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ORIGINAL ARTICLE

Depression, Anxiety, and Heart Rate Variability: A Case-control Study in Taiwan

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Objective: Decreased heart rate variability (HRV) has been reported in persons with major depressive disorder (MDD), but the results obtained are inconsistent. Little is known about the impact of comorbid anxiety disorders on HRV in MDD patients. Both issues necessitate further investigation. **Materials and Methods:** Forty-nine unmedicated, physically healthy, MDD patients without comorbidity, 21 MDD patients with comorbid generalized anxiety disorder (GAD), 24 MDD patients with comorbid panic disorder (PD), and 81 matched controls were recruited. The Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale are employed to assess the severity of depression and anxiety, respectively. The cardiac autonomic function was evaluated by measuring the HRV parameters. The frequency-domain indices of HRV were obtained. **Results:** MDD patients without comorbidity had lower high-frequency (HF)-HRV (which reflected vagal control of HRV) than controls. Any comorbid anxiety disorder (GAD or PD) was associated with significantly faster heart rates, relative to the controls, and caused greater reductions in HF-HRV among MDD patients. MDD participants with comorbid GAD displayed the greatest reductions in HF-HRV, relative to controls. Correlation analyses revealed that the severity of both depression and anxiety were significantly associated with the mean R wave to R wave (R-R) intervals, variance, low-frequency (LF)-HRV, and HF-HRV. **Conclusion:** The present results show decreased HRV in MDD patients, suggesting that reduction in HRV is a psychophysiological marker of MDD. MDD patients with comorbid GAD had the greatest reductions in HRV. Further investigation of the links between MDD and comorbid GAD, HRV, and cardiovascular disease is warranted.

Key words: Major depressive disorder, anxiety disorder, comorbidity, heart rate variability, cardiac autonomic function

INTRODUCTION

Major depressive disorder (MDD) has a prevalence ranging between 8 and 12% worldwide and will be the second biggest disease burden by 2020, after cardiovascular disease (CVD).[1] Depressed patients have been shown to have an augmented risk of cardiovascular morbidity and mortality.[2,3] Even as definite mechanisms for this cardiac vulnerability are unknown, it is assumed that reduction of heart rate variability (HRV) is at least one important pathophysiological factor.[4,5] However, research on HRV and depression has generally been conducted in cardiac patients. Thus, factors concomitant with CVD may influence the observed relationship between depression and HRV. The present study focuses on MDD patients without CVD, in order to avoid overestimation of the association between MDD and HRV.

The frequency-domain analysis of HRV, with its standard procedure and interpretation, first reported in 1996, is a sophisticated and noninvasive tool for the detection of the autonomic nervous system (ANS) regulation of the heart.[6] An important advantage of the frequency-domain analysis of HRV is that it utilizes the spontaneous fluctuations in heart rate to estimate the tonic ANS functions. However, it must be noted that a well-controlled condition is required for spontaneous ANS functional recordings. The present study has used the spectral analysis of HRV when the subjects were in a supine position, at rest, in a quiet and relaxing atmosphere, for a five-minute short recording, because short-term resting-state measures of HRV better reflect the intrinsic HRV.[7]

Most studies[8,9] have found reduced HRV levels in MDD patients in comparison with the control subjects. Importantly, a recent meta-analysis, comprising of a total of 673 MDD patients and 407 healthy controls, showed that

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the MDD patients had lower HRV than the controls, and their depression severity was negatively correlated with the HRV.[10] Nevertheless, other studies on MDD have reported no differences in HRV, as measured by the time-domain measures[5,8] and high-frequency (HF) power.[5,8,11] Some of the contradictory findings reported in the literature might be due to heterogeneity in the relatively small samples, confounded by medication, physical health, habitual physical activity, smoking, psychiatric comorbidities, and reporting of different HRV measures.[12] For example, a critical study on a large sample of participants revealed that a lower HRV in MDD was derived from the effect of antidepressants rather than the diagnosis itself.[13] A study on an unmedicated patient population will serve to better reveal the direct relation between MDD and HRV. In addition, MDD is frequently comorbid with anxiety disorders.[14,15] Anxiety disorders have also been associated with increased risks of cardiovascular morbidity.[16] One potential explanation proposed for this association is the dysregulation of the autonomic control of the heart, because ANS activity is associated with CVD[17,18] and anxiety disorders.[16] Some studies reported low HRV in patients with panic disorder (PD),[19,20] while others found that patients with generalized anxiety disorder (GAD) exhibited an increased HR and decreased cardiac vagal tone during rest, as compared to the controls.[21-23] One might wonder whether the comorbid diagnosis of anxiety disorders in MDD patients is associated with a greater reduction in HRV as compared with MDD patients without any comorbidity. However, little effort has been devoted to examining this. There is only one study so far that has examined the impact of MDD and comorbid anxiety disorders on HRV. The study researched an Australian population and showed that MDD participants with comorbid GAD displayed the greatest reductions in HRV, relative to the controls.[24] The impact of comorbid anxiety disorders on the HRV of MDD patients in the Asian population need further exploration.

