

Depressive Symptoms and Heart Rate Variability in Postmenopausal Women

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Background: Depressive symptoms have been associated with increased cardiac morbidity and mortality rates, but the pathophysiologic mechanism linking depressive symptoms to cardiovascular outcome has yet to be fully understood. Lower heart rate variability has also been associated with increased risk of cardiac events in healthy individuals and in patients with coronary artery disease. Findings regarding a relationship between depressive symptoms and heart rate variability that could explain increased cardiovascular risk have been inconsistent across studies.

Methods: As an ancillary study to the Women's Health Initiative Observational Study, 3372 postmenopausal women aged 50 to 83 years were enrolled for further evaluation using 24-hour ambulatory electrocardiographic monitoring. A shortened version of the Center for Epidemiological Studies Depression Scale and the Diagnostic Interview Schedule were administered. Women with adequate electrocardiographic data and depressive symp-

tom information and without coronary artery disease were analyzed (n=2627).

Results: Two hundred sixty-nine women (10.2%) had depressive symptoms as measured using the 2 instruments. Women with depressive symptoms had a higher mean±SD heart rate (77.4±9.6 vs 75.5±8.5 beats/min) and lower heart rate variability than women without depressive symptoms. All differences remained significant after adjusting for age (P<.01).

Conclusions: Women with depressive symptoms had significant reductions in heart rate variability and higher heart rates, suggestive of increased sympathetic tone. These findings may contribute to the increased cardiac morbidity and mortality rates associated with depression in other studies.

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DEPRESSION HAS BEEN ASSOCIATED with increased morbidity and mortality rates in patients with and without coronary artery disease (CAD). After myocardial infarction (MI), depressed patients have a significantly increased risk of mortality and a prognosis comparable with that of left ventricular dysfunction and a history of MI.¹ Furthermore, depression has been found to be a significant independent risk factor for the development of CAD in otherwise healthy individuals.^{2,3}

*See also pages 1214
and 1229*

Depression is a clinical diagnosis based on the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria (for major or minor depression) determined via a clinical interview. Depressive symptoms refer to responses on questionnaires such as the Center for Epidemiological

Studies Depression Scale that correlate with clinical diagnoses but that are not synonymous with a clinical diagnosis, and they are used primarily in epidemiologic studies.^{4,6}

The pathophysiologic mechanism linking depression and cardiovascular disease has yet to be fully understood. Some studies^{7,8} have attributed factors such as abnormal platelet aggregation and medical noncompliance as possible links. However, a plausible underlying mechanism linking depression and CAD is dysregulation of the cardiac autonomic system. This increased sympathetic tone with decreased parasympathetic modulation has been found in patients with depression, as evidenced by elevated plasma and urinary catecholamine and cortisol levels.⁹

A more commonly used method for assessing the autonomic modulation of cardiac function is to measure heart rate variability (HRV).¹⁰ This technique provides a noninvasive assessment of the changes in cardiac autonomic tone across time using serial changes in HRV. Beat-to-beat variability is modulated primarily through

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Table 1. Screening Items and Unstandardized Coefficients Derived From Logistic Regression Analysis*

Screening Item	Possible Values, Range	Coefficient
1. I felt depressed	0-3	1.078
2. My sleep was restless	0-3	0.185
3. I enjoyed life (reverse scored)	0-3	-0.269
4. I had crying spells	0-3	0.329
5. I felt sad	0-3	-0.280
6. I felt that people disliked me	0-3	0.288
7. In the past year, have you had ≥ 2 wk during which you felt sad, blue, or depressed or lost pleasure in things that you usually cared about or enjoyed?	0-1	2.712
8. Have you had ≥ 2 y in your life when you felt depressed or sad most days, even if you felt okay sometimes? If yes, have you felt depressed or sad much of the time in the past year?	0-1	2.182

* $P = (e^{a + Bx}) / (1 + e^{a + Bx})$, where e indicates natural logarithm; a , -6.543; and Bx , $[(1.078 \times \text{Item 1}) + (0.185 \times \text{Item 2}) - [(0.269 \times \text{Item 3}) + (0.329 \times \text{Item 4})] - [(0.280 \times \text{Item 5}) + (0.288 \times \text{Item 6})] + [(2.712 \times \text{Item 7}) + (2.182 \times \text{Item 8})]$.

