Research Article

Cardiac autonomic dysfunction assessed by heart rate variability in major depression

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ABSTRACT

Background: Very few studies in Indian population have assessed cardiac autonomic functions in depressed patients. Extent of autonomic function derangement needs to be assessed along with any possibility of correlation of such dysfunction with severity of depressive disorder as conflicting results are published on this problem. **Objectives:** The current research work was, therefore, undertaken to study cardiac autonomic functions by heart rate variability (HRV) in major depressive disorder (MDD) without other comorbid conditions in comparison to healthy controls and to find out any correlation between altered HRV parameters and severity of depression. **Materials and Methods:** Autonomic functions were assessed by studying time domain and frequency domain parameters in 60 patients of MDD without comorbid conditions and compared with 35 healthy controls. Association between severity of depression and HRV parameters was assessed in mild, moderate, and severe depression. **Results:** Most of the time and frequency domain HRV parameters showed highly significant alterations as compared to control group (*P* values ranging from <0.01 to 0.0001). Statistically significant differences were noted in low, moderate, and high depression. **Conclusion:** HRV parameters are affected in MDD showing reduced variability with altered sympathovagal balance. Alteration in autonomic activity reflected in altered HRV parameters is associated with severity of depression suggesting possibility of HRV as a prognostic tool in the management of these patients.

KEY WORDS: Autonomic Functions; Hear Rate Variability; Major Depression

INTRODUCTION

Major depressive disorder (MDD) is reported to be associated with increased cardiovascular morbidity and mortality.[1] This has been hypothesized to be because of alterations in the autonomic nervous system among depressed persons. Such alterations are believed to reduce heart rate variability (HRV), a well-known prognostic risk factor for cardiovascular disease and mortality.[2]

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Autonomic function assessment by HRV is relatively new and not used in clinical practice in most of the medical setups in India. Very few studies have been carried out to assess cardiac autonomic functions in depressed patients in Indian population.[3,4] The extent of autonomic function derangement also needs to be assessed along with any possible correlation of degree of autonomic dysfunction with the severity of depressive disorder. Conflicting results are available about correlation of autonomic dysfunction and severity of depression.[3,5] Thus, there is a need to add more research data on HRV in this group of patients, particularly in Indian population.

The aim of this study was, therefore, to study cardiac autonomic imbalance in patients with major depression by comparing their HRV measures (time and frequency domain measures) with mentally and physically healthy age and sex

matched controls and to find out the possible relationship of severity of depression with the extent of autonomic imbalance.

MATERIALS AND METHODS

Subjects

A total of 60 patients diagnosed to have MDD by psychiatrist as per DSM-IV-TR criteria[6] were included in the study. Other inclusion criteria were normal findings on physical examination, electrocardiogram (ECG) and no history, signs, or symptoms of cardiovascular, pulmonary, or endocrine diseases as assessed by thorough history, clinical examination and relevant investigations such as blood sugar and thyroid-stimulating hormone. All patients had at least two prior major depressive episodes and had been taking selective serotonin reuptake inhibitors (SSRIs) for at least 1 year. Tricyclic antidepressants have been reported to reduce HRV; however, most of the studies have not associated reduced HRV with SSRIs.[7] Therefore, the patients undergoing treatment with SSRIs were included in the study group. Patients under SSRI treatment, for at least 1 year, further helped to ascertain the presence of well-diagnosed MDD. 35 physically healthy volunteers assessed by thorough history, clinical examination, and relevant investigations served as comparison subjects. None of the comparison subjects had a mental disorder, as confirmed by a psychiatric interview by psychiatrist. Comparison subjects taking sedatives or anxiolytics, and abusing alcohol, tobacco, or drugs as confirmed by thorough history were excluded from the study.

Study Design

Cross-sectional case-control study.

