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HEART RATE VARIABILITY RESPONSES TO STANDING ARE ATTENUATED IN DRUG NAIVE DEPRESSED PATIENTS

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Abstract : Depression has been linked to altered cardiac autonomic regulation. Previous studies have been inconsistent in terms of measurement of heart rate variability (HRV), selection of depressed patients with cardiac disorders and not controlling for co-morbid conditions such as substance use and anxiety disorders. The objective of this study is to compare the effect of posture on spectral measures of HRV in drug naive healthy patients with major depression with age and gender matched healthy controls. Spectral measures of HRV in supine position and with active standing were obtained (using Task force recommendations). Repeated measure ANOVA revealed an attenuated response in HRV parameters (HF normalized units & LH/HF ratio) to active standing in depressed subjects compared to healthy controls. We conclude that there is an impaired parasympathetic modulation in response to physiological maneuver (orthostatic challenge) in drug naive subjects with major depression (co-morbid medical or psychiatric conditions) compared to healthy controls.

Key words : major depression, autonomic nervous system, heart rate variability, posture, parasympathetic, sympathovagal balance

INTRODUCTION

Longitudinal studies have shown that depression increases the risk of coronary artery disease (1-3). Depression following myocardial infarction is associated with a three-to-four fold increase in the risk of mortality (4-6). Among the various psychosocial risk factors linked to coronary artery disease (CAD) the most robust

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evidence exists for depression (7) and this was independent of smoking and obesity (8). Altered cardiac autonomic regulation may be one of the several possible mechanisms in the link between depression and CAD (9, 10).

Studies have shown that attenuated cardiac vagal modulation is a risk factor for mortality in patients with CAD (11-13) and that decreased Heart Rate Variability (HRV) has been found to be a significant predictor of new cardiac events in the general population (14). While several studies suggest that HRV is markedly reduced in patients with CAD with co-morbid depression compared to those without depression (15-17); others have found no association (18). Similar inconsistencies are noted in physically healthy depressed patients. Some investigators have noted decreased cardiac parasympathetic activity both at rest (19) and after various physiological manoeuvres (20-21); while others did not find any differences in patients with depression (22-25). The inconsistent findings are reflected in the conclusions from two recent meta-analyses. While one observed a very modest association between depression and reduced HRV; depression alone was accounting for only 2% of variance in cardiac vagal control (26); the other study concluded that depressed patients had lower HRV and HF power compared to healthy controls (27). A recent study noted that the association between depression and reduced cardiac vagal control was largely the effect of antidepressant medication and that the severity of depression was not associated with abnormalities in cardiac autonomic control; prompting much discussion in the literature (27-32). There may be several reasons for these inconsistencies. Studies done prior to the Task Force recommendations (33) have used different frequency ranges and without normalization for total power (20,21); while others have used only the time domain method (24, 25, 34). Few studies have used physiological manoeuvres to study differences in HRV measures between depressed subjects and normal controls (20, 21). While simple HRV measures under resting conditions predicted cardiovascular disorders and mortality; while others have noted that various physiological maneuvers such as postural change tend to reveal between group differences in cardiovascular autonomic control than at rest (35-37). Finally, patient characteristics such as melancholic features (20), co-morbid psychiatric conditions such as anxiety (38) and substance abuse, antidepressant medications (22, 39) and age (39) may significantly influence HRV measures. The purpose of the study was to compare the effect of posture on spectral measures of heart rate variability using current recommendations (33) in drug naive patients with major depression who were physically healthy with age and gender matched normal controls. Previous studies have shown that indices based on HRV in response to supine and upright posture can be used as a measure of cardiac sympathetic and vagal activity and hence of sympathovagal balance (40). In addition, this study addressed some of the methodological issues including using normalized data for total power and physiological maneuvers such as active standing.

METHODS

Subjects

Forty-six patients diagnosed with major

depression and gender matched healthy controls were enrolled. Informed written consent was obtained from all the participants and the institutional ethics review board approved the study.