parasympathetic innervation of the heart. Loss of this innervation, as seen in heart transplant recipients or in patients with severe neuropathy, exposes the heart to unopposed sympathetic excitation, which reduces the beat-to-beat variability. Furthermore, patients with mood disorders such as depression have an imbalance in cardiac autonomic tone with excessive sympathetic excitation, which again results in decreased HRV. Alterations in HRV may have substantial clinical implications. Decreased HRV has been associated with increased cardiac mortality.^{11,12} Recent studies have shown decreased HRV to be associated with accelerated development of atherosclerotic CAD¹³ and increased mortality after MI.¹⁴ Decreased HRV has also been shown to be a strong predictor of ventricular arrhythmias and sudden death.¹⁵

The relationship among depression, depressive symptoms, and HRV has yet to be fully established. Recent studies¹⁶⁻¹⁹ in patients with CAD have shown that depression and depressive symptoms are associated with decreased HRV, suggesting a possible mechanism linking depression with increased cardiac mortality. However, the relationship between HRV and depression or depressive symptoms in patients with no known CAD has been inconsistent across all studies.²⁰⁻²² The purpose of this study is to examine the relationship between depressive symptoms and HRV and to improve our understanding of how depression affects cardiovascular health.

METHODS

PARTICIPANTS

A subsample of the Myocardial Ischemia and Migraine Study (MIMS), an ancillary study to the Women's Health Initiative (WHI) Observational Study, participated in the present study. Details of the study design and methods of the WHI have been reported previously.²³ Briefly, the WHI is an ongoing clinical

investigation of strategies for the prevention of common causes of morbidity and mortality among approximately 100 000 postmenopausal women being followed for a mean of 7.5 years in 40 clinical centers. The MIMS is an ancillary study of the WHI that is carried out in 10 of the WHI clinical centers: University of Alabama at Birmingham; University of North Carolina, Chapel Hill; Ohio State University Medical Center, Columbus; Wayne State University, Detroit; George Washington University, Washington, DC; University of Hawaii, Manoa; University of Iowa, Iowa City; University of California at Irvine; University of Nevada, Reno; and Albert Einstein College of Medicine.

The purpose of the MIMS was to examine the associations of 3 putative risk factors for cardiovascular disease: history of migraine, as assessed by the International Headache Society questionnaire; history of panic attacks, as assessed by the Diagnostic Interview Schedule screening form for panic disorder; and daily life ischemia, as assessed by 24-hour Holter monitoring. During the MIMS enrollment period, March 1998 to August 2001, participation in the MIMS was offered to all WHI participants at the 10 WHI clinical sites who did not have pacemakers; 3372 postmenopausal women aged 50 to 83 years were enrolled in the MIMS, of whom 3126 had valid ambulatory electrocardiographic (AECG) monitoring data. Of these 3126 individuals, 499 were excluded for the following reasons: missing depression variables, self-reported heart disease, or AECG monitoring at less than 12 hours. Thus, 2627 individuals were available for analysis.

PROCEDURES

Depression Screening

Depression was measured by an algorithm using an 8-item screening instrument that incorporated 6 items from the Center for Epidemiological Studies Depression Scale²⁴ and 2 items from the Diagnostic Interview Schedule.²⁵ The 8 items and their range of possible values are given in **Table 1**. Participants whose scores were 0.06 or greater on the algorithm were considered to have depressive symptoms (Table 1).²⁶ This instrument has been shown to have high sensitivity and specificity (>85% for both) for the depressive disorders of major depression and dysthymia when applied to a household population and for users of medical and mental health services. For these purposes, it was compared with a standard psychiatric interview (using the Diagnostic Interview Schedule as the criterion). This depression screen was administered at the WHI baseline visit, whereas AECG monitoring was usually performed up to 3 years after the WHI baseline visit, at enrollment into the MIMS.

AECG Monitoring

Each participant underwent 24-hour AECG monitoring using a digital recorder (model 3100-001; Zymed Laboratories Inc, South San Francisco, Calif). Three bipolar leads, corresponding to modified leads MCL₁, MCL₅, and CC₆, were recorded. Participants were instructed to use their event monitor for episodes of chest pain and to record any events in a provided diary log. Analysis of the recordings was performed using a replay system (Zymed 0210, model 108005-003; Zymed Laboratories Inc). Recordings were scanned and analyzed in the AECG Core Laboratory at the University of Florida.

