Differential Association of Cognitive and Somatic Depressive Symptoms With Heart Rate Variability in Patients With Stable Coronary Heart Disease: Findings From the Heart and Soul Study

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Objective: To determine if depression associated with low heart rate variability (HRV) in patients post myocardial infarction (MI), but not in patients with stable coronary heart disease (CHD), may be the result of differential associations of somatic and cognitive depressive symptoms with HRV. **Methods:** To examine the association of somatic and cognitive depressive symptoms with 24-hour HRV, we performed a cross-sectional study of 863 outpatients with stable CHD. The severity of somatic and cognitive depressive symptoms was determined using factor analysis of items of the Patient Health Questionnaire (PHQ-9). Time-domain (SDNN, SDANN) and frequency-domain (VLF, LF, HF, WBF) indices of HRV were derived using ambulatory monitoring. **Results:** Unadjusted analyses revealed that somatic symptom scores were significantly associated with HRV ($r = -.09$ for SDNN; $r = -.08$ for SDANN; $r = -.08$ for LnVLF; $r = -.08$ for LnLF; $r = -.10$ for LnHF; $r = -.08$ for LnWBF). After adjustment for demographic variables, comorbidities, and lifestyle factors, somatic symptom scores were no longer associated with lower HRV, with the possible exception of LnWBF ($r = -.06$). Cognitive depressive symptom scores were not associated with HRV using either unadjusted or adjusted analyses. **Conclusions:** We found that somatic depressive symptoms were associated with lower HRV, although cognitive depressive symptoms were not. The inverse association of somatic symptoms with HRV was largely explained by differences in comorbidities and lifestyle factors. These results suggest that individual symptoms of depression may have differential associations with HRV. **Key words:** depression, heart rate variability, coronary heart disease.

HRV = heart rate variability; **MI** = myocardial infraction; **CHD** = coronary heart disease; **PHQ** = Patient Health Questionnaire; **ANS** = autonomic nervous system; **CFI** = comparative fit index; **RMSEA** = root mean square error of approximation; **SRMR** = standardized root mean residual.

INTRODUCTION

Major depression is associated with cardiovascular morbidity and mortality in patients with coronary heart disease (CHD) (1) and myocardial infarction (MI) (2). Among the suggested mechanisms of how depression may evoke cardiac effects, one of the most promising seems to be altered autonomic nervous system (ANS) activity (3). Low heart rate variability (HRV) is an independent risk factor for cardiac mortality (4,5), and several studies suggest an association of depression and HRV in patients with MI (6–8). Moreover, ANS dysregulation may in part explain the increased mortality in depressed MI patients (9,10).

We previously measured depression and HRV in a sample of 873 outpatients with stable CHD from the Heart and Soul Study, and found no evidence of an association (11). This finding was not consistent with the inverse relationship described in prior studies. A potential explanation is that patients with stable CHD may have different symptoms of depression than patients who have recently experienced an acute cardiac event such as an MI. After an acute event, patients may experience an increase in somatic depressive symptoms (sleeping difficulties, fatigue, and appetite problems) whereas patients with stable CHD may experience more cognitive depressive symptoms (anhedonia, feelings of worthlessness, and difficulty concentrating) (12,13).

An association of somatic but not cognitive depressive symptoms with low HRV would explain the observed lack of association between overall depression and HRV in patients with stable CHD and resolve the discrepancy with studies performed in patients with MI. In the present study, we sought to examine the differential association of somatic and cognitive depressive symptoms with HRV in the same sample of 863 patients with stable CHD for whom we previously found no overall association. We hypothesized that somatic depressive symptoms are associated with HRV, but cognitive symptoms are not. We further hypothesized that the association between somatic symptoms and HRV would be explained by demographics, comorbidities, and lifestyle factors.

METHODS

Design

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with stable CHD. Patients were included in the study between September 2000 and December 2002. Details regarding design have been described elsewhere (14). The current paper concerns a cross-sectional analysis of data collected at baseline. All participants completed a baseline examination including a comprehensive medical history interview, psychiatric assessments, and 24-hour Holter electrocardiographic monitoring.

