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Comparative Study of Heart Rate Variability in Patients with Major Depressive Disorder and Normal Subjects

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ABSTRACT

Introduction: Major Depressive Disorder is a mood disorder diagnosed on the basis of DSM-5 criteria. Cardiovascular disorders are among the most common causes of deaths worldwide, accounting for about one-third of the mortality in both genders. Cardiac illnesses seem to have a bidirectional relationship with depression. Altered cardiac autonomic tone remains one of the most plausible explanations, which also appears to be a central biological substrate linking depression to a number of concurrent physical (e.g., cardiovascular) dysfunctions. Heart Rate Variability has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals (measured in ms) obtained from ECG or plethysmogram.

Material and Method: This study was a prospective observational study involved 150 individuals divided into two groups. Group A – Patients having first episode major depression or new recurrent depressive episode recruited from psychiatric OPD (n=75), Group B– Age, Sex, Height and Weight matched healthy controls (n=75).

Results: In our study, among the time domain indices, mean heart rate was increased in MDD patients in comparison to healthy controls and the difference was statistically significant. Root mean square of successive differences was reduced in MDD patients in comparison to healthy controls and the difference was statistically significant. Standard deviation of NN intervals and percentage of NN intervals differing by >50 ms also showed reduction in depressed patients than controls, but the difference was not statistically significant. The frequency domain indices Total power, very low frequency, High frequency were reduced in MDD patients in comparison to healthy controls and the difference was statistically significant. Low Frequency and Low Frequency / High Frequency ratio were increased in patients of MDD in comparison to healthy controls and the difference was statistically significant.

Conclusion: From our study we can conclude that HRV is reduced in MDD patients. We suggest that HRV parameters can be used as diagnostic or predictive biomarkers of depression.

Key Words: Major Depressive Disorder (MDD), cardiovascular disease (CVD), Heart Rate Variability (HRV), Time Domain Indices, Frequency Domain Indices.

INTRODUCTION

Major Depressive Disorder is a mood disorder diagnosed based on DSM-5 criteria and includes the following symptoms: depressed mood, loss of pleasure or interest, significant weight loss, insomnia or hypersomnia, psychomotor agitation or delay, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate

guilt, decreased ability to think or concentrate or indecision, recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt.

Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms are not due to the physiological effects of a substance or to another medical condition. Five or more of the above symptoms must occur within the same two-week period and represent a change from previous functioning [1].

Depressive disorders are common mental disorders that occur in people of all ages in all regions of the world and were the second leading cause of the number of years lived with disability in 2010. Globally, depression affected an estimated 322 million people in 2015 [2]. The prevalence of depressive disorders (MDD) ranges from 8% to 12% worldwide, and it has been projected to be the second largest burden of disease after cardiovascular disease by 2020 [3]. By 2030, HIV/AIDS, unipolar depressive disorders, and ischemic heart disease will be among the top three causes of disease burden [4].

In India, there are an estimated 57 million people (18% of the global estimate) affected by depression [2]. A survey found that nearly 1.8 million adults (45% of the adult population) in the Kashmir Valley suffer from symptoms of psychological distress, with 41% showing signs of probable depression, 26% of probable anxiety, and 19% of probable post-traumatic stress disorder (PTSD)

Cardiovascular disease is one of the leading causes of death worldwide, accounting for about one-third of mortality in both sexes [6]. In India, cardiovascular diseases affect nearly 30 million people. Heart disease appears to have a bidirectional relationship with depression. On the one hand, depression appears to increase the risk of heart disease, especially coronary artery disease. On the other hand, heart disease is associated with increased rates of depression [7]. Despite evidence of a strong clinical association between affective disorders and cardiovascular disease, little is known about the pathophysiology and potential biomarkers underlying these comorbid disorders. Altered autonomic cardiac tone remains one of the most plausible explanations [8], which also appears to be a key biological substrate linking depression to a number of concurrent physical (e.g., cardiovascular) dysfunctions [9]. Increased sympathetic or decreased parasympathetic nervous system activity predisposes patients with CHD to ventricular tachycardia, ventricular fibrillation, and sudden cardiac death [10,11]. Therefore, it is not surprising that an accurate, noninvasive assessment of autonomic nervous system activity–as obtained by measuring heart rate variability (HRV)–has become extremely popular in a variety of research areas, from cardiology to psychiatry.