HRV ANALYSIS

Heart rate variability was analyzed using 3 standard time domain measures: standard deviation of all analyzed N-N intervals; average of all 5-minute standard deviations of N-N inter-

Table 2. Medical and Demographic Characteristics by Depressive Symptom Status

Characteristic	Depressive Symptoms (n = 269)	No Significant Depressive Symptoms (n = 2358)	P Value
Age, mean (SD), y	64.9 (7.1)	66.0 (7.1)	.01
Diabetes mellitus, %	6.7	4.8	.16
Hypercholesterolemia, %	13.1	13.8	.73
Hypertensive medication use, %	27.6	22.6	.07
Current tobacco use, %	8.9	4.6	.003

Table 3. Time Domain Indexes by Depressive Symptom Status*

Variable	Depressive Symptoms		P Value
	Present	Absent	
Heart rate, beats/min	77.4 (9.6)	75.5 (8.5)	.002
SDNN, ms	113.34 (30.5)	119.1 (32.2)	.005
ASDNN, ms	42.2 (14.1)	44.8 (16.6)	.006
SDANN, ms	102.4 (29.7)	108.6 (32.6)	.003

Abbreviations: ASDNN, average of all 5-minute standard deviations of N-N intervals; SDANN, standard deviation of the 5-minute average of N-N intervals; SDNN, standard deviation of all analyzed normal N-N intervals.

*Data are given as mean (SD).

vals, and standard deviation of the 5-minute average of N-N intervals. All 3 measures are highly correlated with HRV. Greater HRV reflects increased parasympathetic tone or decreased sympathetic tone and has been associated with better cardiovascular outcomes in patients with CAD. Mean HR was also obtained by calculating the mean cycle length of the N-N complexes.

STATISTICAL ANALYSIS

Mean HRV variables were compared using 2-sample *t* tests or analysis of variance. Categorical variables were compared using χ^2 tests of association. Pearson correlation coefficient estimates were used to examine the relationship between age and HRV. Linear regression models were used to examine the effect of covariates and depression status on HRV variables. A priori, covariates that were thought to play a role in HRV were identified for inclusion in these models, along with depression status. A $P < .05$ was considered statistically significant.

RESULTS

This analysis included 2627 postmenopausal women without self-reported CAD; 269 of these women (10.2%) had depressive symptoms as measured by the Center for Epidemiological Studies Depression Scale/Diagnostic Interview Schedule. The demographic and medical characteristics of the study participants are reported in **Table 2**. Women with depressive symptoms were slightly younger and were more likely to be current smokers than those without depressive symptoms. The 2 groups also differed in their use of hypertensive medications, although this difference did not reach significance ($P = .07$).

Table 4. Heart Rate Variability Indicator Values by Medical and Demographic Characteristics*

Characteristic	HR, beats/min	SDNN, ms	ASDNN, ms	SDANN, ms
Current tobacco use				
Yes (n = 133)	79.1	107.1	37.2	99.7
No (n = 2476)	75.5	119.1	44.9	108.4
P value	<.001	<.001	<.001	.003
Diabetes mellitus				
Yes (n = 129)	77.7	106.6	39.8	98.8
No (n = 2491)	75.6	119.1	44.8	108.4
P value	.007	<.001	<.001	.001
Hypercholesterolemia				
Yes (n = 356)	75.7	116.7	42.9	106.2
No (n = 2242)	75.7	118.8	44.8	108.2
P value	.89	.27	.04	.29
Hypertensive medication use				
Yes (n = 604)	75.0	113.0	42.58	102.07
No (n = 2007)	75.9	120.1	44.99	109.41
P value	.03	<.001	.003	<.001
Age (n = 2627)				
r	-0.13	-0.07	-0.06	-0.07
P value	<.001	<.001	.003	<.001

Abbreviations: ASDNN, average of all 5-minute standard deviations of N-N intervals; HR, heart rate; SDANN, standard deviation of the 5-minute average of N-N intervals; SDNN, standard deviation of all analyzed normal N-N intervals.

*Data are given as means.

In participants with depressive symptoms, all 3 time domain indexes were significantly lower than in nondepressed participants (**Table 3**). The *P* values differ from *t* test *P* values in cases in which *t* tests for unequal variances were used. Mean (SD) values for standard deviation of all analyzed N-N intervals were 113.3 (30.5) in participants with depressive symptoms and 119.1 (32.2) in those without depressive symptoms ($P = .005$). Mean (SD) values for average of all 5-minute standard deviations of N-N intervals and standard deviation of the 5-minute average of N-N intervals were also lower in participants with depressive symptoms compared with those without depressive symptoms (**Table 3**). Furthermore, participants with depressive symptoms were found to have an increased mean (SD) HR of 77.4 (9.6) compared with 75.5 (8.5) in participants without depressive symptoms ($P = .002$). Heart rate and the time domain indexes varied significantly for tobacco use, diabetes mellitus, and hypertensive medication use (**Table 4**), and all showed a slight, but statistically significant, negative correlation with age.