Participants

Administrative databases were used to identify outpatients with documented CHD at 12 centers: two Veterans Affairs medical centers, one university medical center, and nine public health clinics in northern California. Inclusion criteria included a history of MI or coronary revascularization, angiographic evidence of at least 50% stenosis in at least one coronary vessel,

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or a diagnosis of CHD by an internist or cardiologist. Patients were excluded if they had an MI in the past 6 months, were unable to walk one block, or were planning to move from the local area within 3 years. The protocol was approved by the respective hospital review boards, and all participants provided written informed consent.

A total of 1024 enrolled patients completed a baseline assessment. For the present analyses, 151 patients were excluded because of a paced rhythm, atrial fibrillation, or inability to collect 24-hour Holter HRV data. Ten other patients were excluded because of an incomplete 9-item Patient Health Questionnaire (PHQ-9). A total of 863 participants were used for the current analyses.

Assessment of Depressive Symptoms

The presence and severity of depressive symptoms were assessed using the PHQ-9 (15), which is a self-report checklist derived from the interview used in the Primary Care Evaluation of Mental Disorders (16). The nine symptoms in the PHQ-9 are based on the Diagnostic and Statistic Manual-IV (DSM-IV) criteria for major depression and include (I) lack of interest, (II) depressed mood, (III) sleeping difficulties, (IV) tiredness, (V) appetite problems, (VI) negative feelings about self, (VII) concentration problems, (VIII) psychomotor agitation/retardation, and (IX) suicidal ideation. For all symptoms, the patients were asked to what extent the symptoms were present during the last 2 weeks (0 = not at all; 1 = on several days; 2 = most of the time; 3 = all of the time).

Somatic and Cognitive Depressive Symptoms

We anticipated a distinction between two symptom dimensions of depression: somatic versus cognitive symptoms (17–20) (Table 1). To make this assessment, a confirmatory factor analysis of individual items on the PHQ-9 using the program Mplus was performed, allowing for factor analysis of ordered categorical variables. We specified two factors, which were free to be correlated. In Table 1, factor loadings for the individual items on the two factors are shown. The fit indices for the anticipated factor structure were: CFI = 0.989; TLI = 0.995; RMSEA = 0.06; SRMR = 0.03. The fit indices thus indicated an excellent fit. No item overlap between the two factors was found in the present sample. The error-free factors were correlated 0.60.

TABLE 1. Expected and Observed Factor Loadings of the PHQ-9 Depressive Symptoms

	Expected[a]		Confirmatory Factor Analysis[b]	
	Somatic	Cognitive	Factor 1	Factor 2
Lack of interest		[c]	—	0.83
Depressed mood	+	+	—	0.84
Sleeping problems	+		0.55	—
Fatigability	+		0.71	—
Appetitive problems	+		0.56	—
Negative feelings about self		+	—	0.68
Concentration problems		[d]	—	0.58
Psychomotor agitation/retardation	[e]		0.58	—
Suicidal ideation		+	—	0.58

PHQ-9 = 9-item Patient Health Questionnaire.

[a] Expected based on previous factor analysis with Beck Depression Inventory (BDI) (17).

[b] Confirmatory factor analysis of 9 items on Patient Health Questionnaire. Fit indices: CFI = 0.989; TLI = 0.995; RMSEA = 0.06; SRMR = 0.03. CFI = comparative fit index; TLI = Tucker-Lewis Index; RMSEA = root mean square residual; SRMR = standardized root mean square residual.

[c] Not included in BDI.

[d] Not included in BDI, however, the item indecisiveness loaded on both the somatic and cognitive factor.

[e] Not included in BDI, however, the items work difficulty and loss of libido loaded only on the somatic factor.