Study Protocol

Clearance of Institutional Ethical Committee was obtained. A depression scale in vernacular developed by National Institute of Mental Health, India, based on Beck's Depression Inventory which has 96 items was administered to assess subjects' self-reported severity of depression. The subjects were divided into three groups as low, moderate, and high depressive group on the basis of score. Males with scores between 87 and 152 were considered as low depression patients while for females low depression scores were between 140 and 187. Moderate depression scores for males were between 153 and 232 while for females moderate depression scores were 188-251. Scores above 232 for males and 251 for females were considered as high depression.[8] Informed consent was obtained from all participants of the study.

Digital ECG recordings during resting supine position were obtained for cases as well as controls on a computerized data acquisition and analysis system (Polyrite, Recorders and Medicare Systems, Chandigarh, India) in quiet room after the subject had 10 min of adjustment in the supine position. The recordings were made between 10:00 am and 12:00 noon for all the participants to nullify diurnal influences. In female subjects, recording was done during the proliferative phase of the menstrual cycle.

Technical specifications recommended by task force on HRV[9] for recording digital ECG were followed. Both frequency and time domain parameters of HRV were analyzed. For frequency domain analysis, fast Fourier transformation was done using Welch's periodogram method with a Hann window. Entire spectrum of frequencies was divided into three major bands, very low frequency (LF) (0-0.04 Hz), (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.4 Hz). From the same data, time domain measures of HRV were obtained. In the time domain, the SD of normal-to-normal RR intervals (SDNN) was taken as an index of overall HRV. Root mean square of successive differences (RMSSD) and pNN50 were also calculated. For computing HRV indices during supine rest, recommendations of the task force on HRV were followed.[9]

Statistical Analysis

Study group and control group were compared for anthropometric parameters such as age, height and weight with Student's *t*-test and for sex with Chi-square test. Normality of data distribution was tested for all the parameters by Kolmogorov–Smirnov test. As data distribution for different HRV parameters was not having normal distribution, non-parametric test, Mann–Whitney *U*-test, was used for comparison of study parameters between two groups. For comparison of HRV parameters and autonomic function tests in low, moderate, and high depression groups, Kruskal–Wallis non-parametric test was used. The statistical calculations were done using Data Analysis tool of Microsoft Excel and Systat 12 (Systat Software, Inc., Chicago).

RESULTS

Study and control groups were similar for basic parameters such as age, sex, height, and weight ($P > 0.05$, Table 1). HRV parameters in depression and control group are shown in Table 2 (time domain) and Table 3 (frequency domain). HRV in low, moderate, and high depression groups is presented in Table 4 (time domain) and Table 5 (frequency domain).

DISCUSSION

Measures of HRV are more sensitive to subtle changes than traditional tests of autonomic function.[10] SDNN, which encompasses all components responsible for RR variability, is a simple time domain measure of overall HRV. High-frequency spectral power reflects parasympathetic

Table 1: Comparison of study and control group

Parameter	Mean±SEM		Student *t*-test	Remark
	Control (*N*=35)	Major depression (*N*=60)		
Age (years)	34.14±1.063	37.8±1.389	*t*=1.727 *P*=0.0873	NS
Height (cm)	159.54±1.825	163.4±1.322	*t*=1.714 *P*=0.0848	NS
Weight (kg)	58.02±1.24	57.1±1.06	*t*=−0.538 *P*=0.591	NS
Sex				
Male	11	25	Chi-square test *P*=0.321	NS
Female	24	35		

SEM: Standard error mean

Table 2: Resting supine time domain heart rate variability parameters in study and control group (±standard error of mean)