Subjects and healthy controls selection

Drug naive patients with a possible diagnosis of major depression were referred to the study team by psychiatrists from the out-patient clinic of St. John's Medical College Hospital, a tertiary care hospital located in Bangalore, India. Using MINI PLUS (41) interview a research investigator confirmed the primary diagnosis of major depression as per DSM-IV TR criteria (42). Subjects with psychotic symptoms and or co-morbid anxiety, alcohol and other substance abuse disorder and pregnant or lactating females were excluded from the study. Patients with a diagnosis of bipolar depression were also excluded. Patients had to obtain a score of >14 at baseline on the 17-item Hamilton Depression Rating Scale to be included in the study (43). All patients were otherwise physically healthy as assessed by history, clinical examination and laboratory investigations including an electrocardiogram. Age and gender matched healthy controls were recruited from the staff and relatives of the hospital and were screened with the General Health Questionnaire 28 item version to rule out psychological distress (44).

Measurement of HRV

All recording took place in the research laboratory located in the department of psychiatry in the morning after an overnight fast and subjects were advised to abstain from smoking and caffeinated beverages for 12 hours. Our previous study showed that resting HRV measures following cessation of smoking for 12 hours was comparable to that of non-smokers (45). In the case of female subjects, HRV was measured during the early follicular phase of the menstrual cycle (i.e., 1-2 days after the menstrual phase). After 10 minutes of rest in the laboratory, the subjects underwent a lead II ECG recording for 10 minutes in the supine posture after which the subjects actively stood up without support. Details regarding electrocardiograph (ECG) signal acquisition and power spectral analysis of heart rate time series are reported elsewhere (37, 46). Briefly, the ECG signal was amplified through the AC-6016 module of the Nihon-Kohdon RM 6000 polygraph system (Nihon Kohdon, Tokyo, Japan) and a signal manifold, which digitized the signal using a CIO-AD Jr A/D card (CVMS, World Precision Instruments Inc., Sarasota, FL, USA). The digitized signal was subjected to a spectral analysis after verifying the waveform characteristics using a specific software (CVMS, World Precision Instruments Office, Sarasota, FL, USA). The data were digitized online at 1000 Hz using a personal computer. 256-point data sets were created after the data segments of 128 s duration were sampled at 2 Hz. The linear trend was removed from each data set to avoid its contribution to the low frequency power. The 'spectral leakage' was attenuated by using a Hanning window in the time domain. A direct Fast Fourier Transform method was used to evaluate the Spectral analysis. The average of spectra obtained for the different data sets were used to reduce variance and to sharpen reproducible spectral peaks. Power was calculated in three bands, namely very low frequency power (VLF), low

frequency power (LF) and high frequency power (HF). The 0.04-0.15 band is referred to as the LF power and the 0.15-0.4 Hz band is referred to as the HF power. LF and HF power were also expressed in normalized units, which represent the relative value of each power component in proportion to the total power minus the VLF component (33). We calculated the ratio of LF and HF power in normalized units as a reflection of sympathovagal activity.

Statistical analysis

Normality of HRV parameters was examined using Kolmogrov-Smirinov test and they were not normally distributed. Hence, the variables were expressed as median and interquartile range. Spectral measures of HRV of patients with major depression were compared with age and gender matched control subjects using Mann-Whitney U test (two tailed). The effect of posture and of group (major depression vs. age and gender matched control) on log transformed HRV parameters was tested using repeated measure ANOVA and the interaction effect of posture and group was also examined in this model. BMI which was different between the groups was considered as a covariate in the model. The null hypothesis was rejected at $P<0.05$. Data was analyzed using SPSS for Windows (SPSS software package, version 15, SPSS Inc., Chicago, Illinois).

RESULTS

The average age of both depressed and healthy control groups was 36 SD 10 years (95% CI, 33.7 to 37.9). The mean BMI of depressed group was significantly lower than that of the healthy control (21.9 SD 3.5 vs 23.6 SD 3.8, P=0.031, (95% CI, –3.24 to –0.15]). The mean HDRS score in the depressed subjects was 22.77 SD 4.9 and the controls was Zero (95% CI, 21.31 to 24.22).

HRV measures in supine posture and standing separately did not demonstrate any differences between the two study groups. Repeated measure ANOVA revealed that there was no significant difference between the groups for any of the HRV parameters. However, HF absolute units and HF normalized units were lower on active standing while LF absolute units and LF/HF ratio were higher. There was a significant interaction effect between the groups and posture for HF normalized units ($F=4.8$, df = (1, 86), $P=0.032$) and LH/HF ratio ($F=5.4$, df = (1, 86), $P=0.023$). The drop in HF normalized units from supine to standing was moderately higher (effect size = 0.27) in the control group as compared to the depressed group [Fig. 1 (a)]. Similarly, the increase in LH/HF ratio from supine to standing was significantly higher in the control group as compared to depressed group [Fig. 1(b)]. There was no significant interaction for the other spectral measures of HRV (Table I). The interactions remained significant even after adjusting for BMI, which was different between the two groups.