In concordance with previous work on the Beck Depression Inventory, the two PHQ-9 factors were interpreted as somatic (factor 1) and cognitive (factor 2) (17–20). Internal consistency coefficients (Cronbach's α) were 0.77 for factor 1 and 0.84 for factor 2, with corrected item-total correlations ranging between 0.50 and 0.66 for factor 1, and 0.50 to 0.76 for factor 2. Two factor scores (somatic and cognitive) were calculated for each participant using the standardized item factor loadings, divided by the square root of the number of items per scale, yielding a sample mean of 0 and a standard deviation (SD) of 1 for each of the two factors.

Heart Rate Variability

Three-channel 24-hour ambulatory Holter electrocardiography was used to assess HRV, as recommended by the Task Force of the European Society of Cardiology (21) and the North American Society of Pacing and Electrophysiology (22). Tapes were scanned at 500 times real time, with data digitized at a sampling frequency of 128 Hz. Computer software (General Electric Medical System Software for Holter Analyses, GE Healthcare, Waukesha, Wisconsin) was used to detect and label each QRS complex (part of electrocardiographic wave representing ventricular depolarization) using beats with normal morphology and cycle length <20% duration of the preceding cycle length. An independent and blinded reviewer processed all Holter electrocardiograms and modified any inappropriate computer labels with particular focus on periods with the highest and lowest average RR intervals.

The annotated QRS data were processed to allow both time- and frequency-domain characterizations. Time-domain characterizations included SD of NN intervals (SDNN) in milliseconds and SD of 5-minute mean NN intervals (SDANN). Frequency-domain characterizations included very low frequency (VLF; 0.0033–0.04 Hz), low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.40 Hz), and wideband frequency (WBF; 0.0033–0.04 Hz) power, expressed as milliseconds squared, using standardized fast Fourier transformation.

Other Baseline Characteristics

Age, gender, ethnicity, living situation, medical history, physical activity, smoking status, and alcohol use were determined by questionnaire. We measured weight and height and calculated body mass index (BMI; weight in kilograms divided by the square of height in meters). We assessed left ventricular ejection fraction using resting echocardiography. A symptom-limited, graded exercise treadmill test according to a standard Bruce protocol was performed and the Wall motion score index at peak exercise during stress echocardiography was calculated (22). Creatinine clearance was calculated from 24-hour urine collections.

Statistical Analyses

A somatic symptom score and a cognitive symptom score were calculated for each participant using the factor loadings for individual responses on the PHQ-9. Differences in characteristics between the highest versus lower 3 quartiles of somatic and cognitive symptom scores were compared using t tests for continuous variables and χ^2 tests for categorical variables.

Linear regression analyses were used to assess associations of continuous somatic and cognitive factor scores with HRV. To examine the effect of confounding or mediation, we examined the extent to which β coefficients for the association of factor scores with HRV were affected by sequential adjustment for demographic factors, cardiac disease severity, comorbidities, and lifestyle characteristics. Furthermore, a series of exploratory analyses in which patients were stratified on gender, BMI, diabetes, smoking and clinical depression were performed. Analyses were performed using SPSS.

RESULTS

Of the 863 participants, 218 (25%) had somatic symptom factor scores in the highest quartile, and 215 (25%) had

TABLE 2. Characteristics of 863 Participants With Stable Coronary Heart Disease by Quartile of Somatic and Cognitive Symptom Factor Scores

