Depressive Symptoms Predict Heart Rate Recovery After Exercise Treadmill Testing in Patients With Coronary Artery Disease: Results From the Psychophysiological Investigations of Myocardial Ischemia Study

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Background: Depression is associated with increased risk of death among patients with coronary disease. Cardiovascular autonomic dysregulation may be one of the mechanisms by which depression exerts its effects on cardiovascular function. The purpose of this study was to determine whether depressive symptoms are associated with low heart rate variability (HRV) and prolonged HR recovery after exercise testing in patients with coronary artery disease (CAD). **Methods:** The Psychophysiological Investigation of Myocardial Ischemia (PIMI) was a large, multicenter study designed to assess psychological and physiological correlates of stress in patients with CAD. One hundred and eighty-eight patients with CAD as evidenced by at least 50% blockage of one major artery and a previous positive exercise stress test were included in this study. Patients included in this report were not taking beta blockers. Cardiovascular functioning was assessed by a modified Bruce protocol treadmill stress test. Measures of psychological functioning, including the Beck Depression Inventory (BDI), were also obtained. **Results:** BDI scores were negatively correlated with HR recovery ($r = -0.15$, $p = .04$). Depression scores accounted for 3.5% of the variance in HR recovery when controlling for participant age ($p < .01$). Depressive symptoms were related to two HRV indices (ultra-low frequency, high frequency). **Conclusions:** Depressive symptoms are associated with cardiovascular autonomic nervous system dysfunction as assessed by HR recovery. This relationship is not merely due to an association of depression severity with beta blocker usage or a failure of depressed patients to achieve an adequate chronotropic response. **Key words:** coronary disease, depression, heart rate recovery, autonomic nervous system.

ANS = autonomic nervous system; **CAD** = coronary artery disease; **HR** = heart rate; **HRV** = heart rate variability; **PIMI** = Psychophysiological Investigation of Myocardial Ischemia

INTRODUCTION

Depression is associated with increased risk of death among patients with coronary disease (1–10). For example, the presence of depression during or shortly after hospitalization for myocardial infarction confers a twofold to threefold increase in risk for mortality or nonfatal cardiac events. In the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, however, psychological treatment had modest effects on depression and social support but did not reduce risk of mortality (11).

The results of the ENRICHD trial underscore the importance of identifying the mechanisms whereby depression is associated with increased risk. A number of possible mechanisms have been investigated, including associations with other cardiac risk factors (e.g., alcohol consumption, smoking) and poor adherence to treatment recommendations and lifestyle modification (e.g., medication adherence, regular exercise) (12–15). One that has received considerable empirical support is autonomic nervous system (ANS) dysregulation. A growing body of literature documents compromised ANS functioning among cardiac patients. Heart rate variability (HRV) during ambulatory monitoring has been used to assess cardiovascular autonomic dysregulation in a number of studies (16–19). HRV has been shown to predict mortality among cardiac patients (20–22), and it was recently shown to partially mediate the relationship between depression and mortality in an ENRICHD ancillary study (23).

The ANS also modulates the rate at which HR returns to resting levels after the cessation of exercise (HR recovery). The rapid decrease in HR after exercise is predominantly accomplished by parasympathetic reactivation, making HR recovery a marker of parasympathetic control of the heart (24–28). Prolonged HR recovery during exercise treadmill testing (ETT) has been shown to predict mortality (25,26,29–37). In one study, for example, prolonged HR recovery was associated with increased risk of sudden cardiac death over a 23-year follow-up period among healthy men after controlling for several potential confounders (38). Recently, symptoms of depression were shown to be associated with slower HR recovery from ETT among 260 patients starting cardiac rehabilitation (39). After controlling for age, sex, and beta-blocker usage, Beck Depression Inventory (BDI) (40) scores were associated with slower HR recovery after maximal exercise on an ETT. Furthermore, estimated METS from the ETT helped to explain the association of depressive symptoms and HR recovery. This is consistent with the hypothesis that depression leads to physical inactivity and low aerobic capacity, which then contributes to ANS dysregulation. Although the results of this study were promising, the fact that over 80% of the sample was taking beta-blockers was a serious limitation.

Therefore, the purpose of this investigation was to replicate the association of depressive symptoms and HR recovery in patients who were not taking beta blockers or who were temporarily withdrawn from beta blockers before testing. In keeping with previous findings, we hypothesized that depres-

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sive symptoms are inversely related to HR recovery from ETT. We also hypothesized that physical fitness, estimated from total exercise time during the ETT, help to account for the relationship between depression and HR recovery.

As a secondary aim, we evaluated the relationship between depressive symptoms and HRV measures derived from 48 hours of Holter monitoring. HRV measures are complementary to HR recovery, and there are far more reports of a relationship between depression symptoms and HRV. However, few studies have incorporated both of these measures of ANS regulation. Employing both measures provided a basis for evaluating whether similar relationships with depression would be observed. Finally, we explored the relationship between HR recovery, and HRV measures from 48 hours of Holter monitoring.