DISCUSSION

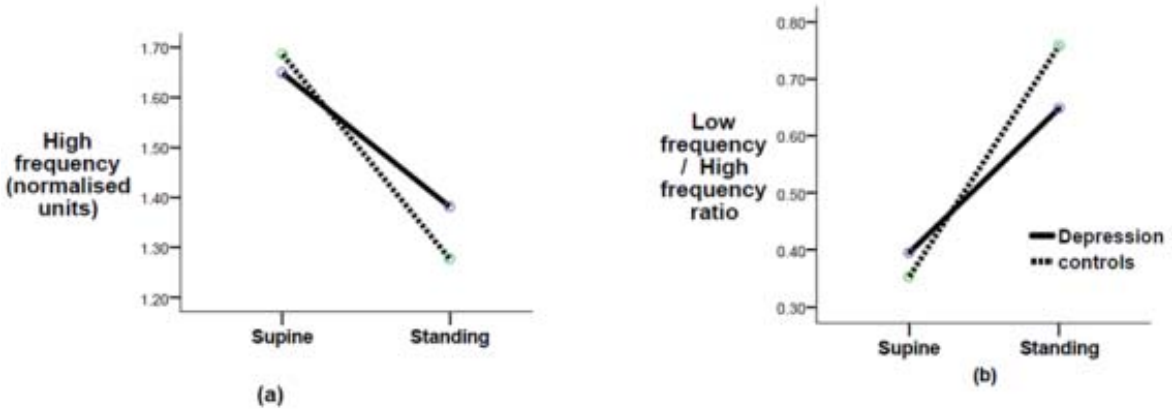
The present study examined the effect of posture on various heart rate variability measures in patients diagnosed with major depression without concomitant cardiovascular conditions compared to age and gender matched healthy controls. We found that

TABLE I: Comparing the spectral measures and effect of posture between depressed and control subjects.

Heart rate variability	*Control Group*		*Depression Group*		*Group effect (G) (P value)*	*Effect of posture (P) (P value)*	*G×P 'P' value*
	Supine	*Standing*	*Supine*	*Standing*			
LF power (ms^2)	291.62 (157.87, 802.16)	615.14 (260.28, 914.57)	297.78 (181.37, 619.07)	354.51 (166.12, 597.23)	0.27	0.16	0.08
HF power (ms^2)	332.79 (112.01, 725.21)	116.97 (40.14, 274.37)	301.10 (138.97, 534.44)	113.75 (47.08, 318.01)	0.69	< 0.001	0.64
Total power (ms^2)	987.73 (511.39, 2098.09)	1074.83 (702.96, 1621.25)	951.43 (511.21,1610.46)	993.20 (491.76, 1403.90)	0.44	0.36	0.40
LF nu	58.41 (47.17, 67.06)	88.49 (73.87, 97.83)	57.79 (43.95, 75.12)	82.80 (67.31, 93.99)	0.42	< 0.001	0.180
HF nu	50.86 (40.63, 62.64)	22.86 (11.42, 36.11)	50.22 (33.06, 62.30)	27.45 (16.51, 40.10)	0.47	< 0.001	0.03
LF/HF ratio	1.17 (0.76, 1.62)	4.07 (2.24, 8.49)	1.16 (.72, 2.28)	2.93 (1.65, 5.26)	0.46	< 0.001	0.02
Heart rate (bpm)	71.53 (67.91, 75.75)	84.77 (74.64, 92.75)	71.59 (67.80, 77.17)	86.96 (81.21, 95.73)	0.26	< 0.001	0.94

Data are Median, 25th–75th percentile; Statistical test used is Repeated measures ANOVA; G×P = Group × Effect of Posture interaction; LF, low frequency; HF, high frequency; nu, normalized unit.