Heart rate variability (HRV) is a physiological phenomenon that reflects the influence of the autonomic nervous system on the heart. HRV has become the commonly accepted term for describing variations in both instantaneous heart rate and RR intervals (measured in ms) obtained from the ECG or plethysmogram. It must be emphasized that the interval between successive heartbeats is analyzed, not the heart rate per se. HRV reflects the regularity of heartbeats: more regularity means lower HRV and vice versa [12].

HRV can be assessed in two ways, either as a time domain analysis or in the frequency domain as a power spectral density (PSD) analysis. In both methods, the time intervals between each successive normal QRS complex are first determined. Any abnormal beats that are not generated by depolarization of the sinus node are removed from the HRV analysis [12]. Very few studies have been conducted to evaluate cardiac autonomic function in depressed patients in the Indian population [13,14]. The extent of autonomic dysfunction also needs to be investigated, as well as a possible correlation between the degree of

autonomic dysfunction and the severity of depressive disorder. There are conflicting results on the correlation of autonomic dysfunction and severity of depression [13,15]. Therefore, there is a need to collect further research data on HRV in this patient group in Indian population, especially in Kashmir.

MATERIALS AND METHODS

This study was a prospective observational study, conducted in the Postgraduate Department of Physiology in collaboration with the Postgraduate Department of Psychiatry of Govt. Medical College Srinagar after obtaining clearance from IEC and getting written informed consent from all the subjects. The study was completed within a period of 18 months. The study design involved 150 individuals divided into following two groups.

Group A – Patients having first episode major depression or new recurrent depressive episode recruited from psychiatric OPD at General Community Hospital Unit, Institute of Mental Health and Neurosciences, SMHS Hospital, Srinagar. (n=75)

Group B– Age, Sex, Height and Weight matched healthy controls (n=75)

Inclusion criteria

Group A

1. Males and females who met DSM-5 criteria for MDD and fell in Moderate category of MDD having a score between 20-34 as per Montgomery-Asberg Depression Rating Scale (MADRS) [16] diagnosed in Psychiatric OPD.
2. First episode or recurrent type, who were otherwise physically healthy and gave a written informed consent.
3. Index episode has to be of at least 2 weeks duration and not having any psychopharmacological treatment over the preceding four weeks.
4. Age 18 to 60 years.

Group B

1. Healthy controls both males and females (Age, Sex, Height and Weight matched).
2. Age 18 to 60 years.

Exclusion criteria

1. Active suicidality
2. Patients with psychotic symptoms
3. Hypertension
4. Diabetes mellitus
5. Thyroid disorders
6. Heart Diseases
7. History of smoking or substance abuse.
8. Female subjects who were pregnant, lactating, or taking oral contraceptives.

METHODOLOGY

MDD patients who fit into the inclusion criteria were enrolled in Group A of the study after obtaining written informed consent. Baseline HRV was assessed before the start of treatment.

Age, Sex, Height and Weight matched healthy controls were enrolled in Group B of the study. In control group MDD was ruled out using MADRS, individuals who showed a score between 0 and 6 were taken as controls.

Method of recording heart rate variability

The study of heart rate variability was conducted in AFT lab in the Department of Physiology. The MDD patients recruited from psychiatric OPD were asked to report to the AFT lab next day. They were advised not to take psychotropic medication till their baseline HRV was recorded. The subjects in both study and control groups were asked to refrain from ingesting any beverages containing caffeine or alcohol for at least 12 hours prior to the study. They were asked to report between 10 AM to 12 noon to the lab with light breakfast. Details of procedures were explained to the subject before carrying out the tests. It was ensured that subjects were physically and mentally relaxed by asking them to rest in quiet room with ambient temperature (23-27^{0}C) for 15-30 minutes in supine position. Then their basal parameters (e.g., pulse rate, respiratory rate, Systolic Blood Pressure & Diastolic Blood Pressure) were recorded.