Linear regression analysis was performed for each of the HRV variables and for HR to examine the joint effect of covariates and depressive symptoms. A priori, age, hypercholesterolemia, diabetes mellitus, smoking status, medication use for hypertension, and depressive symptoms were included in each model. All models were significant ($P < .001$), and the results were consistent with and mimicked the bivariate analysis results. For each model, age, diabetes mellitus, current smoker, medication use for hypertension, and the presence of depressive symptoms were significant (**Table 5**). Note that these models explained only 2% to 3% of the variability in HR and HRV

Table 5. Results of Linear Regression Analysis

Model	Variable Estimate (SE)	P Value
Mean heart rate		
Age	-0.13 (0.02)	<.001
Hypercholesterolemia	0.32 (0.50)	.52
Diabetes mellitus	2.16 (0.78)	.006
Past smoker	0.17 (0.35)	.63
Current smoker	3.21 (0.78)	<.001
Hypertensive medication use	-0.82 (0.41)	.046
Depressive symptoms	1.59 (0.55)	.005
SDNN		
Age	-0.28 (0.09)	.002
Hypercholesterolemia	-0.48 (1.85)	.80
Diabetes mellitus	-10.50 (2.92)	<.001
Past smoker	-0.64 (1.31)	.63
Current smoker	-11.85 (2.90)	<.001
Hypertensive medication use	-5.57 (1.52)	<.001
Depressive symptoms	-5.11 (2.07)	.01
ASDNN		
Age	-0.12 (0.05)	.008
Hypercholesterolemia	-1.27 (0.95)	.18
Diabetes mellitus	-4.14 (1.49)	.006
Past smoker	1.05 (0.67)	.12
Current smoker	-7.12 (1.48)	<.001
Hypertensive medication use	-1.53 (0.78)	.049
Depressive symptoms	-2.38 (1.06)	.02
SDANN		
Age	-0.30 (0.09)	.001
Hypercholesterolemia	-0.48 (1.87)	.80
Diabetes mellitus	-7.58 (2.95)	.01
Past smoker	-1.79 (1.33)	.18
Current smoker	-9.10 (2.92)	.002
Hypertensive medication use	-5.96 (1.54)	<.001
Depressive symptoms	-5.48 (2.09)	.009

Abbreviations: ASDNN, average of all 5-minute standard deviations of N-N intervals; SDANN, standard deviation of the 5-minute average of N-N intervals; SDNN, standard deviation of all analyzed normal N-N intervals.

variables. According to the regression models, current smoker and depressive symptoms independently contribute to low HRV (Table 5). We examined whether the inclusion of an interaction term of current smoker and depressive symptoms would significantly improve any of the 4 models, and this was not the case for any of the models.

COMMENT

The relationship between decreased HRV and depression in patients with CAD has been well established. Carney et al¹⁷ previously reported decreased HRV in depressed patients with stable CAD. Carney et al¹⁶ also recently reported that depressed patients after MI have significantly decreased HRV compared with participants without depression. These findings are consistent with those of previous studies^{18,19} of decreased HRV in patients with CAD and after MI.

Although the relationship between decreased HRV and depression in patients with CAD has been well established, this relationship has not been conclusively evaluated in a general population cohort. Yeragani et al^{20,21} studied depression and HRV in a group of healthy young participants and found no significant difference in HRV in those with depression compared with those without

depression. Furthermore, in studying sex differences in the relationship between HRV and depressive symptoms in a group of healthy young college students, Thayer et al²² found that men with depressive symptoms had decreased HRV compared with men without depressive symptoms. However, women with depressive symptoms were found to actually have increased HRV compared with their counterparts.

In contrast to the findings of Yeragani et al^{20,21} and Thayer et al,²² the present study shows that in participants with no known CAD, depressive symptoms are related to decreased HRV. All the time domain indexes of HRV were significantly lower in participants with depressive symptoms compared with those without depressive symptoms. Consistent with earlier findings, mean HR was also elevated in those with depressive symptoms. These differences also remained statistically significant after adjusting for medical and demographic covariates.

