

Impact of Antidepressant Treatment on Heart Rate Variability in Patients with Depression - A Cross Sectional Study

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Abstract

Heart rate variability (HRV) is a non-invasive index of cardiac autonomic regulation. HRV is reduced in depression, which indicates decreased Autonomic Nervous System flexibility. It is associated with an increase in the frequency of cardiac co-morbidities. Depression medications usually take six months for complete remission, but no data on patients on antidepressants for more than six months. Therefore, it becomes necessary to determine if anti-depressants have a better impact on HRV. The current study focused on analyzing the correction of HRV parameters after six months of antidepressant therapy. A cross-sectional study was conducted from February to September 2021 at the AFT lab inpatients. They were recruited from the Psychiatry department, Victoria Hospital, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India. The sample size was calculated to be 40 (20 Patients and 20 Healthy controls). AFT was done on all participants using Power Lab equipment and analyzed using Lab Chart 8 software. Heart rate variability parameters (AFT results) were analyzed using statistical software. The results with a p-value of $>0.05\%$ were considered statistically significant and taken up for the study. 55% of the patients with depression in our study were in the age group of 18-25 years, and the mean Ham-D (Hamilton Depression Rating Scale) score was found to be 9.8. There is a reduction in autonomic function flexibility among patients who are on antidepressants when compared to healthy controls, even after six months of treatment. No conclusion could arrive on the class of antidepressant which was more beneficial owing to its effect on autonomic functions. Hence, randomized controlled studies comparing various classes of antidepressants to assess efficacy in reducing autonomic complications of depression should be taken up.

Keywords: Autonomic Nervous System, Depressive Disorder, Anti-depressive agents

Introduction

Depression may be described as sadness, loss, or anger that interferes with a person's everyday activities. Depression is a chronic illness with an annual prevalence of 5.25%.¹ In addition, there are multiple consequences of untreated depression.² Thus, choosing a treatment modality that adequately addresses all effects of depression is critical.

HRV (resting heart rate variability) is a critical indicator for mental health and cardiovascular outcomes. Autonomic neuropathy, a prevalent and underdiagnosed consequence of common medical diseases discovered by evaluating autonomic reflexes, has a reduced resting HRV.^{3,4} Heart rate variability parameters can indirectly assess autonomic nervous system

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tone.⁵ Cardiac reflex tests are gold standard diagnostic tests for cardiovascular autonomic dysfunction, but heart rate variability analysis is an easy and reliable alternative.^{6,7}

Reduced heart rate variability is a marker of decreased parasympathetic system activity, such as a reduced capacity to respond to microenvironmental changes in the autonomic system.⁸ Patients with depression show decreased HRV before antidepressant treatment.⁹ Decreased HRV indicates a risk of increased cardiovascular accidents owing to autonomic dysfunction. Therefore, the symptoms have to be treated adequately and on time. The severity of depression also plays a role in determining HRV, such that the higher the depressive symptoms, the lesser the HRV.^{10,11}

Studies have shown that Tricyclic antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI) prescribed for depression tend to have more effect on the heart rate and its variability compared to other classes of antidepressants.¹² However, there is a paucity of evidence on the level of autonomic function recovery after prolonged treatment of depression. Our study tried to compare and analyze the heart rate variability of patients on antidepressants for more than six months and healthy controls. The goal was to identify if there were any lacunae in the recovery of autonomic flexibility. The objective of the current study was to assess recovery of autonomic function after six months of antidepressant therapy.

Methods

A cross-sectional study during the study period (February to September 2021) in AFT lab in the Victoria Hospital attached to Bangalore Medical College and Research Institute, Bengaluru, and patients were recruited from the Psychiatry department in the hospitals

attached to Bangalore Medical College and Research Institute, Bengaluru. Institutional Ethics Committee Clearance was obtained (Reference number – BMCRI/PS/210/2019-2020 dated 29.01.2020), and informed consent was obtained from all the study participants.

The sample size was calculated using the RMSSD (Root Mean Square of successive RR interval differences) values for healthy controls and patients with depression as per the study by Hartmann R et al.¹³ An α was taken to be 0.05 and β was taken to be 0.1, which lead to a sample size of 36. It was then rounded off to the next multiple of ten, and the final sample size was 40 (20 Patients and 20 Healthy controls).

Age and gender were analyzed using percentages, and a Chi-square test was performed to assess the comparability between groups. In addition, Mann Whitney U test was used to determine the difference between the two groups.