The resting HRV was recorded in Lead II using POWER LAB 26T (AD Instruments, Sydney, Australia) in supine position for 5 minutes. Both time and frequency domains of HRV were analyzed. The details of the subjects were recorded in proforma.

STATISTICAL ANALYSIS

Data was entered in a Microsoft Excel spreadsheet and analyzed using statistical software Graph Pad Prism version 8.4.3. Continuous variables were summarized as Mean and SD. Categorical variables were summarized as percentages. Unpaired t test was used to evaluate the difference in HRV among MDD patients and Controls.

Chi-Square test was used to evaluate the relationship between two categorical variables. All p values were two-sided and p value <0.05 was considered statistically significant.

RESULTS

Our study included a total of 150 subjects. 75 patients suffering from MDD were taken as cases (Study Group). 75 healthy subjects were taken as controls. The data obtained was statistically analysed and the results observed are tabulated as follows.

Table 1: Shows comparison of anthropometric data between the two groups

Parameter	Study Group (Cases) n = 75	Control Group (Healthy subjects) n =75	p- value
Age(years) (Mean ±SD)	39.92±13.32	37.03±12.29	0.169(NS)
Gender (Male/Female)	35/40	43/32	0.191(NS)
Height (meter) (Mean ± SD)	1.65±0.13	1.63±0.08	0.524(NS)
Weight (Kg) (Mean ± SD)	64.64±11.73	61.79±9.23	0.100(NS)
BMI(Kg/m2) (Mean ± SD)	24.12±5.11	23.14±3.13	0.159(NS)

NS- not significant (p value>0.05)

Table 2: Shows comparison of baseline heart rate, baseline respiratory rate, systolic and diastolic blood pressures between the two groups

Parameter	Study Group (Cases) n = 75	Control Group (Healthy subjects) n =75	p- value
Baseline Heart Rate(beats/min) (Mean ± SD)	78.45±7.08	75.79±7.17	0.023(S)
Baseline Respiratory Rate (breaths/min) (Mean ± SD)	14.88±0.82	14.97±0.82	0.488(NS)
Baseline SBP (mmHg) (Mean ± SD)	121.3±5.99	120.1±7.28	0.262(NS)
Baseline DBP (mmHg) (Mean ± SD)	77.49±5.08	78.03±6.29	0.569(NS)

SBP- Systolic blood pressure, DBP- Diastolic blood pressure, S- significant (p value<0.05), NS- not significant (p value>0.05)

Table 3: Shows comparison of time domain indices of HRV (heart rate variability) between the two groups

Parameter	Study Group (Cases) n = 75	Control Group (Healthy subjects) n =75	p- value
MHR (beats/min) (Mean ± SD)	75.82±8.82	72.86±7.59	0.029(S)
SDNN (ms) (Mean ± SD)	59.18±17.39	64.39±17.84	0.072(NS)
RMSSD (ms) (Mean ± SD)	54.25±18.02	62.09±17.50	0.008(HS)
pNN50 (%) (Mean ± SD)	23.05±13.31	28.56±10.65	0.079(NS)

MHR- Mean heart rate, SDNN- Standard deviation of NN intervals, RMSSD- Root mean square of successive differences, pNN50- percentage of NN intervals differing by >50 ms, ms- milliseconds, NS- not significant (p value>0.05), S- significant (p value<0.05), HS- highly significant (p value<0.01)

Table 4: Shows comparison of frequency domain indices of HRV (heart rate variability) between the two groups

Parameter	Study Group (Cases) n = 75	Control Group (Healthy subjects) n =75	p- value
TP (ms2) (Mean ± SD)	1534.4±474.3	2305.3±509.6	<0.001(HS)
VLF (ms2) (Mean ± SD)	841.2±238.01	1379.7±336.5	<0.001(HS)
LF (n.u.) (Mean ± SD)	46.03±15.70	36.97±13.89	0.003(HS)
HF (n.u.) (Mean ± SD)	35.93±18.20	44.34±11.55	0.009(HS)
LF/HF ratio (Mean ± SD)	1.79±1.23	0.91±0.49	<0.001(HS)