	Somatic Symptoms Factor Score			Cognitive Symptoms Factor Score		
	Quartiles I, II, III (n = 645)	Quartile IV (n = 218)	p	Quartiles I, II, III (n = 645)	Quartile IV (n = 218)	p
Sociodemographics						
Age (mean ± SD)	67 ± 10	64 ± 11	<.0001	68 ± 10	63 ± 11	<.0001
Male	84	78	.03	85	74	.001
White	60	53	.09	59	57	.63
Living alone	35	38	.49	35	39	.27
Life style						
Current smoker	16	32	<.0001	16	31	<.0001
Regular alcohol use	29	26	.47	27	33	.23
BMI (mean; SD)	28 ± 5	29 ± 6	.001	28 ± 5	29 ± 5	.14
Regular exercise	71	43	<.0001	70	46	<.0001
Cardiac function						
Resting heart rate (mean ± SD)	67 ± 12	68 ± 13	.11	67 ± 12	68 ± 13	.36
Wall motion score (mean ± SD)	1.2 ± 0.3	1.2 ± 0.4	.10	1.2 ± 0.3	1.2 ± 0.4	.22
LVEF % (mean ± SD)	62 ± 10	61 ± 9	.20	62 ± 10	62 ± 9	.46
Inducible ischemia	22	25	.43	23	23	.98
Comorbidities						
Revascularization	60	57	.44	59	60	.95
Diabetes mellitus	24	33	.006	25	30	.15
Myocardial infarction	54	58	.26	55	56	.66
Congestive heart failure	14	22	.007	14	22	.005
Hypertension	69	78	.01	70	77	.03
COPD/asthma	15	21	.08	16	20	.20
Stroke	14	18	.17	13	19	.05
Creatinine clearance (mean ± SD)	81 ± 27	84 ± 31	.33	82 ± 27	84 ± 30	.29

SD = standard deviation; BMI = body mass index; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease. Percentage unless otherwise stated.

cognitive symptom factor scores in the highest quartile (Table 2). Compared with participants who had somatic factor scores in the lower 3 quartiles, those with scores in the highest quartile were younger, more likely to be female, to smoke, to be overweight, less likely to exercise, and more likely to have comorbid illnesses. Compared with participants who had cognitive factor scores in the lower 3 quartiles, those with cognitive factor scores in the highest quartile were also younger, more likely to be female, to smoke, less likely to exercise, and more likely to have comorbid illnesses such as hypertension and congestive heart failure.

In linear regression analyses, continuous somatic symptom scores were inversely associated with SDNN ($p < .01$), SDANN ($p = .02$), LNLF ($p = .02$), and LnHF ($p < .01$) (Table 3). Adjustment for demographic factors and cardiac disease severity had only small effects on the β coefficients (Table 4). However, further adjustment for either medical comorbidities or lifestyle factors reduced the β coefficients by at least 50%, and rendered the comparisons nonsignificant. Continuous cognitive factor scores were not significantly associated with HRV in either unadjusted or adjusted analyses. We found no evidence for interactions of factor scores with gender, diabetes, smoking, obesity, coronary artery bypass graft, medications, and major depression (all p values for interaction >.10). We added medication use (i.e., β blockers, aspirin, statin, and ace inhibitors) and resting heart rate to our models as potential confounders. Adding these variables did not alter the regression analyses in a meaningful way. Finally, we evaluated whether our findings may be due to a restriction of range in HRV in our sample. For this purpose, we selected a subsample of relatively unaffected patients (n = 161; 16% of

TABLE 3. Linear Regression of HRV Parameters by Somatic and Cognitive Symptom Factor Scores: Unadjusted and Adjusted Standardized Regression Coefficients

	Somatic Symptom Scores		Cognitive Symptom Scores	
	β	p	β	p
Unadjusted standardized regression coefficients				
SDNN, ms	−0.09	<.01	−0.02	.58
SDANN, ms	−0.08	.02	−0.01	.73
LnVLF, ms^2	−0.08	.09	−0.01	.89
LnLF, ms^2	−0.08	.02	−0.01	.87
LnHF, ms^2	−0.10	<.01	−0.05	.11
LnWBF, ms^2	−0.08	.09	−0.01	.92
Adjusted standardized regression coefficients				
SDNN, ms	−0.00	.99	0.06	.13
SDANN, ms	0.01	.78	0.06	.12
LnVLF, ms^2	−0.02	.79	0.08	.16
LnLF, ms^2	−0.02	.53	0.05	.20
LnHF, ms^2	−0.06	.12	0.00	.97
LnWBF, ms^2	−0.02	.79	0.08	.14