Following are the participant eligibility criteria

Inclusion Criteria

1. Patients of either sex aged between 18-60 years.
2. Patients willing to give written informed consent
3. Patients on antidepressant medications for more than six months fulfilling the criteria of ICD-10 (International Classification of Diseases -10, WHO)

Exclusion Criteria

1. Patients with suicidal ideation
2. Pregnant and lactating women
3. Patients with ECG abnormalities
4. Patients with Psychotic depression, Bipolar disorder, Schizophrenia
5. Presence of epilepsy, mental retardation, mental disorders other than depression
6. Patients on drug treatment which can affect HRV

Out-patients in the Department of Psychiatry fulfilling the inclusion/exclusion criteria were enrolled in the study. Patient demographic details, clinical evaluation, disease characteristics, and treatment were recorded in the study proforma.

AFT was done on all the patients using Power Lab equipment and analyzed using Lab Chart 8 software. Instructions given were as follows - participant should withhold coffee and nicotine at least 3-4 hours for at least 8 hours before testing, should not have food at least 2 hours before the test, and if possible, sympathomimetic/ sympatholytic drugs should be stopped for 24-48 hours before testing and anticholinergic for 48 hours.⁵ The subject was seated down for 30 min in a quiet room with neutral temperature and humidity, and the patient's pulse rate and blood pressure were recorded.

The AFT procedure followed was also described as follows. The patient was made to lie in a supine position, the chest area was exposed to all the metal, and magnetic objects were removed. ECG leads were attached to the participant, and instructed to keep their eyes open and not fall asleep.

Baseline Blood Pressure (BP) was recorded before the start of each procedure, and 5 minutes of rest in between each procedure so that the BP goes to the baseline. The recording was taken for a minimum duration of 20 minutes. The first five minutes were empirically omitted from the analysis. HRV analysis was performed every 5 min intervals starting from 5 min. One 5 min segment for analysis was selected with the least number of outliers and no limb or chest movements leading to artifacts.

Results and Discussion

A total of 40 study participants underwent HRV analysis. The mean age was 25.85 and 23.68 years in the antidepressant arm and healthy control arm, respectively. 70% of the patients had a Ham-D (Hamilton Depression Rating Scale) of 8-16. A ham-D score of less than 7 indicates the patient has remission (no depressive symptoms), and a score of 8-16 indicates (mild depression). 60% of the patients had been under treatment for depression for more than a year.

Moreover, age and sex distribution was also depicted in Table 1. A chi-square test was performed to assess the comparability between the two groups. The Chi-square value was found to be 0.5169, but the p-value was not significant at a 95% confidence interval.

The usual discussion may not be possible because of the lack of similar studies in the past. Though there are studies on HRV and major depression, none of them measure the impact of antidepressants on HRV. One study by Hartmann et al. does measure but only takes readings at the end of 2 weeks of antidepressant treatment.¹³ Antidepressants take at least to show improvement in depressive symptoms, but it may take around six months for complete remission.¹⁴ Therefore, we have compared participants with more than six months of treatment with antidepressant therapy, which was not done before. Hence, ours is a novel study and a first of its kind.

There are two issues with a head-to-head comparison of AFT studies: device calibration and non-uniform units. Most devices are calibrated using a minimum of 100 human participants at that particular center. Differences can be based on the device brand, build, and the sample population considered. The parameters measured are SDDN (Standard deviation of NN intervals), RMSSD

Table 1. Demographic Parameters of the Study Subjects

		Antidepressant Arm	Healthy Control Arm	Total
Age	< 25 years	11	10	21
	> 25 years	9	10	19
Gender	Males	13	11	24
	Females	7	9	16

Table 2. Heart Rate Variability Parameters

	Antidepressant - Mean (SD)	Healthy Control - Mean (SD)	P value
Heart rate (bpm)	77.31 (9.13)	80.83 (21.7)	0.79
SDDN (in ms)	84.94 (10.25)	133.83 (38.13)	<0.001*
RMSSD (in ms)	50.46 (5.48)	31.23 (12)	<0.001*
LF (in ms ²)	990.17 (423.7)	1116.48 (398)	0.42
HF (in ms ²)	1351.7 (350)	920.2 (219)	<0.001*
LF:HF ratio	0.80 (0.46)	0.97 (0.41)	0.17

