non linear domain was then derived using the Kubios software.

Statistical Analyses:

The data collected and interpreted through Kubios computer software was segregated into groups separately as time domain, frequency domain and non linear domain. Each domains' data was arranged according to the type of readings derived from RR intervals. Using Jamovi software median, mean with standard deviation and standard error was calculated. Also degree of freedom, mean difference, standard error difference and Cohen's d effect size was calculated. Using these values, Student's t test and Wilcoxon w test was applied to calculate p value.

RESULTS

Demographics and Clinical Characteristics:

Out of 12 participants, male participants were 9 (75%) and female was 3 (25%). The mean age of onset of bipolar affective disorder was found to be 28 years with 7.47 standard deviation. The frequency distribution of participants based on BMI categories reveals that 25% have a BMI below 18.5 kg/m², 17% fall within the range of 18.5–22.9 kg/m², another 17% range between 23.0–24.9 kg/m², and the majority, comprising 41%, have a BMI of 25 kg/m² or higher. This distribution highlights the varying BMI profiles within the participant cohort.

Table 1 : Age-wise Distribution of Participants

Age distribution	Percentage (%)	Number of patients
Below 20years	8%	1
21-25 years	8%	1
26-30 years	17%	2
31-35 years	8%	1
36-40 years	17%	2
41-45 years	8%	1
46-50 years	34%	4

Twenty-five percent of participants had history of previous suicide attempt, while the remaining 75% did not attempt.

Among the participants, 26% had no previous hospitalizations, while 8% had been hospitalized once. The majority of participants, comprising 58%, had been hospitalized twice, indicating a significant proportion with recurrent hospitalizations. Additionally, 8% of participants had been hospitalized thrice.

Table 2: Range of Occurrence of Different Types of Episodes during Course of Illness

Previous episodes	Range
Mania	01-Apr
Mixed	0 - 1
Depression	0 - 2

Table 2 illustrates the range of occurrences of different types of episodes throughout the course of illness among participants. It indicates that participants experienced a range of 1 to 4 manic episodes, with mixed episodes occurring between 0 to 1, and depression episodes ranging from 0 to 2. This data underscores the variability in the occurrence of different types of episodes, providing insights into the longitudinal course of bipolar affective disorder among the study population.

HRV Parameters:

Table 3: Differences in between States of Mania and Euthymia in Heart Rate Variability and Effect Size

	Mania	Euthymia	P-value	Cohen's d
Time Domain				
MeanRR bmp	689	754	0.058	0.4
MeanHR 1/min	89	80.1	0.947	0.5
SDNN ms	53	52.6	0.506	0.004
RMSSD ms	59.9	59.7	0.502	0.00156
pNN50%	10.64	5.46	0.127	0.3
Frequency Domain				
LF ms2	4091	5765	0.38	0.09
HF ms2	2065	2492	0.422	0.0585
LF/HF ms2	3.35	2.82	0.678	0.13
Non-linear Domain				
SD1 ms	42.3	42.2	0.5	0.00151
SD2 ms2	60.8	58.6	0.53	0.024
SD2/SD1	1.95	1.82	0.6	0.13
ApEn	1.23	1.25	0.4	0.02
EntSample	1.26	1.37	0.32	0.12
DFA alpha1	1.03	1.09	0.6	0.13
DFA alpha2	0.526	0.613	0.14	0.323

As shown in table 3, Mean heart rate per minute calculated for twelve patients when presented in mania was 89 beats per minutes and when in euthymia it was observed to be 80 beats per minute. The p value calculated with Student t test was 0.94 and Wilcoxon w was observed to be 0.94. Mean of all the values of root mean squared of successive differences calculated for mania phase was 59.9 and for euthymia phase was 59.7. The p value calculated using student's t test was 0.502 and with Wilcoxon, w was 0.788.

The mean of all the observations made under Spectral components of low-frequency (0.04–0.15 Hz) during the phase of mania was 4091ms2 and during euthymia was 5765ms2. The p value when calculated using student t test was 0.380 and through Wilcoxon, w was 0.810. The mean of all the observations of spectral components of high frequency (0.15–0.40 Hz) for mania phase was found to be 2065 ms2 and for euthymia phase was 2492 ms2. The p value found through student's t test was found to be 0.422 and with Wilcoxon W was 0.825. The mean of ratio between low frequency and high frequency components during the time of mania was 3.35 and when reached euthymia was 2.82.