The aim of the present study is to examine two hypotheses:

1. Physically healthy, unmedicated MDD patients, without comorbidity, have decreased resting HRV, as compared to the age- and sex-matched controls.
2. MDD patients with comorbid anxiety disorders display greater reductions in resting HRV than those without comorbidity.

MATERIALS AND METHODS

Subjects

This study was approved by the Institutional Review Board for the Protection of Human Subjects at the Tri-Service General Hospital, a medical teaching hospital of the National Defense Medical Center in Taipei, Taiwan. Written informed consent was obtained from all the participants, to whom the procedures of the study had been fully explained. The initial study entry criterion was an age between 20 and 65 years. After detailed questionnaire screening, clinical examination, and a chart review, subjects with pregnancy, smoking, diabetes, cancer, neuropathy, any cardiovascular disease that affects HRV or those engaged in regular physical training exceeding 10 hours a week, were excluded. Subjects who used any medication that had been reported to affect ANS functioning for at least two weeks before evaluation were also excluded.

The same methodology used in our previous research was adopted.[25] In brief, each patient was evaluated using the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Lifetime (SADSL)[26] to reach the DSM-IV criteria for a primary diagnosis of MDD. Our previous study has reported diagnostic data with satisfactory interrater reliability.[27] Here, individuals with a history of substance dependence, organic brain disease or any concomitant major psychiatric disorders other than GAD or PD were further excluded. MDD patients without comorbidity were recruited in the MDD group (n = 49). MDD patients, who met the criteria for an additional current diagnosis of GAD and PD were recruited in the MDD with GAD group (n = 21) and MDD with PD group (n = 24), respectively. The severity of MDD was assessed with the 17-item version of the Hamilton Depression Rating Scale (HAM-D). Only subjects with a minimum score of 18 on the HAM-D were included in the study. The control subjects (n = 81) were recruited from the community. The modified Chinese Version of SADSL was employed to exclude individuals with psychiatric conditions. The subjects in the control group had no lifetime history of a mental disorder. All patient groups were matched to the control group for age, gender, and education.

Assessment of anxiety severity

All participants have been assessed using self-report measures of anxiety, namely Beck Anxiety Inventory (BAI).[28] The BAI contains 21 items that measure anxiety-related symptoms and it has been shown to have good test–retest reliability and fair concurrent validity. The subjects were asked to rate the severity of their anxiety on a four-point Likert scale (0-3). They were also assessed by an attending psychiatrist (HAC) using a clinician-rated scale, the Hamilton Anxiety Rating Scale (HAM-A).[29] Both BAI and HAM-A provide global indices of anxiety severity. To avoid multiple testing of the same hypothesis, the analysis of the relationship between the HRV parameters and global anxiety severity was determined according to the HAM-A. The results remained the same regardless of whether the interviewer's or self-reported measures of anxiety severity were used as an outcome.

Assessment of depression severity

All participants were interviewed by HAC using the 17-item HAM-D, an objective scale for assessing the severity of depression. In addition, the Beck Depression Inventory (BDI), a 21-item questionnaire, was employed, to assess the subjects' self-reported severity of depression.[30] The results were scored by summing the responses to each of the items in order to obtain a total depression score (range, 0-63).