Parameters	Control group	Depression study group	Mann–Whitney *U*-test	Remark
Resting supine heart rate	70.71±1.554	79.56±2.031	Student *t*-test	*P*=0.00038
Maximum RR (sec)	0.992±0.0202	0.862±0.0228	*U*=526 *Z*=4.04	*P*=0.0001
Minimum RR (sec)	0.733±0.0119	0.680±0.0167	U=625 *Z*=3.28	*P*=0.001
Mean RR (sec)	0.860±0.0166	0.777±0.020	*U*=633 *Z*=3.21	*P*=0.0013
Maximum RR/minimum RR ratio	1.355±0.0212	1.265±0.0128	*U*=626.5 *Z*=3.26	*P*=0.0011
SDNN (ms)	43.406±2.1044	32.143±1.704	*U*=561 *Z*=3.77	*P*=0.0002
pNN50 (%)	12.782±1.714	7.226±1.227	*U*=594.5 *Z*=3.51	*P*=0.0004
RMSSD (ms)	35.014±1.425	28.0101±2.2013	*U*=714 *Z*=2.59	*P*=0.0096

Table 3: Resting supine frequency domain heart rate variability parameters in study and control group (±standard error of mean)

Parameters	Control group	Depression study group	Mann–Whitney *U*-test	Remark
HR variance (total power) (ms^2)	2034.7±198.89	1219.57±115.12	*U*=561 *Z*=3.77	*P*=0.0002
Absolute LF power (ms^2)	181.55±30.129	97.2407±14.342	*U*=605 *Z*=3.43	*P*=0.0006
Absolute HF power (ms^2)	80.076±17.541	31.929±4.993	*U*=557 *Z*=3.8	*P*=0.0001
LF%	8.139±0.585	9.918±1.3001	*U*=1017.5 *Z*=0.25	*P*=0.8026
HF%	3.306±0.406	3.1833±0.5225	*U*=851 *Z*=1.53	*P*=0.126
LF/HF ratio	2.8091±0.1237	3.2977±0.111	*U*=1404.5 *Z*=−2.73	*P*=0.0063

modulation of RR interval at respiratory frequency. LF power in absolute unit of power quantifies baroreflex-mediated modulation of RR interval in 0.04-0.15 Hz range. Changes in sympathetic as well as vagal nerve traffic to the heart are thought to contribute to LF power. Vagal activity is the major contributor to the HF component. Total power calculated as the sum of LF and HF power is also an index of overall HRV.[9]

This study depicted that all the time domain HRV parameters, viz., maximum RR, minimum RR, mean RR, max RR/min RR ratio, SDNN, pNN50, and RMSSD showed very highly

Table 4: Resting supine time domain heart rate variability parameters in low, moderate, and high depression patients (±standard error of mean)

Parameters	Low depression	Moderate depression	High depression	Kruskal-Wallis test
Maximum RR (sec)	0.938±0.044	0.882±0.038	0.812±0.025	*H*=4.82 *P*=0.0898
Minimum RR (sec)	0.686±0.032	0.692±0.027	0.668±0.019	*H*=0.47 *P*=0.7906
Mean RR (sec)	0.821±0.04	0.793±0.033	0.746±0.022	*H*=2.64 *P*=0.2671
Maximum RR/minimum RR ratio	1.37±0.029	1.273±0.024	1.215±0.014	*H*=13.92 *P*=0.0009
SDNN (ms)	43.133±4.064	33.81±3.204	26.011±1.663	H=12.06 *P*=0.0024
pNN50 %	13.454±4.238	8.313±1.803	3.630±1.127	*H*=3.85 *P*=0.1459
RMSSD (ms)	34.594±4.716	27.922±3.251	25.301±3.115	*H*=3.5 *P*=0.1738

SDNN: SD of normal-to-normal RR intervals, SD: Standard deviation, RMSSD: Root mean square of successive differences

Table 5: Resting supine frequency domain heart rate variability parameters in low, moderate, and high depression patients (±SEM)