Fig. 1: Effect of posture on High frequency (normalized units) and Low and High frequency ratio between the depressed and the healthy controls.



posture had a varying effect on heart rate variability measures between depressed and healthy controls. There was a greater decrement in HF power expressed in normalized units in healthy controls compared to depressed subjects on active standing. The smaller reduction in normalized HF power in depressed subjects with standing is reflective of an attenuated parasympathetic activity (37). The effect of posture was in the main

reflected by significant change in the HF power expressed in normalized rather than the absolute units. This is agreement with previous reports (38), and normalization may be important when patterns of changes in total power with physiological maneuvers are different across study groups (37).

Few studies have examined the impact of posture on HRV in physically healthy depressed subjects (20, 21). Our finding of between group differences in autonomic nervous control with posture is in consonance with earlier observations that physiological maneuvers such as orthostatic challenge tend to reveal between group differences in cardiovascular autonomic control which are not apparent with baseline measures of HRV (36, 37). It has been shown that resting cardiac vagal control and vagal reactivity are distinct constructs (47) and this might also account for some of the negative findings in the literature pertaining to autonomic cardiovascular function and depression (23, 34). In addition, measuring cardiac vagal modulation in response to environmental challenge is theoretically meaningful as cardiac vagal modulation is a dynamic system and it is important to assess its reactivity to challenging conditions (48). We chose to examine the effect of posture through active standing although others have advocated the use of tilt table (49).

The strength of the present study was the inclusion of subjects with major depression without concomitant medical (including cardiovascular conditions) and psychiatric co-morbidity and in drug naïve conditions. In addition, the use of physiological maneuver (orthostatic challenge) to assess changes in cardiac autonomic measures as opposed to resting HRV measures is in keeping with the dynamic nature of cardiac autonomic control. Healthy controls in the study were drawn from the hospital staff and not from a community based sample. This may have resulted in between group differences as hospital based staff would have been more familiar with laboratory settings and thus experienced less anxiety during cardiac autonomic measurements.

In the present study there was an impaired parasympathetic modulation in drug naive subjects with depression compared to age and gender matched healthy controls as reflected by an attenuated response in normalized HF power. The alteration in cardiac autonomic tone especially the parasympathetic component may partly explain the association seen between depression and the risk of CAD. Thus deficiencies in vagal modulation that is associated with depression might be one of the mechanisms underpinning the relationship between depression and increased risk of CAD and mortality. In a population based study of middle aged men and women low HRV was predictive of an increased risk of CAD and mortality and this was independent of cardiovascular risk factors and underlying disease (50).

The impact of treatment of depression on cardiac autonomic modulation is confounded by findings of antidepressant medication induced changes on measures of HRV. This is a contentious issue with some investigators arguing for a causal relationship between selective serotonin reuptake inhibitors and HRV in respiratory frequency range (HRV-Respiratory Sinus

arrthymia) and quitting selective serotonin reuptake inhibitors reversing the effect on HRV-Respiratory Sinus arrthymia (32) while others (30, 31) reporting that major depression without cardiovascular disorders is associated with reductions in HRV and the use of antidepressants in the short term did not impact the observed reductions in HRV. This merits further study. Carney et al (2000) reported that treating depression using cognitive behavior therapy increased short-term HRV (15). A newer therapy such as HRV biofeedback that appears to be a useful adjunctive treatment for major depression has been shown to augment cardiac vagal modulation (51). Similar findings of changes in cardiac vagal modulation with treatment have been observed with phototherapy (52) and acupuncture therapy (53). Thus, augmenting cardiac vagal modulation is important as deficient cardiac vagal modulation in addition to its association with depression and CAD, has been linked to an array of adverse physical and psychological health outcomes (26).

Conclusion

In the present study we found impaired parasympathetic modulation in response to physiological maneuver (orthostatic challenge) in drug naive subjects with major depression who did not have co-morbid medical or psychiatric conditions compared to healthy controls. Recent reports have repeatedly stressed the importance of nonlinear techniques to study HRV in health and disease conditions as physiological systems are characterized by complex interactions of multiple mechanisms and the use of simple linear measures may be insufficient to capture the complexity of HRV. Several investigators using various indices of non-linear measures of HRV have shown that major depression is associated with decreased cardiac vagal function (54,55). In addition; a recent study suggested that analysis of blood pressure variability might be more sensitive in detecting changes in cardiac autonomic function compared to HRV in depressed subjects (56).

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