Measurements of heart rate variability

Detailed procedures have been reported previously.[31] In short, after sitting quietly for 20 minutes, a lead I electrocardiogram was taken for five minutes with the subject lying quietly and breathing normally. An HRV analyzer (SSIC, Enjoy Research Inc., Taiwan) acquired, stored, and processed the electrocardiogram signals. Under a sampling rate of 512 Hz, the signals were recorded using an 8-bit analog-to-digital converter. Stationary R-R interval values were resampled and interpolated at a rate of 7.11 Hz, to produce continuity in a time domain. Power spectral analysis was performed using a nonparametric method of fast Fourier transformation (FFT). The direct current component was deleted and a Hamming window was employed to attenuate the leakage effect. The power spectrum was then quantified into the standard frequency-domain measurements defined previously,[31] which consisted of variance (variance of RR-interval values), low-frequency (LF: 0.04-0.15 Hz), high-frequency (HF: 0.15-0.40 Hz) measurements, and the ratio of LF to HF (LF/HF). All the measurements were logarithmically transformed to correct the skewed distribution.[31] Vagal control of HRV was represented by HF, whereas, the vagal and sympathetic control of HRV were jointly represented by LF. The LF/HF ratio is considered by some investigators to mirror the sympathovagal balance or sympathetic modulations.

Statistical analyses

The SPSS (Version 13.0, SPSS, Taipei, Taiwan) statistical software was used for all analyses. Discrete variables in patients and controls were compared using the chi-square test. Differences between continuous variables were evaluated using the student's t-test when normally distributed; otherwise, the Mann-Whitney U test was used. Analysis of variance (ANOVA) with the post hoc test was utilized to compare the HRV indices and other continuous variables in group comparisons. To evaluate relations between variables with normal distribution, the Pearson's correlation test was used. For non-normal distribution, the Spearman's correlation test was used. The associations between HRV measures and age, body mass index (BMI), and habitual physical activity were analyzed by using product-moment correlations, whereas, point-biserial correlations were employed to assess relationships with gender. Results of the point-biserial correlations were identical to those arising from comparisons using t tests. Linear regression analyses were utilized to primarily assess the associations of the scores of HAM-A, HAM-D, against the HRV indices. To control the confounding effect, multiple regressions were performed on the HRV indices, with HRV-associated factors as covariables. All results were two-tailed and a probability value of $P < 0.05$ was considered statistically significant.

RESULTS

Demographics and clinical characteristics

The groups did not differ significantly on the demographic data — BMI, systolic/diastolic blood pressure, and habitual physical activity [Table 1]. Group comparisons showed significant differences in the scores of HAM-A, BAI, HAM-D, and BDI. The post-hoc test revealed greater scores of HAM-A and BAI for three MDD groupings versus controls, MDD with the GAD group versus the MDD group and MDD with PD versus the MDD group. It also showed greater scores of HAM-D and BDI for the three MDD groupings versus controls.

Heart rate variability parameters

Group comparisons showed significant differences in the mean R-R intervals ($P = 0.001$), variance ($P < 0.001$), LF ($P < 0.001$) and HF ($P < 0.001$), and LF/HF ratio ($P = 0.031$). As seen in Figure 1, the MDD with GAD group and the MDD with PD group had significantly faster HRs (shorter RR intervals) than the controls (778.48 ± 138.79 and 795.17 ± 98.7 vs. 890.53 ± 144.67 milliseconds). As compared to the controls, the MDD with GAD group and the MDD with PD group had a significantly lower variance [6.02 ± 0.97 and 6.21 ± 0.79 vs. 7.12 ± 0.79 ln(ms^2)] and LF [4.24 ± 1.43 and 4.66 ± 1.11 vs. 5.56 ± 1.07 ln(ms^2)]. All three MDD groupings had significantly lower HF than controls [(5.48 ± 0.87 ln(ms^2)). Among the three MDD groupings, the post hoc test in HF showed the lowest values in the MDD with GAD group [3.53 ± 1.17 ln(ms^2)], the greatest values in the MDD group [4.95 ± 0.77 ln(ms^2)], and intermediate values in the MDD with PD group [4.3 ± 1.13 ln(ms^2)]. The MDD with GAD group had a significantly higher LF/HF ratio than the controls (0.72 ± 1.13 vs. 0.08 ± 0.86).