* P-value <0.05 was considered statistically significant

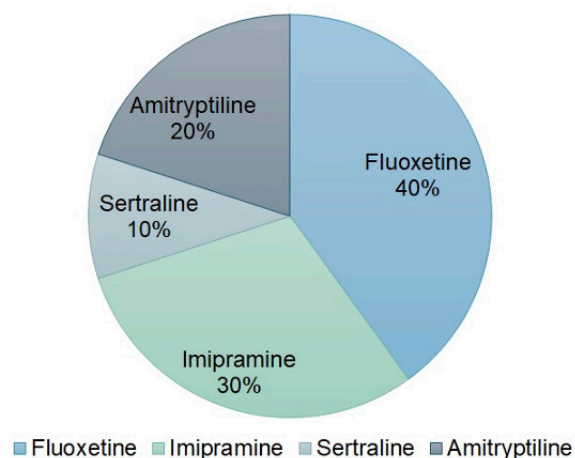


Figure 1. Antidepressants prescribed for ≥ 6 months for Major Depressive Disorder

(Root Mean Square of successive RR interval differences), LF (Relative power of the low-frequency band), HF (Relative power of the high-frequency band), and HF:LF ratio (ratio of LF to HF). SDDN and RMSSD are measured in milliseconds, whereas HF and LF are measured using four units (Percentage, Millisecond squared, Normal Units, and Hertz).

Our study clearly demonstrates that though antidepressants tend to bring HRV back to normal, the damage to autonomic function cannot be completely reversed. There is a statistically significant difference between SDDN, RMSSD, and HF values between a healthy adult and a patient with depression on antidepressants for more than six months, as depicted in Table 2.

A study by Hartmann et al. measuring the effect of antidepressants in patients before treatment and two weeks after treatment show normalization of HRV parameters and improvement of symptom severity of depression in correspondence to an increase in HRV parameter values. SDDN and RMSSD values were 50.46 versus 48.03 (Healthy versus depression) and 41.547 versus 28.872 (Healthy versus depression), respectively. This study shows a significant difference in HRV between healthy adults and depressed patients not on treatment, and our study states that there is a statistically significant difference in HRV between healthy adults and patients on antidepressants for six months.¹³

There is a link between depression and alterations in autonomic cardiac control.¹⁵ Autonomic function influences depression risk rather than the other way around.¹⁶ The administration of antidepressant medications may help to minimize the correlation between depression severity and cardiovascular health.¹⁷ Therefore, in the management of

depression, autonomic symptoms should be taken into account.¹⁸

Depression severity and the concomitant risk of mortality due to cardiac and vascular complications are clearly evident. Therefore, in some populations, depression may be the only marker of an underlying cardiovascular disease.¹⁹ In addition, our study sheds light on diagnosing autonomic dysfunction in patients with depression with no other clinical suspicion. Altered mood states are often associated with multiple physical dysfunctions, most of which are attributed to a central biological substrate leading to depression. For example, it is seen that depression promotes vagal withdrawal leading to a reduction of heart rate variability indices.²⁰

Although there is a clear understanding of how depression causes autonomic dysfunction, scarce studies are in the direction of how it can be reversed. Exercise, customized physiotherapy, and pressure stockings are non-specific treatment options for autonomic dysfunction.

Treatment with steroids, immunosuppressants, and intravenous immunoglobulins should be speculated if an immune mechanism is speculated.²¹ Treatment of autonomic dysfunction though being beyond the scope of our current study, has to be augmented with antidepressants for depression.

The strengths of the current study were cheaper and easier to conduct due to the cross-sectional study. In addition, healthy controls were used to prevent errors due to device calibration. However, the limitations were as follows - small sample size, data before starting antidepressant treatment, and HRV on follow-up visits would have given a more precise answer to our research question.

In addition, to determine which antidepressant helped improve autonomic functions, a randomized controlled design would have been better. Most of the studies measured HRV parameters only after a month of treatment. Therefore, a randomized controlled trial can be taken up in the future involving only newly diagnosed patients with baseline HRV variables and HRV changes with the drug prescribed at multiple follow-up visits. If more research findings support that HRV is not reverted despite antidepressant therapy, an effort should be made to supplement antidepressant therapy with specific treatment for autonomic dysfunction.

Conclusion

There is a reduction in autonomic function flexibility among patients who are on antidepressants for more than 6 months when compared to healthy controls. Statistically significant evidence was obtained that RMSSD and HF were more markedly affected. No conclusion could arrive on the class of antidepressants and their effect on autonomic functions.

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Conflict of Interest

None

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