TP- Total power, VLF- Very low frequency, LF- Low frequency, HF- High frequency, ms- millisecond, n.u.- normalised units, HS- highly significant (p value<0.01)

DISCUSSION

Major depressive disorder (MDD) is reported to be associated with increased cardiovascular morbidity and mortality [17]. This has been hypothesized to be because of alterations in the autonomic nervous system among MDD patients. Such alterations are believed to reduce heart rate variability (HRV), a well-known prognostic risk factor for cardiovascular disease and mortality [18]. A total of 150 subjects were included in this study, 75 patients suffering from major depressive disorder and 75 healthy subjects as control group. The groups were compared for anthropometric parameters (Age, gender, height, weight and BMI) and HRV. Supine resting HRV was assessed at the start of study in both groups.

Anthropometric parameters between the two groups where comparable and statistically non-significant. The basal heart rate was higher in study group as compared to controls and the difference was statistically significant. (p value<0.05). Similar observation of high basal heart rate in MDD has been found by Pardeshi S et al. (2017) [19] Higher resting heart rate may be due to decreased vagal tone in MDD patients.20. The two groups were statistically comparable with respect to baseline heart and respiratory rates, and baseline systolic and diastolic blood pressures (p value> 0.05).

Comparison of Heart Rate Variability in MDD patients and healthy controls:

Time domain indices: In our study, among the time domain indices of HRV, MHR was increased in MDD patients in comparison to healthy controls and the difference was statistically significant (p value<0.05). RMSSD was reduced in MDD patients in comparison to healthy controls and the difference was statistically significant (p value <0.05). SDNN and pNN50 also showed reduction in depressed patients than controls, but the difference was not statistically significant. (p value>0.05). [Table 3]

Frequency domain indices: The frequency domain indices TP, VLF and HF were reduced in MDD patients in comparison to healthy controls and the difference was statistically significant (p value<0.05). LF and LF/ HF ratio were increased in patients of MDD in comparison to healthy controls and the difference was statistically significant. (p value<0.05). [Table 4]

Our results are similar to a study conducted by Surekha P et al. (2017) who compared HRV between newly diagnosed MDD patients and age and sex matched controls and found decreased HRV as indicated by a decrease in RMSSD, a time domain index of HRV in patients of MDD and increase in the frequency domain indices LF and LF/HF) [19]. The results of our study are also in concordance with a study conducted by

Wang Y et al. (2013) in which they studied the correlation between depression severity and Heart Rate Variability (HRV) related indices and observed significantly lower values of RMSSD and HF in the depression group compared to the control group. They also found increased LF and LF/HF ratio in depressed patients than healthy controls. These findings indicate a reduced HRV as a result of dysfunction of cardiac autonomic nervous system [20].

Significant reductions in indices of parasympathetic activity (RMSSD and HF) imply that MDD patients have reduced parasympathetic activity. These observations can be explained on the basis of reduced cardiac vagal modulation of heart in depressed patients. Reductions in parasympathetic tone may be a consequence of reduced activation within the central autonomic network (CAN), [21] a network of brain regions that control a variety of visceromotor, neuroendocrine, and behavioral responses critical for goal-directed behavior and behavioral flexibility [21].

The observation of significant increase in LF and LF/HF ratio reflecting sympathetic activity can be explained on the basis that depressed patients have disinhibition of sympathoexcitatory influences that are mediated by deficits in the central autonomic network, leading to reduced flexibility in responding to environmental demands and appropriate responsiveness [22].

CONCLUSION

From our study we can conclude that HRV is reduced in MDD patients. We suggest that HRV parameters can be used as diagnostic or predictive biomarkers of depression. Further studies are needed to determine whether HRV may improve clinician's ability to early identify people at risk for depression who can benefit from targeted prevention by psychiatric and psychological interventions.

Declaration by Authors

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