TABLE 4. Linear Regression of HRV Parameters by Somatic and Cognitive Symptom Factor Scores, Adjusting for Sociodemographic Data, Severity of Heart Disease, Comorbidity, and Lifestyle Factors: Unstandardized Regression Coefficients

	Unstandardized β Coefficients (95% Confidence Interval)									
	Unadjusted	*p*	Model 1	*p*	Model 2	*p*	Model 3	*p*	Model 4	*p*
Somatic factor										
SDNN, ms	−3.8 (−6.5–1.0)	.008	−3.7 (−6.7–0.8)	.01	−1.5 (−4.6–1.7)	.36	−1.9 (−5.0–1.2)	.23	−0.01 (−3.3–3.3)	.99
SDANN, ms	−3.0 (−5.6–.4)	.02	−3.0 (−5.7–0.2)	.04	−0.9 (−3.9–2.0)	.54	−1.3 (−4.3–1.6)	.36	−0.5 (−2.7–3.5)	.78
LnVLF, ms^2	−0.1 (−0.2–0.0)	.09	−0.1 (−0.2–0.0)	.20	−0.1 (−0.2–0.0)	.02	−0.1 (−0.2–0.0)	.27	−0.0 (−0.1–0.1)	.79
LnLF, ms^2	−0.1 (−0.2–0.0)	.02	−0.1 (−0.2–0.0)	.02	−0.0 (−0.1–0.0)	.33	−0.1 (−0.2–0.0)	.08	−0.0 (−0.1–0.1)	.53
LnHF, ms^2	−0.1 (−0.2–0.0)	.004	−0.1 (−0.2–0.0)	.01	−0.1 (−0.2–0.0)	.11	−0.1 (−0.2–0.0)	.03	−0.1 (−0.2–0.0)	.12
LnWBF, ms^2	−0.1 (−0.2–0.0)	.09	−0.1 (−0.1–0.0)	.22	−0.1 (−0.2–0.0)	.03	−0.1 (−0.2–0.1)	.33	−0.0 (−0.1–0.1)	.79
Cognitive factor										
SDNN, ms	−0.6 (−2.7–1.5)	.58	0.1 (−2.1–2.1)	.97	0.8 (−1.–3.1)	.52	0.8 (−1.5–3.1)	.48	1.9 (−0.5–4.3)	.13
SDANN, ms	−0.3 (−2.3–1.6)	.73	0.2 (−1.8–2.1)	.83	0.8 (−1.4–3.0)	.46	0.8 (−1.3–3.0)	.45	1.8 (−0.5–4.2)	.12
LnVLF, ms^2	0.0 (−0.1–0.1)	.89	0.0 (−0.1–0.1)	.90	0.0 (−0.1–0.1)	.88	0.0 (0.0–0.1)	.50	0.1 (−0.0–0.1)	.16
LnLF, ms^2	0.0 (−0.1–0.1)	.87	0.0 (−0.1–0.1)	.99	0.0 (0.0–0.1)	.49	0.0 (0.0–0.1)	.50	0.0 (0.0–0.1)	.20
LnHF, ms^2	−0.0 (−0.1–0.0)	.11	0.0 (−0.1–0.0)	.42	0.0 (−0.1–0.1)	.76	0.0 (−0.1–0.0)	.63	0.0 (−0.1–0.1)	.97
LnWBF, ms^2	0.0 (−0.1–0.1)	.92	0.0 (−0.1–0.1)	.85	0.0 (−0.1–0.1)	.97	0.0 (0.0–0.1)	.39	0.1 (0.0–0.1)	.14

Model 1: controlling for sociodemographics (male gender, white, age, living alone) + severity of heart disease (ventricular ejection fraction, wall motion score index, inducible ischemia); Model 2: controlling for model 1 + comorbidity (CABG, PTCA, diabetes mellitus, myocardial infarction, congestive heart failure, stroke, hypertension, COPD, creatinine clearance); Model 3: controlling for model 1 + lifestyle factors (current smoking, regular alcohol use, regular exercise, BMI); Model 4: controlling for model 1 + comorbidity + lifestyle factors.

the sample) who had no prior revascularization, did not smoke, had a BMI <30, and had no diabetes mellitus. In this subsample, we computed again the associations between HRV and the two depression dimensions. Although not significant (due to smaller sample size), a pattern emerges in which the cognitive symptoms are not associated with decreased HRV (all β coefficients >0.0) although the somatic symptoms are (notably with respect to LnLF and LnHF, β coefficients, respectively −0.07 and −0.09).