Important differences exist between this study and the previous studies of Yeragani^{20,21} and Thayer²² and their colleagues. Both previous studies reported results from relatively small samples. Yeragani et al performed 2 studies^{20,21} with sample sizes of 39 and 45 (mean age range, 32-37 years), and Thayer et al²² described 26 participants with a mean age of 20 years. Furthermore, participants were relatively young and healthy, with no major medical problems. In contrast, we studied a cohort of 2627 postmenopausal women without CAD aged 50 to 83 years.

Although the relationship linking depression and CAD has been established, the underlying pathophysiologic mechanism of this relationship has yet to be fully understood. What is clear is that depressed patients with known CAD, or after MI, have decreased HRV, which places them at higher risk for cardiac morbidity and mortality. Furthermore, depression itself places otherwise healthy individuals at risk for CAD. The prevalence of depressive symptoms in our sample (10.2%) is higher than that in other studies with similar healthy participants. This may be because our sample consists of women only or because it is a volunteer sample and not a strictly random sample of the general population.

Heart rate variability reflects cardiac autonomic tone. Decreased HRV reflects an imbalance in sympathetic and parasympathetic tone, resulting in dysregulation of autonomic tone. The present study is the first to establish this finding in a cohort of individuals without CAD. Furthermore, our study is the only one of its kind to examine this relationship in a group of postmenopausal women. Our finding may actually be understated because participants who are depressed might be less likely to volunteer for a study.

LIMITATIONS

Our findings were obtained at a single point in time in a cross-sectional manner and, therefore, are limited in terms of demonstrating causality. One limitation of this study is that HRV measures were not recorded at the same time as depressive symptoms (see the "Participants" subsection of the "Methods" section). It would have been ideal to collect this information at the same time, but this was not possible in this study. We believe that any bias in-

roduced should have been to the null. Nevertheless, future studies should collect these measures at the same time. Another potential limitation is the lack of frequency domain measures. However, the Task Force recommendations¹⁰ state that for 24-hour recordings, the results of time domain measures are equivalent to those of frequency domain measures.

MEDICAL COMORBIDITIES THAT RELATE TO DEPRESSION AND DEPRESSIVE SYMPTOMS

Women with depressive symptoms were statistically significantly younger (64.9 vs 66.0 years) and were more likely to be smokers than those without depressive symptoms. Because of these differences in factors that could have differentially affected HRV, we controlled for these variables in the analysis. It has been demonstrated previously that smoking is more prevalent in depressed populations and may in fact also at least partially account for adverse outcomes associated with depression because it is a risk factor for CAD.²⁷ We have limited information on comorbid disease; the WHI observational group tended to be healthy. A total of 72 (2.3%) of the 3132 participants enrolled reported heart disease, and these women were excluded from the analysis. Of the women included in the analysis, 129 (4.9%) of 2620 had diabetes mellitus, 356 (13.7%) of 2598 had hypercholesterolemia, and 604 (23.1%) of 2611 took hypertensive medications. We controlled for these variables in the multivariate analysis so that we could assess the impact of depressive symptoms, taking these medical conditions into account. Also, age is a well-recognized risk factor for CAD, and it has been recognized as a factor that needs to be controlled for in analyses of HRV.^{10,28,29}

The direct physiologic effects of smoking on HRV are difficult to assess because smokers have different rates of exposure based on their habits, and there are multiple compounds in cigarette smoke in addition to nicotine. Nevertheless, it is certainly possible that smokers may have had increased depressive symptoms related to their habit and that smoking may have also affected HRV. Previous researchers^{28,29} have also found differences in HRV comparing groups with depression, groups with depressive symptoms, and controls with and without prevalent CAD. In fact, Krittayaphong et al¹⁹ found results similar to those of the present study by comparing time domain HRV measures in patients with CAD who had abnormally elevated Minnesota Multiphasic Personality Inventory depression scores without overt symptoms of depression. Those differences remained when age and sex were controlled for and the patients were not taking antidepressant agents.¹⁹

In conclusion, the results of this study show that in a large cohort of postmenopausal women, depressive symptoms are significantly related to decreased HRV. This relationship remained even after adjusting for medical and demographic covariates. Therefore, decreased HRV may not only contribute to increased cardiac morbidity and mortality in participants with CAD but also may be a link that places individuals with depressive symptoms or clinical depression with

no known history of CAD at risk for cardiovascular disease.

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