Factors associated with heart rate variability

Associations between HRV measures and those potentially confounding variables are summarized in Table 2. Men had a significantly lower LF/HF ratio than women. Older subjects had reduced LF and HF. However, the HRV indices were not associated with BMI and physical activity.

Table 1. Sample characteristics

Clinical and demographic data	MDD	MDD with GAD	MDD with PD	Healthy control	Omnibus I-value	Significant comparisons
Number of participants	49	21	24	81		
Age, mean±SD, years	44.08±4.81	45.29±3.59	44.00±9.92	42.98±8.36	0.59	
Female sex (%)	39 (79.59)	17 (80.95)	19 (79.17)	66 (81.48)	0.99	
BMI, mean±SD, kg/m^2	22.84±3.40	22.68±4.12	22.49±3.42	22.06±2.89	0.58	
Weekly regular exercise, hours	0.65±1.27	0.57±0.68	0.17±0.82	0.73±1.20	0.20	
SBP, mean±SD, mmHg	115.00±14.52	121.23±20.71	121.63±17.67	116.27±13.54	0.20	
DBP, mean±SD, mmHg	71.61±8.89	73.52±10.79	74.46±13.39	73.33±9.23	0.66	
HAM-A scores, mean±SD	17.53±5.70	28.86±5.85	27.21±4.78	5.69±2.98	<0.001	MDD vs. Healthy control, MDD with GAD vs. Healthy control, MDD with PD vs. Healthy control, MDD with GAD vs. MDD, MDD with PD vs. MDD
BAI scores, mean±SD	19.94±6.06	34.67±8.14	33.17±7.28	7.68±3.13	<0.001	MDD vs. Healthy control, MDD with GAD vs. Healthy control, MDD with PD vs. Healthy control, MDD with GAD vs. MDD, MDD with PD vs. MDD
HAM-D scores, mean±SD	28.71±10.77	30.57±8.09	29.17±8.83	4.49±2.37	<0.001	MDD vs. Healthy control, MDD with GAD vs. Healthy control, MDD with PD vs. Healthy control
BDI scores, mean±SD	32.22±10.98	33.57±8.66	33.17±8.79	6.77±2.57	<0.001	MDD vs. Healthy control, MDD with GAD vs. Healthy control, MDD with PD vs. Healthy control

SD = standard deviation; BMI = body mass index (calculated as weight in kilograms divided by height in meters squared); SBP = systolic blood pressure; DBP = diastolic blood pressure; HAM-A = hamilton Anxiety Rating Scale; BAI = beck Anxiety Inventory; HAM-D = hamilton Depression Rating Scale; BDI = beck Depression Inventory

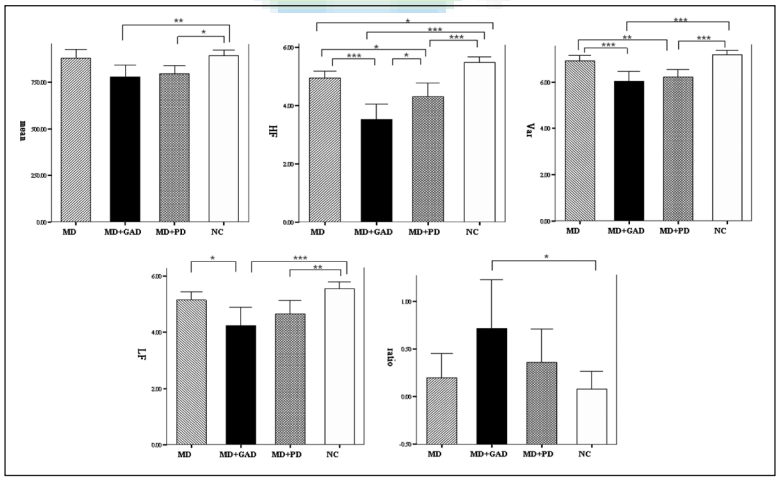

Figure 1. Mean R-R Intervals and all measures of HRV for MDD group, MDD with GAD group, MDD with PD group and controls. Asterisks indicate significant between-groups differences, *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Var, total variance [ln(ms2)]; LF, low frequency power [ln(ms2)]; HF, high frequency power [ln(ms2)]; LF/HF, ratio of LF to HF [ln(ratio)].

