

Original Article

Comparative Study of Heart Rate Variability (HRV) in Major Depressive Disorder (MDD) & Healthy Individuals

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Abstract

The present study was carried out to compare HRV between 50 newly diagnosed MDD patients & 50 age & sex matched controls. The purpose of this study is to understand the interplay between autonomic nervous system (ANS) and cardiovascular system (CVS) in the patients of MDD. ECG was recorded for 5 minutes on MEDICAID STUDENTS PHYSIOPAC in lead II in supine position after 30 minutes of relaxation. HRV was analyzed by using Kubios version 2.1 software. Resting heart rate was significantly increased in MDD patients. There was significant decrease in time domain indices of HRV i.e. SDNN, RMSSD, NN50, PNN50. Low frequency (LF) was significantly increased ($p < 0.05$) while high frequency (HF) was found to be significantly decreased in cases compared to controls. LF/HF ratio was increased in cases. MDD patients have higher resting heart rate and decreased HRV suggestive of decreased parasympathetic activity as compared to controls pointing towards cardiac autonomic modulation.

Introduction

Major Depressive Disorder (MDD) will be the second leading cause of burden of disease worldwide by 2030 attributable to 4.1% of Disability Adjusted Life Year (DALY) (1, 2). India with its population of more than one billion has nearly 100 million people suffering from mental and neurological problems, who require professional help at any point in time.

Exposure to prolonged emotional stress is associated with numerous adaptations in neurobehavioral response affecting both central nervous system and autonomic nervous system. Nearly all recent studies on depression and heart disease document increased cardiovascular morbidity and mortality in patients with depressive symptoms or major depression. Cardiovascular responses work in close association with ANS. MDD can be associated with autonomic dysfunction which can act as an independent risk factor in development of coronary artery disease, rather than merely a secondary emotional response to cardiovascular illness (3, 4). HRV is a reflection of cardiovagal interaction allowing quantitative estimation of ANS function.

As per DSM-IV-TR (4), MDD is characterized by one

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(Received on March 12, 2017)

or more major depressive episodes (MDE) without a history of manic, mixed, or hypomanic episodes.

The purpose of this study was to understand the interplay between autonomic nervous system and cardiovascular system in the Patients of MDD and to investigate the influence of MDD on ANS and cardiovascular complexity by measuring the various components of HRV.

Aims & Objectives

1. To compare resting Heart Rate (HR) between MDD patients & controls.
2. To compare time domain indices (SDNN, RMSSD, NN50, PNN50, MEAN RR) between MDD & controls.
3. To compare frequency domain indices (LF, HF, LF/HF RATIO) between MDD & controls.

Materials and Methods

The present study was conducted in the Department of Physiology & Department of Psychiatry. Before commencement of the project, approval was taken from the Institutional Ethical Committee.

The study design involved 100 individuals which were divided in two groups.

Group I – Diagnosed patients of MDD as per Hamilton Rating Scale for depression (HAMD) (n=50)

Group II – Age & sex matched healthy controls (n=50)

Written informed consent was taken before doing the clinical examination of the subject.

Inclusion criteria

1. Age group 18-48 years.
2. Healthy controls including both males & females.
3. Diagnosed patients of MDD.

Exclusion criteria

1. Subjects with history or symptoms suggestive of hypertension, hypotension, cardiovascular diseases e.g. (myocardial infarction, ischemic heart disease), respiratory diseases, Diabetes Mellitus, sleep disorders, hyperthyroidism, hypothyroidism, neurological disorders e.g. (epilepsy, stroke).
2. Subjects with history of addiction to tobacco and alcohol and drug abuse.

Procedure

The subjects 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 have adequate sleep at night and to refrain from any medications throughout the study period. They were asked to report between 10 a.m–12 p.m. in the lab with light breakfast. Details of procedures were explained to the subject before carrying out the tests. It was ensured that subject was physically and mentally relaxed by asking to rest in quiet room for 30 minutes. Then his/her basal parameters (e.g. pulse rate, respiratory rate, Systolic Blood Pressure & diastolic Blood Pressure) were recorded.

Method of recording heart rate variability

The study of heart rate variability was conducted in a quiet room in the Department of Physiology. The subject was asked to relax in supine position for 30 minutes. The resting heart rate was recorded in Lead II using MEDICAID STUDENTS PHYSIOPAC in supine position for 5 minutes.

Physiopac is 8 channelled polygraph. In the present study it was used for recording ECG. After placement of ECG limb leads, polygraph machine was started, channel for ECG was selected and ECG was recorded in lead II for duration of 5 minutes.