Measurements under non-linear domain were recorded and calculated mean during the mania phase was found to be 1.23 and during euthymia was 1.25-. The p value calculated using student's t test was 0.461 and using Wilcoxon W was 0.285. The mean value of sample entropy calculated for mania phase was 1.26 and for euthymia phase was 1.37. The p value calculated via student's t test was 0.332 and through Wilcoxon W was 0.212.

The measurement recorded under poincare plot - SD1 was calculated and had mean of 42.3 during mania and 42.2 during euthymia. The p value when calculated through Student's t test was found to be 0.502 and when calculated through Wilcoxon W was found to be 0.795. The measurement recorded under poincare plot - SD2 was calculated and had mean of 60.8 during mania and 58.6 during euthymia. The p value

when calculated through Student's t test was found to be 0.533 and when calculated through Wilcoxon W was found to be 0.810. The measurement recorded under poincare plot - SD2/SD1 was calculated and had mean of 1.95 during mania and 1.82 during euthymia. The p value when calculated through Student's t test was found to be 0.641 and when calculated through Wilcoxon W was found to be 0.850.

The measurement recorded under detrended fluctuation analysis (DFA) α1was calculated for mean during mania as 1.09 and during euthymia as 1.03. The p value was then calculated through Student's t test and was found to be 0.680 and when calculated through Wilcoxon W was found to be 0.689. The measurement recorded under detrended fluctuation analysis (DFA) α2 was calculated for mean during mania as 0.526 and during euthymia as 0.613. The p value was then calculated through Student's t test and was found to be 0.144 and when calculated through Wilcoxon W was found to be 0.194.

Table 4: Severity Score and HRV Scoring

	Spearman's rank correlation	P-value
Time Domain		
Mean RR bpm	-0.26	0.414
Mean HR 1/min	0.264	0.577
SDNN ms	-0.281	0.376
RMSSD ms	-0.418	0.176
pNN50%	0.06	0.854
Frequency Domain		
LF ms2	0.025	0.939
HF ms2	-0.401	0.197
LF/HF ms2	0.278	0.382
Non-linear Domain		
SD1 ms	-0.418	0.176
SD2 ms2	-0.236	0.461
SD2/SD1	0.545	0.067
ApEn	-0.039	0.905
EntSample	0.042	0.896
DFA alpha1	0.396	0.238
DFA alpha2	-0.330	0.294

Table 4 presents Spearman's rank correlation coefficients and corresponding p-values between severity scores and heart rate variability (HRV) measures across time, frequency, and non-linear domains. Notable correlations include negative associations between severity scores and RMSSD (time domain), SD1 (non-linear domain), and SD2/SD1 ratio, with p-values indicating moderate significance. Additionally, a positive correlation is observed between severity scores and DFA alpha1 (non-linear domain). Other correlations exhibit weaker associations with higher p-values, suggesting less significant relationships between severity and HRV measures across various domains.

DISCUSSION

This study involves patients diagnosed as bipolar affective disorder who presented with episode of mania at the time of initial heart rate variability measurements. These patients were then evaluated again during the phase of euthymia. Participating patients acted as both subject and control in order to avoid confounding factors, which is one of the major advantage in this study.

Heart rate variability in bipolar affective disorder was assessed in other studies where patients were considered as subject and healthy individuals were considered as control.[5]

This study in contrast with other studies of past, shows the trend of heart rate variability which develops during the course from mania to euthymia phase of bipolar affective disorder.[6] In a similar study done by Kemp et-al, trend of heart rate variability was observed, where only male participants were selected, whereas in this study, selected population comprises both male and female, which brings better generalization of the study to the local population.[7]

In this study, the mean RR observed during mania was lower than the mean RR of euthymia phase. This outcome stays consistent with that of previous studies, making the evidence of low heart rate variability in mania phase more stronger.[8] This evidence is suggestive of autonomic dysfunction during phase of mania and it becoming comparatively stable at the time of euthymia. The significance of this difference stays low as p value observed was 0.058, whereas moderate effect size was observed with 0.4 Cohen's d value.