Association between depression/anxiety severity and heart rate variability

As can be seen in Table 3, subjects with higher scores of HAM-D/HAM-A had significantly faster HRs (shorter RR intervals). Both the HAM-D and HAM-A scores were inversely associated with variance — LF and HF. The HAM-A, but not the HAM-D scores were associated with a greater LF/HF ratio. Further adjustment for gender and age did not alter the above-mentioned association in a meaningful manner [Table 4]. To analyze the specific influence of depression/anxiety severity

on HRV, a stepwise multiple regression, with HAM-D/HAM-A scores as predictors of mean RR intervals and all HRV indices, was performed. It was found that the HAM-D scores significantly explained the variation of HF (r^2 = 0.192, F(1, 173) = 41.12, P < 0.001, b = −0.03; Figure 2a), variance (r^2 = 0.16, F(1, 173) = 33.03, P < 0.001, b = −0.03), LF (r^2 = 0.1, F(1, 173) = 19.28, P < 0.001, b = −0.03), and mean RR intervals (r^2 = 0.055, F(1, 173) = 10.01, P = 0.002, b = −2.4). To a greater extent, the HAM-A scores explained significantly the variation of HF (r^2 = 0.25, F (1, 173) = 57.55, P < 0.001, b = −0.06; Figure 2b), variance (r^2 = 0.17, F(1, 173) = 34.45, P < 0.001, b = -0.04), LF (r^2 = 0.11, F (1, 173) = 21.01, P < 0.001, b = −0.038), and mean RR intervals (r^2= 0.07, F (1, 173) = 12.61, P < 0.001, b = −3.73).

Table 2. Factors associated with resting HRV indices among all participants

	RR interval	Var	LF	HF	LF/HF
Gender(Women/men)†	−0.006	−0.03	−0.1	0.02	−0.16*
Age‡	0.04	−0.12	−0.16*	−0.20**	0.04
BMI‡	0.07	0.04	−0.08	−0.08	−0.001
Physical activity‡	0.03	0.06	0.08	0.09	−0.003

BMI = body mass index; Var, total variance [ln(ms²)]; LF = low frequency power [ln(ms²)]; HF = high frequency power [ln(ms²)]; LF/HF, ratio of LF to HF [ln(ratio)]; †Point-biserial correlations; first category in parentheses is the reference group; ‡Product-moment correlations. *P < .05; **P < .01; ***P < .001

Table 3. Correlations between HRV indices and scores of HAM-A and HAM-D among all participants

	HAM-D	HAM-A
Heart rate variability measures		
RR interval, mean±SD, ms	−0.23**	−0.26***
Var, mean±SD	−0.40***	−0.41***
LF, mean±SD	−0.32***	−0.33***
HF, mean±SD	−0.44***	−0.50***
LF/HF, mean±SD	0.13	0.20*

Var, total variance [ln(ms²)]; LF = low frequency power [ln(ms²)]; HF = high frequency power [ln(ms²)]; LF/HF, ratio of LF to HF [ln(ratio)]; HAM-A = hamilton anxiety rating Scale; HAM-D = hamilton depression rating scale; *P < .05; **P < .01; ***P < .001

DISCUSSION

This study found that MDD patients had lower HF-HRV than the healthy controls. This finding is consistent with the previous investigations;[8,9] however, the largest study published so far reported that MDD patients did not differ from the controls in HRV and that the lower HRV in the current MDD was attributed to the effect of antidepressants rather than the diagnosis itself.[13]

Nevertheless, the current results must be reliable because this study has three important strengths.

1. This research has used the frequency-domain analysis of HRV, which is a sophisticated tool for the detection of cardiac autonomic regulation and can add information on the quantification of the parasympathetic and sympathetic nervous system function over the time-domain analysis of HRV.[16,32] Although the sample size of the study undertaken by Licht and colleagues is impressive, only time-domain measures are used. It is possible that very subtle autonomic changes accompany MDD and a time-domain analysis of HRV is insufficient to detect such small differences.