HRV from the recorded ECG was analysed by using Kubios HRV version 2.1 software. The software was developed by Biosignal Analysis and Medical Imaging Group (BSAMIG) at the Department of Applied

Physics, University of Eastern Finland, Kupio, Finland. For calculating HRV, guidelines of Task Force of European Society of Cardiology & The North American Society of Pacing & Electrophysiology were followed (5).

In frequency domain, low frequency (LF) 0.04-0.15 Hz determines cardiac sympathetic activity, high frequency (HF) 0.15-0.4 Hz determines cardiac parasympathetic activity & LF/HF Ratio indicates Sympathovagal balance.

Statistical analysis:

Statistical analysis of the observations was carried out using SPSS version 16 and graph pad prism 6. The data was expressed in terms of mean and standard deviation and statistics were determined using unpaired t test. Statistical significance was tested at 5% & expressed in terms of 'p' value with $p < 0.05$ = statistically significant.

Observations and Results

TABLE I: Table showing comparison of Resting Heart Rate of subjects.

	Case Mean±S.D	Control Mean±S.D	P Value
Resting HR	85.14±10.11	78.30±10.56	<0.05*

There was significant increase in HR in case group compared to control group ($p < 0.05$).

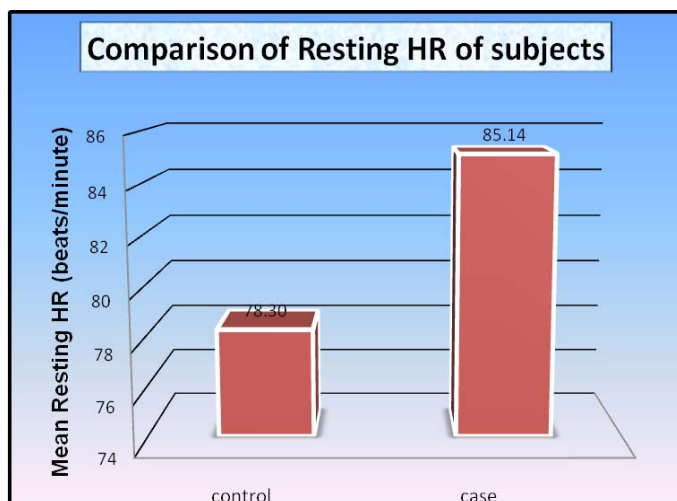


TABLE II: Table showing comparison of time domain indices of HRV of subjects.

	Case Mean±S.D	Control Mean±S.D	P Value
Mean RR (ms)	702.22±92.02	792.35±105.35	<0.05*
RMSSD (ms)	9.49±3.69	23.96±6.13	<0.05*
SDNN (ms)	77.15±21.93	129.28±19.07	<0.05*
NN50 (count)	3.45±1.86	8.24±6.89	<0.05*
PNN50 (%)	1.79±1.14	4.01±3.45	<0.05*

There was significant decrease in time domain indices of HRV in case group compared to control group ($p < 0.05$).

TABLE III: Table showing comparison of frequency domain indices of HRV of subjects.

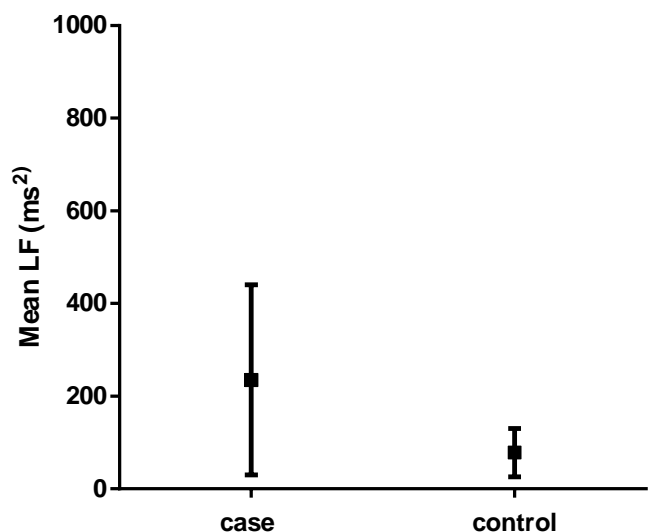
	Case Mean±S.D	Control Mean±S.D	P Value
LF (ms ²)	235.08±205.34	77.96±52.08	<0.05*
HF (ms ²)	96.01±83.25	241.22±149.67	<0.05*
LF (n.u.)	74.33±6.49	65.66±9.28	<0.05*
HF (n.u.)	24.76±7.33	34.32±9.37	<0.05*
LF/HF ratio	3.18±1.01	2.09±0.78	<0.05*

There was significant increase in Low Frequency power in case group compared to control group ($p < 0.05$).