Parameters	Low depression	Moderate depression	High depression	Kruskal-Wallis test
HR variance (total power) (ms^2)	2025.69±352.64	1369.654±233.63	745.75±81.700	*H*=12.06 *P*=0.0024
Absolute LF power (ms^2)	193.55±50.38	91.67±14.07	61.419±10.812	*H*=10.95 *P*=0.0042
Absolute HF power (ms^2)	61.34±18.134	35.79±6.19	16.058±2.049	*H*=14.67 *P*=0.0007
LF%	11.05±3.065	8.813±1.410	10.415±2.083	*H*=1.47 *P*=0.4795
HF%	3.654±1.205	3.5±0.927	2.703±0.449	*H*=1.34 *P*=0.5117
LF/HF ratio	3.221±0.185	2.915±0.170	3.668±0.191	*H*=7.61 *P*=0.0223

LF: Low frequency, HF: High frequency, HR: Heart rate, SEM: Standard error mean

significant differences as compared to HRV parameters in control groups. The probability of difference in study and control group ranged from $P < 0.01$ to $P = 0.0001$ (Table 2).

Similarly, all the resting supine frequency domain HRV parameters in depression group except LF% and HF% showed statistically very highly significant differences as compared to control group. LF% showed increase in depression group, whereas HF% showed decrease in depression group, though these differences were not statistically significant (Table 3).

When HRV parameters were studied according to the severity of depression, declining trend was observed in HRV parameters from low to moderate to high depression. SDNN, total power, LF power, HF power, and LF/HF ratio showed statistically significant difference in low, moderate, and high depression (Tables 4 and 5). Alteration of most of the HRV parameters in low depression was very less as compared to alteration in moderate and high depression.

Resting HR in the study group was statistically more in depression as compared to controls. Similar observations of higher resting HR in depression have been recorded earlier by many workers.[11-13] Increased resting HR is a marker of hemodynamic and autonomic nervous system states that can cause elevations in cardiovascular mortality by inducing atherosclerosis and producing rhythm disturbances.[14] Tachycardia *per se* increases cardiac work and represents a marker of increased sheer force in large vessels that, independently of blood pressure, can be conducive to high arterial rigidity and thus atherosclerosis.[15]

In depressed patients, there is considerable decrease in parasympathetic activity as can be seen from decreased HF power and RMSSD components of HRV in comparison with healthy control group. Depressed mood has been shown to be related to the magnitude of decrease in parasympathetic cardiac control during stressors in healthy men and women.[16] RMSSD which primarily reflects parasympathetic activity has been reported to be lower in severely depressed patients

compared with those with mild depression and healthy controls,[13] which is corroborated by our findings.

These findings are in conformity with observations made by most of the studies.[17] Nahshoni, et al.[1] have done a remarkable study in which comparison has been made between normal healthy controls, major depression patients and mentally healthy heart transplant recipients. Their results supported the hypothesis that cardiac autonomic imbalance (reduced vagal modulation) to the extent of cardiac neuropathy is present in depression. They opined that autonomic cardiac regulation in severe depression patients is like denervated heart. However, Sayar et al. have reported contradictory finding that in physically healthy depressed adults HRV does not differ from mentally healthy subjects.[18] Jangpangi et al.[4] have also reported similar SDNN and RMSSD values in physically healthy depressed patients and physically and mentally healthy controls.

Udupa et al.[3] have reported no significant correlation between severity of depression and autonomic parameters. Contrary to our results, this finding may be because of newly diagnosed patients of depression in their study where the duration of the diseased state was not known and probably patients were not having long standing MDD. However, association of reduced HRV measures and severity of depression has been noted by Kemp et al. in a meta-analysis.[19]

Although sample size was limited, strength of the study was well diagnosed long-standing major depression in the study group with removal of the confounding factors like drugs with effect on HRV and finding out association of HRV derangement with the severity of depression in view of previous conflicting results.