Table 4. Multiple regressions of HRV parameters by scores of HAM-A and HAM-D, after adjusting for gender and age factors: unstandardized regression coefficients

	Unstandardized β coefficients (95% confidence interval)					
	Unadjusted	P	Model 1	P	Model 2	P
HAM-D scores						
Mean RR interval	–2.40 (–0.9-3.9)	0.002	–2.40 (–0.9-3.9)	0.002	–2.47 (–1.0-4.0)	0.002
Var	–0.03 (–0.017-0.035)	<.001	–0.03 (–0.017-0.035)	<.001	–0.03 (–0.016-0.034)	<.001
LF	–0.03 (–0.014-0.038)	<.001	–0.03 (–0.014-0.038)	<.001	–0.03 (–0.013-0.036)	<.001
HF	–0.03 (–0.024-0.045)	<.001	–0.04 (–0.024-0.045)	<.001	–0.03 (–0.0243-0.044)	<.001
LF/HF	0.01 (0.0-0.02)	0.09	0.01 (0.0-0.02)	0.07	0.01 (0.0-0.02)	0.07
HAM-A scores						
Mean RR interval	–3.73 (–1.66-5.81)	<.001	–3.75 (–1.66-5.84)	<.001	–3.86 (–1.76-5.97)	<.001
Var	–0.04 (–0.03-0.05)	<.001	–0.04 (–0.03-0.05)	<.001	–0.04 (–0.02-0.05)	<.001
LF	–0.04 (–0.02-0.05)	<.001	–0.04 (–0.02-0.05)	<.001	–0.04 (–0.02-0.05)	<.001
HF	–0.06 (–0.04-0.07)	<.001	–0.06 (–0.04-0.07)	<.001	–0.05 (–0.04-0.07)	<.001
LF/HF	0.02 (0.0-0.03)	0.012	0.02 (0.0-0.03)	0.005	0.02 (0.01-0.032)	0.005

Model 1: Controlling for gender; Model 2: Controlling for model 1 + age; Var, total variance [ln(ms²)]; LF = low frequency power [ln(ms²)]; HF = high frequency power [ln(ms²)]; LF/HF, ratio of LF to HF [ln(ratio)].