The mean heart rate observed in patients during time of mania was more than the mean heart rate of patients at the time of euthymia. This difference stayed insignificant as p value was higher than 0.05 and effect size stayed moderate. Findings related to mean heart rate was observed to be different from the findings of previous studies in term of significance, and effect size, as previous studies claimed to show mean heart rate to be significantly higher during mania when compared to euthymia.[9]

The SDNN (standard deviation of the average of normal R-R interval) measurement denotes the heart's adaptability in between parasympathetic and sympathetic autonomic nervous systems.[10] In this study, mean of SDNN measurements during the mania phase and at the time of euthymia showed insignificant differences with lesser effect size, which may suggest of no difference in heart's mechanism for sympathetic and parasympathetic signals from mania to phase of euthymia.

Other components of time domain including root mean squared of successive differences (RMSSD) and percentage of adjacent RR intervals differing by duration longer than 50 milliseconds (pNN50) also showed differences in their measurements when taken in mania phase and euthymia phase, which stayed insignificant and with small size effect.

When frequency domain measurement were analyzed it was seen that in low frequency parameter which was observed during phase of mania had lower values than the euthymia phase values. This difference was found statistically insignificant but on the other side it had large effect size. High frequency parameter in analysis showed lower mean frequency in mania phase when compared to euthymia, but difference in the mean values of both were not significant and had moderate size effect. In frequency domain analyses high frequency parameters are considered to be better for analyzing vagal tone changes under sympathetic and parasympathetic influences, but it also have a drawback as it changes regularly under the influences of breathing and change in position.[11] Therefore in this study mean of LF/HF ratio is also calculated, which was found to be more in mania in comparison to euthymia phase. This difference of mean of LF/HF ratio was not significant and had small size difference, which signifies that sympathovagal activity did not showed significant

difference during mania phase and euthymia phase in patients of bipolar affective disorder.

Measurements involving non linear domains are meant to shows the behaviour of heart in a visually summarized pattern.[12-15] In this study the mean differences of all three variables of poincare plot including SD1, SD2 and SD2/SD1 ratio, had insignificant differences when compared between mania and euthymia phase. However the effect size measured through Cohen's d stayed small for SD2/SD1 ratio. Means of sample entropy and approximate entropy variable were analyzed and were found to have no significant difference and effect size also stayed small. Therefore these findings indicates that heart's behaviour stays unpredictable and repetition of patterns of heart rate stays complex during both mania and euthymia phase.

The Spearman correlation coefficient for relation between heart rate variability measurements during mania and severity of mania, was found to be loosely correlated to each other and lacked significance. These results stayed consistent with previous studies' findings. [6]

CONCLUSION

In conclusion, heart rate variability was found to be low during mania phase when compared to euthymia, which indicates of autonomic dysfunction and low cardiac adaptability during the mania phase of bipolar disorder in Indian population. However the difference was not significant, but some components of heart rate variability has shown large effect size suggestive of parasympathetic and sympathetic imbalance leading to higher risk for cardiovascular morbidity during mania phase. Other variables including nonlinear domain measurements had shown that the unpredictability of pattern shown by cardiac system stayed high, which is suggestive of complex network of central nervous system involvement in maintaining cardiac rhythm. Therefore, this study suggests for necessary evaluation of cardiovascular risks in patients of bipolar affective disorder in order to prevent any serious cardiac morbidity. This study also opens the way for future research to evaluate heart rate variability as an useful tool for assessing cardiovascular risk in bipolar affective disorder.

LIMITATION

This study has several constraints. The study's limitations include a small sample size, potentially affecting the significance of outcomes. Measurements taken in a lying position for only 20 minutes may not fully capture variations seen in hyperactive states during mania. Exclusion of patients with increased psychomotor activity could impact results, particularly in assessing mania severity. Additionally, the use of a heart rate chest strap for measurements, while common, may raise reliability concerns. Finally, as a single study conducted in South India, generalizing findings to the broader population of the country may be limited.

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Conflicts of Interest: There are no conflicts of interest**.**

Ethical Statement:

Institutional ethical committee accepted this study. The study was approved by the institutional human ethics committee, Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Vinayaka Missions Research Foundation (DU), Salem. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. The confidentiality of the study participants was maintained.

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Authors' Contributions:

Dr.C.Bhaskar- conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing; ***Dr. C. Pradeep & Dr Lakshmi Dorai B***-conceptualization, methodology, writing—original draft, writing—review and editing; ***Dr M.Akshaya & Dr. Ayush Lall*** - methodology, writing—original draft, writing, review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript***.***

Data Availability:

All datasets generated or analyzed during this study are included in the manuscript.

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