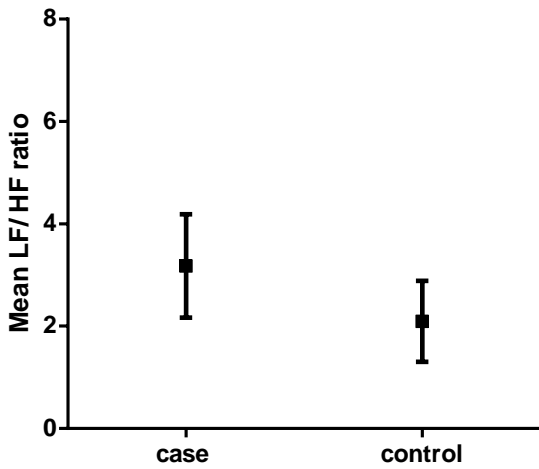
There was significant decrease in high frequency power in case group compared to control group ($p < 0.05$).

There was significant increase in LF/HF ratio in case group compared to control group ($p < 0.05$).

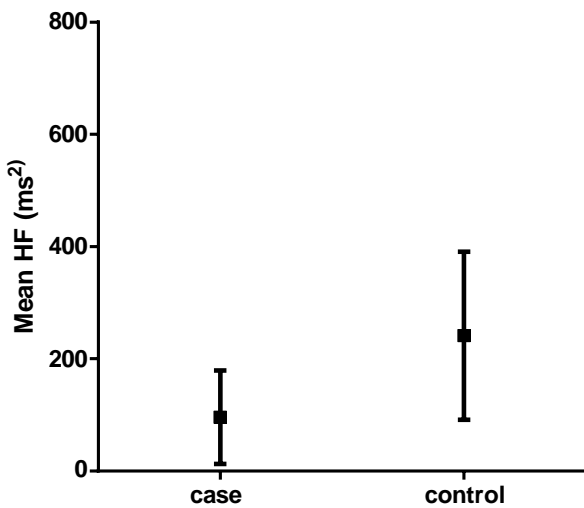
Comparison of LF (ms²) of subjects



Comparison of LF/ HF ratio of subjects



Comparison of HF (ms²) of subjects



Discussion

The ‘autonomous’ heart rate that lacks any Autonomic Nervous System control is about 100 beats per minute while tonic vagal activity lowers this rate to about 65 beats per minute (9).

Various studies have shown close association between depression and cardiovascular diseases.

Lahmeyer & Bellur (1987) observed that HR was greater during wakefulness and remain elevated in MDD patients (HR=73.04) (n=28) compared to

controls (HR=5.35) (p<0.001). As all effects were independent of age higher heart rate points to change in autonomic regulation of heart rate in depression.

Moser et al (1998) observed higher HR (76.60) in MDD patients (n=26) compared to controls (HR= 69.50). He recorded ECG for 10 minutes after 20 minutes of relaxation.

In our study, vagal tone is reduced indicated by decreased HF (decreased parasympathetic activity). Higher resting HR may be due to decreased parasympathetic activity or increased autonomous HR. It is not clear that whether our findings reflect the fact that depressed patients have less well trained hearts resulting from history of reduced physical exercise or higher autonomous heart rate is actually physiological state marker of depression.

RMSSD is reported to be a better parameter than pNN50 to convey changes in resting HRV, as it is not affected by changes in the mean heart rate and is highly reproducible. Investigators have shown that modulation of both the sympathetic and parasympathetic cardiac inputs contributes to the LF power and modulation of only cardiac parasympathetic activity to the HF power. However, investigations involving various manoeuvres have led to the association of LF power with sympathetic activity and HF power with parasympathetic activity (10). The distribution of the power and the central frequency of LF and HF are not fixed but may vary in relation to changes in autonomic modulations of heart period. The measurement of VLF, LF and HF power components is usually made in absolute values of power (milliseconds squared). The representation of LF and HF in normalized units emphasizes the controlled and balanced behaviour of the two branches of the autonomic nervous system. LF/HF ratio is the ratio of the extent of fluctuations of the sympathetic tone to that of the parasympathetic tone (11).