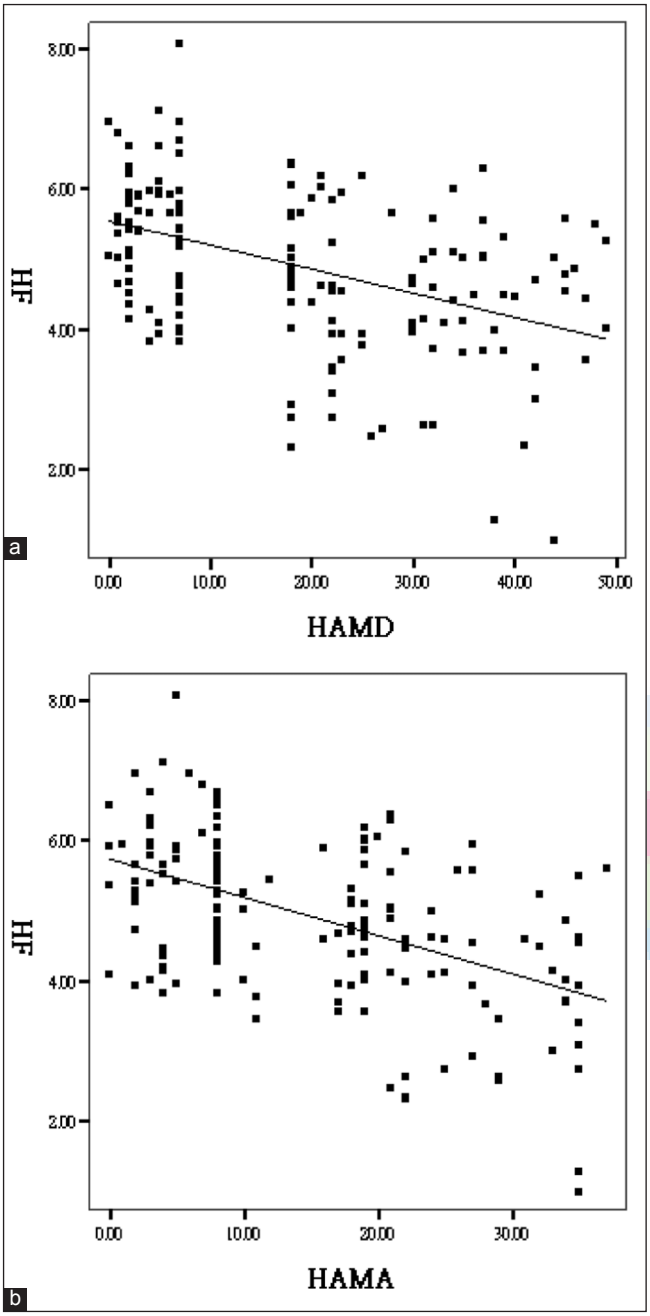

Figure 2. Stepwise multiple regression analyses showed that the HAM-D scores explain 19.2% of HF variation (a), and the HAM-A scores explain 25% of HF variation (b)

2. Subjects with psychiatric and physical comorbidities, who could potentially confound the association between MDD and cardiac autonomic functions, have been excluded in this study. MDD patients have been interviewed with the modified Chinese Version of SADSL[26] to rule out any psychiatric comorbidity. Thus, a false-positive finding due to inclusion of anxiety disorders or substance use disorder in the MDD group is at present unlikely.
3. Other confounding factors that may suppress or magnify the true effects of MDD on HRV, including medication, age, smoking, BMI, and physical activity levels have been controlled.[12] For example, all study subjects neither smoked nor had a history of smoking. Current smoking clearly depresses HRV, and even among those who have recently quit, HRV remains lower compared with that of normal nonsmokers.[33] Therefore, smoking must be taken into account in any study that evaluates the effect of MDD on HRV, because a substantial proportion of MDD patients smoke or have a history of smoking.[34]

The results revealed no difference in LF/HF ratio between MDD patients and controls, although it was hypothesized that reduced vagal modulation was accompanied by a subsequent displacement of the sympathovagal balance (as indexed by the LF/HF ratio) in favor of sympathetic modulation. Several reasons could account for this unexpected finding:

1. The traditional interpretations of HRV measures used in this study were that HF power estimated vagal tone, while LF power reflected both vagal and sympathetic influences. However, it was also reported that when LF power was assessed in the supine position, administration of atropine (a potent inhibitor of parasympathetic muscarinic receptors) eliminated most of the LF region of the power spectrum.[35] Elimination of the LF region did not occur when LF power was assessed in the sitting position, suggesting that the resting LF power in this study could have primarily reflected vagal influences.[36]
2. The LF/HF ratio was calculated from the absolute values of both the LF and HF power for each subject, and was taken as an indicator of the sympathovagal balance or sympathetic modulations. However, increasing evidence against the LF/HF ratio representing sympathovagal balance was noted. For example, Goedhart *et al*.[37] reported that the LF/HF ratio did not show the expected correlation in the pre-ejection period, an established measure of cardiac sympathetic control. More specifically, Goldstein *et al*. regarded LF power as an index, not of the cardiac sympathetic tone, but of the baroreflex function, during the supine rest.[38] Additional studies are recommended (e.g., cardiac noradrenaline spillover) for adequately assessing the sympathetic nerve activity.

Major depressive disorder is frequently comorbid with anxiety disorders. Approximately 20% of the patients with a lifetime diagnosis of MDD retrospectively report GAD[14] and 11.2% of the MDD patients have lifetime comorbidities of PD.[15]

Longitudinal studies show that GAD[39] and PD[40] are associated with an augmented risk of CVD. Even as definite mechanisms for the anxiety disorder-associated cardiac vulnerability are unknown, the reduction of HRV plays an important role.[16] The current data revealed that comorbid anxiety disorders (either GAD or PD) would cause greater reduction in the HRV of MDD patients. One potential explanation was the cumulative effect, that is, a combination of the psychophysiological impact of MDD and anxiety disorders. Previous research showed that both GAD[22,23] and PD[19,20] were associated with decreased HRV. A plausible scenario could be that MDD patients, with any comorbid anxiety disorder, would have a greater reduction in HRV than those with only MDD diagnosis. This explanation seems to be supported by the current finding that the severity of both depression and anxiety significantly explain the variation in the HRV indices [Figure 2]. Overall, the current data provide an important extension to our prior work on MDD,[25] indicating that comorbid anxiety disorders are associated with greater reductions in HRV.