CONCLUSION

To conclude, this study clearly demonstrates that depression is associated with a significant cardiac autonomic imbalance in spite of the limitations of the study in the form of hierarchically lower study design. Although exact mechanisms underlying altered autonomic functions in depression are not clear, Srinivasan has postulated "HRV to be a psychophysiological marker for adaptive emotional regulation as it indexes integration of central nervous system and autonomic nervous system. Vagally mediated component of HRV reflects adaptivity (maladaptivity) to environmental challenges and indexes ability (inability) to modulate affect responses."[20] In addition to establishing an association between depression and altered HRV parameters, the study has also demonstrated a direct relationship of severity of depression with the extent of autonomic imbalance suggesting possibility of HRV as a prognostic tool in the management of these patients. Future research on autonomic alterations in depressed patients involving larger sample size and prospective studies is needed to know the effect of different treatment modalities and to study the role of alternative and complementary methods such as yoga and meditation in altering the autonomic balance favorably.

REFERENCES

1. Nahshoni E, Aravot D, Aizenberg D, Sigler M, Zalsman G, Strasberg B, et al. Heart rate variability in patients with major depression. Psychosomatics. 2004;45(2):129-34.
2. Pozuelo L, Zhang J, Franco K, Tesar G, Penn M, Jiang W. Depression and Heart disease: What do we know and where are we headed? Cleve Clin J Med. 2009;76(1):59-70.
3. Udupa K, Satyaprabha TN, Thirthalli J, Kishore KR, Lavekar GS, Raju TR, et al. Alteration of cardiac autonomic functions in patients with major depression: A study using heart rate variability measures. J Affect Disord. 2007;100(13):137-41.
4. Jangpangi D, Mondal S, Bandhu R, Kataria D, Gandhi A. Alteration of heart rate variability in patients of depression. J Clin Diagn Res. 2016;10(12):CM04-06.
5. Yeh TC, Kao LC, Tzeng NS, Kuo TB, Huang SY, Chang CC, et al. Heart rate variability in major depressive disorder and after antidepressant treatment with agomelatine and paroxetine: Findings from the Taiwan Study of Depression and Anxiety (TAISDA). Prog Neuropsychopharmacol Biol Psychiatry. 2016;64:60-7.
6. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. 4th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2000. p. 369-76.
7. Roose SP. Depression, anxiety, and the cardiovascular system: The psychiatrist's perspective. J Clin Psychiatry. 2001;62 Suppl 8:19-22.
8. Karim S, Tiwari R. Manual for depression scale. Agra Psychol Res Cell. 1986;1:1-10.
9. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Eur Heart J. 1996;17(3):354-81.
10. Srinivasan K, Vaz M, Sucharita S. A study of stress and autonomic nervous function in first year undergraduate medical students. Indian J Physiol Pharmacol. 2006;50(3):257-64.
11. Lehofer M, Moser M, Hoehn-Saric R, McLeod D, Liebmann P, Drnovsek B, et al. Major depression and cardiac autonomic control. Biol Psychiatry. 1997;42(10):914-9.
12. Moser M, Lehofer M, Hoehn-Sarric R, McLeod DR, Hildebrandt G, Steinbrenner B, et al. Increased heart rate in depressed subjects in spite of unchanged autonomic balance. J Affect Disord. 1998;48(2):115-24.
13. Carney RM, Freedland KE, Stein P, Skala JA, Hoffman P, Jaffe AS. Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosom Med. 2000;62(5):639-47.
14. Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens. 1997;15(1):3-17.
15. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Noce CL, et al. Heart rate as a predictor of mortality: The MATISS project. Am J Public Health. 2001;91(8):1258-63.
16. Hughes JW, Stoney CM. Depressed mood is related to

high-frequency heart rate variability during stressors. Psychosom Med. 2000;62(2):796-803.
17. Nemeroff CB. Recent findings in the pathophysiology of depression. Focus. 2008;4(1):1-12.
18. Sayar K, Gulec H, Gokce M, Ismail AK. Heart rate variability in depressed patients. Bull Clin Psychopharmacol. 2002;12(3):130-3.
19. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. Biol Psychiatry. 2010;67(11):1067-74.
20. Srinivasan K. Childhood psychopathology and autonomic dysregulation: Exploring the links using heart rate variability. J Indian Assoc Child Adolesc Ment Health. 2007;3(4):96-104.

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