DISCUSSION

Our primary finding was that, in a sample of 863 stable CHD patients, two symptom dimensions of depression were differentially related to several indicators of HRV. In unadjusted analyses, somatic symptoms were associated with lower HRV whereas cognitive symptoms were not. The association of somatic depressive symptoms with lower HRV seemed to be explained by greater comorbidity and lifestyle factors among those with somatic symptoms. Our results corroborate with previous work suggesting that depression in the context of heart disease may not be a homogeneous condition and that only some aspects of depression may be associated with a worsened cardiovascular prognosis (17). Moreover, these findings may explain the lack of association between overall depression and HRV in stable CHD patients (11), and reconcile the strong associations reported in MI patients (9,10) with the negative findings reported in patients with stable CHD, where somatic symptoms may be less prominent than immediately after an acute coronary event.

What does this mean with respect to the association between depression and cardiovascular prognosis in patients with CHD? Our present findings suggest that, in patients with stable CHD, the association between depression and HRV may be restricted to somatic symptoms, including sleeping problems, fatigue, and appetitive problems. As the effects of these symptoms on HRV seem to be explained by comorbidities and lifestyle characteristics such as smoking, alcohol use, and lack of exercise, perhaps these are good targets to focus on in preventing the cardiac effects of somatic depressive symptoms. However, it is also possible that somatic depressive symptoms are mere consequences of greater somatic comorbidity, suggesting that interventions should be focused on decreasing the impact of the comorbid medical conditions that often accompany heart disease. Still, another possibility may be that in subjects with stable CHD but multiple comorbidities—like our present sample—depression no longer has an additional effect on HRV.

We did observe a potential association of somatic depressive symptoms with decreased high frequency power. These results are in contrast to acute MI patients in whom Carney et al. (23) found no association between depression and high frequency power after controlling for age, gender, diabetes, and smoking status. Stein (24) suggested that high frequency power can be affected by unstable or erratic sinus rhythm. Although we excluded subjects who had a paced rhythm or atrial fibrillation, this exclusion may have influenced this finding.

One possibility that might explain the lack of associations between depression and HRV in patients with stable CHD reported earlier (11), and between HRV and cognitive symptoms of depression as observed in the present study, is that there may be a restriction of range in HRV. However, even when we selected the relatively unaffected patients (i.e., those without prior revascularization, obesity, diabetes, and those who did not smoke), the same pattern of associations emerged. We therefore have no reason to believe that this hypothesis can explain our findings.

Among the strengths of this study are the sample size and the extensive data allowing for adjustment for comorbidities, cardiac disease severity, and lifestyle factors. Several limitations should be considered. First, the study utilized cross-sectional data only, and causality therefore cannot be inferred. We investigated whether somatic and cognitive symptoms of depression are differentially associated with HRV, but we do not claim that somatic symptoms are either cause or result from low HRV. Second, as a result of a change in HRV analysis software halfway through the study, some HRV indicators were only available for half of the participants and some indicators were analyzed using different software. However, in a blinded repeat analysis of 20 tapes, we found >99% concordance in reading between the two methods. Third, we did not use nonlinear techniques to measure HRV, and nonlinear techniques may be more sensitive to depression than those used in our study (25). Finally, most of our participants were urban men, so our results may not generalize to other patient populations.

In conclusion, we found that somatic depressive symptoms were inversely associated with heart rate variability in a sample of 863 participants with stable CHD. Future studies should be mindful of the possible heterogeneity of depression in CHD patients with respect to cardiovascular prognosis and possible mediating mechanisms.

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