Our study indicated that HF-HRV is reduced the most in MDD patients with comorbid GAD, consistent with a recent study highlighting that comorbid GAD caused the greatest reductions in the HRV of MDD patients relative to controls.[24] This observation is reinforced by the significantly elevated HRs in the MDD with GAD group [Figure 1]. Given the large contribution of vagal control to resting HRs, findings for resting HF-HRV in any single study will theoretically parallel the findings for resting HRs. In this study, these reductions in HF-HRV are not attributed to depression severity. All three MDD groupings rated similarly on levels of depression severity and anxiety severity, and there were no significant differences in anxiety severity between MDD patients with GAD and MDD patients with PD or other potential confounding variables. Two reasons can explain why HF-HRV is the most reduced in comorbid GAD:

1. The Polyvagal theory proposed by Porges highlights the importance of the vagal pathway in attention, emotion expression, social bonding, and flexible adjustment to environmental demands,[41] and all of them are compromised in GAD.[42] Vagal influences on the heart serve to dampen the sympathetic reactions to stress[43] and to promote calm behavioral states and self-regulation.[44] Without this protective function of the vagal tone, subjects may become vulnerable to anxious apprehension and worry, involving pre-attentive biases to threat information, and rigid and inflexible response patterns, which characterize GAD.[42] The inability to disengage threat detection, serves to perpetuate hyperarousal and worry, even when no real threat exists.[45] It may cause a chronic withdrawal of vagal activity and long-term reductions in HRV, which subsequently increases the risk for CVD. In line with this explanation, two prospective follow-up studies on patients with stable CAD reported GAD as having a distinctly negative impact on the subsequent cardiovascular events.[39,46]
2. The comorbidity between MDD and GAD may recognize a unique group of patients.[47] Indeed, the nosological rules of DMS-IV reflect an uncertainty as to whether MDD and GAD represent two separate diagnostic entities. For example, the symptoms of GAD do not occur exclusively during a major depressive episode, while one can only make a diagnosis of GAD in individuals with MDD if the GAD symptoms also occur outside a major depressive episode. The current data provide further evidence for the possibility that individuals with comorbid MDD and GAD can be distinguished according to the psychophysiological correlates (for example, HF-HRV) from those with MDD alone. Moreover, it is worth mentioning that Frasure-Smith *et al*. have found that MDD alone, GAD alone, and concurrent MDD and GAD all enhance the possibility of a poor cardiac outcome among CAD patients.[39] However, patients with comorbid MDD and GAD are not at a greater risk for major adverse cardiac events than those with only one risk factor.[39] Consequently, the present results must be deemed preliminary. Nonetheless, this study draws attention to a potential relationship between comorbid GAD and an increased CVD risk in MDD.

Our findings highlight that MDD patients with comorbid GAD display the greatest reductions in HRV, relative to controls. It is conceivable that early therapeutic intervention in those with decreased HRV may prevent the development of cardiac autonomic dysfunction, which may then moderate the chances of adverse cardiac outcomes. As suggested above, these vulnerable patients may benefit from cardiovascular risk reduction strategies such as exercise, smoking cessation or undergoing treatment to restore the autonomic function. For instance, mindfulness meditation has been reported to significantly increase cardiac parasympathetic activity[48] and reduce symptoms of GAD.[49] Moreover, cognitive behavior therapy–based psychotherapy applied in a forest environment can be helpful in the achievement of depression remission, while increasing the parasympathetic nerve tone.[50] Larger randomized control trials in MDD patients with comorbid GAD are warranted, to validate these study results.

This study has several limitations:

1. LF power is interpreted as sympathetic activity with caution, because the level of modulation of LF HRV by the sympathetic branch is still a subject of debate.
2. HRV has been shown to fluctuate during different phases of female menstrual cycle;[51] however, this study fails to

provide information regarding the menstrual cycle of the female participants.
3. Nonlinear techniques that may be more sensitive to MDD than those used in this study have not been employed to measure HRV.[10]

In conclusion, the current results suggest that reduction in HRV is a psychophysiological marker of MDD. MDD patients with comorbid GAD show the greatest reductions in HRV. Further investigation of the links between MDD and comorbid GAD, HRV and cardiovascular disease, is warranted.

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