In our study we found decreased High Frequency (HF) which mainly contributes to parasympathetic activity and increased LF/HF ratio pointing towards Sympathovagal imbalance. We observed that HF is particularly reduced in 28 to 38 years male subjects

(25.86 ± 10.21) compared to other age group and LF/HF ratio is comparatively more in 18 to 28 years female subjects (3.65 ± 0.95). The finding of the present study is in accordance with finding of Yiming et al.

Yiming et al studied 53 MDD patients with age and sex matched healthy controls and recorded 24 hour ECG data. He speculated that the relative increase in sympathetic tone and corresponding reduction of parasympathetic tone may be a mechanism associated with this phenomenon and arrhythmia induction indicating that people with depression are more vulnerable to arrhythmias, especially supraventricular arrhythmias. This is in general agreement with the concept that there is a relationship between arrhythmia and emotional turbulence, which may be related to increased sympathetic nervous system activity (12). Hyper-responsivity of sympathetic nervous activity may also constitute a risk factor for the development or progression of CVD.

A stable endocrine system plays an important part in the overall integrity and normal functioning of the cardiovascular system (13). Potentially, many neuroendocrine pathways exist by which acute or chronic psychiatric conditions may contribute to the development of cardiovascular diseases through metabolic and homeostatic actions. Psychological stress results in hypothalamic-adrenocortical and sympathoadrenal hyperactivity (14). This can induce raised corticosteroid and catecholamine concentrations leading to multiple metabolic and autonomic effects. Chronic activation of these pathways has been shown to promote atherosclerosis by causing increases in glucose, cholesterol and free fatty acids, and a blunting of the action of insulin, besides a rise in blood pressure. Sympathoadrenal activation can also contribute to cardiovascular disease through a direct effect of on cardiac function, blood vessels, and platelets (15,16).

The primary output of the Central Autonomic Network (CAN) is mediated through preganglionic sympathetic and parasympathetic neurons that innervate the heart via the stellate ganglia and vagus nerve, respectively. The interplay of these inputs to the cardiac sino-

atrial node produces the complex variability that characterizes the HR time series (17). Thus, the output of the CAN is directly linked to HRV. Notably, vagal influences dominate cardiac chronotropic control (18). In addition, sensory information from peripheral end organs such as the heart and the immune system are fed back to the CAN. Thus, HRV is an indicator of central-peripheral neural feedback and CNS-ANS integration.

Moreover, the CAN has many features of a dynamic system. First, the components of the CAN are reciprocally interconnected, allowing for unbroken positive and negative feedback interactions and integration of autonomic responses. Second, the CAN consists of numerous parallel, distributed pathways, which permit multiple avenues to a given response. For example, a HR change of 72 to 90 beats/minute can be attained by various permutations of sympathetic and vagal input, including increased sympathetic or decreased vagal activity or some combination of the two, or by other processes such as circulating hormones. Moreover, within the CAN, direct and indirect paths can regulate output to preganglionic sympathetic and parasympathetic neurons. Third, CAN activity is state dependent and thus sensitive to initial conditions.

There are several reasons for this autonomic dysfunction in major depression. We examined our patients at rest and not during an intervention to induce a shift in autonomic modulation. Shinba and co-workers found significant correlations between depressiveness and anxiety in healthy subjects while calculating task/rest ratios (19). Our sample size was large enough and we excluded conditions which can affect HRV. Proper functioning of the sympathetic-parasympathetic dynamic balance at rest as well as in response to various internal/external stimuli is important for organisms flexibility, adaptability and health. Therefore, the autonomic imbalance typically with sympathetic over activity associated with parasympathetic hypo activation, indexed by low heart rate variability, could represent potential mechanism leading to increased risk of cardiovascular adverse outcome and all-cause mortality.

Another explanation for altered HRV in MDD might be the recently reported reduced physical fitness in these patients (20).

Conclusion

Following conclusions can be drawn from the present study.

- Increase in resting heart rate in Major Depressive Disorder patients could be due to increased sympathetic activity or due to increased autonomous heart rate.
- Major Depressive Disorder patients had decreased

parasympathetic activity than did controls.

- As Heart Rate Variability (HRV) test is simple to perform, non-invasive, we can also follow up patients & can see effect of antidepressant drugs in the long run.

Acknowledgements

Authors acknowledge the immense help received from the scholars whose articles are cited and included in the references of this manuscript. Authors are also grateful to Professor and Head of the Department of Physiology & Psychiatry for their guidance and help from time to time.

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