METHODS

These data are from the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study and were collected during 1993 through 1994. The PIMI methodology is described more fully an earlier report (41).

Participants

Participants in the PIMI study were originally recruited from clinical sites of the Asymptomatic Cardiac Ischemia Pilot (ACIP) study (42). Eligibility criteria included having verified coronary artery disease, a history of myocardial infarction, or evidence of myocardial ischemia on an exercise treadmill test while off medications (43). Exclusion criteria for the PIMI study included pregnancy, myocardial infarction within 3 months of the ETT, percutaneous transluminal coronary angioplasty (PTCA) within 6 months of the qualifying ETT, cardiac surgery requiring thoracotomy, unstable angina within 4 weeks of the qualifying ETT, serious noncardiac illness, inability to discontinue medications before assessments, and neurologic disease (e.g., stroke, dementia). For these analyses, three participants taking beta-blockers were also excluded. Four participants were taking antidepressants and were included in the analyses. The protocol was approved by the institutional review board at each participating medical center. Informed consent was obtained from all participants.

The current report includes data from 188 patients (162 men and 26 women). Participants were predominantly white (87%). Additional patient characteristics are reported in Table 1.

TABLE 1. Clinical and Demographic Characteristics of Study Population

	N	Percent
Age (years)		
41–50	17	9
51–60	44	24
61–70	87	46
71–80	39	21
Gender (male)	162	86
Race (Caucasian)	164	87
Current smoker	32	17
History of diabetes	28	15
History of MI	80	43
Medications		
Beta blockers	0	0
Calcium channel blocker	3	2
Digitalis	0	0
Nitrates	0	0

Procedures

The participants were asked to stop antianginal medications before all study assessments, for a period ranging in duration from 1 hour (e.g., sublingual nitroglycerin) to 3 days or five half-lives, whichever was longer (e.g., beta blockers). They were asked to discontinue sedatives and analgesics for 24 hours, and other medications (digitalis, theophylline, steroids, ACE inhibitors, antipsychotic medications) for 2 to 4 weeks. They were also asked to fast and to abstain from nicotine products for 12 hours before testing.

Exercise Stress Testing

An ETT was performed during the morning hours with patients off antianginal medications except for sublingual nitroglycerin, if needed. Resting HR, maximum HR, exercise capacity, and HR recovery measures were derived from the ETT results. The treadmill exercise test was conducted according to a modified ACIP protocol (43) using standard criteria for stopping. Heart rate and BP were recorded during each exercise stage and for each minute of recovery. HR recovery was defined as the difference in HR from maximum HR (HR at exercise termination) to HR 1 minute later (25,29). Exercise capacity in METS was not recorded in the PIMI database, and so total exercise time was used as an estimate of physical fitness. Exercise duration has been used as an estimate of physical fitness in other studies that also employed oxygen consumption at peak exercise (44,45).

Uniform interpretation and execution of this and other aspects of the PIMI study protocol were facilitated by training, pilot testing, and certification of study staff based on performance criteria. All data were centrally reviewed and entered by the PIMI Clinical Coordinating Center. Results of ETT were sent to their respective core laboratories for blinded analysis.

HRV From Ambulatory ECG Monitoring

After the ETT, the patients were asked to wear an Applied Cardiac Systems AM cassette AMBULATORY ECG (AECG) monitor (Laguna Beach, California) for 48 hours, producing two 24-hour tapes. The recordings were analyzed at the PIMI AECG Core Laboratory at the Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Standard 24-hour time and frequency domain HRV indices were obtained. The frequency domain indices are reported as the natural log of milliseconds squared. Specifically, the ultra-low frequency (ULF; 0.0001–0.003 Hz), very-low frequency (VLF; 0.003–0.04 Hz), low frequency (LF; 0.04–0.015 Hz), and high-frequency (HF; 0.15–0.4 Hz) components of HRV are reported. The values from tape 1 and tape 2 were averaged to increase reliability. HRV data were available for 163 of the 188 participants in this study. Missing data were related to poor recording quality, and the 25 patients with missing HRV data were not different from the larger sample with respect to study variables (i.e., age, gender, race, smoking status, history of diabetes, resting HR, peak HR, HR recovery, BDI score, and total exercise time).

Depressive Symptoms

The BDI (40) is a 21-item questionnaire used to assess symptoms of depression. Each item consists of four statements representing increasing degrees of severity with scores ranging from 0 to 3. Patients select the statement that best described themselves in the previous 2 weeks. Scores can range from 0 to 63, and a cutoff score of 10 or higher is widely used to screen for clinically significant depression (40).

Data Analysis

All statistical analyses were performed using SAS 9.1 software (SAS, Cary, NC). The criterion for statistical significance was set at 0.05 per analysis. The distribution of HR recovery values was skewed, so they were square-root transformed to normalize the distribution. The primary analyses, evaluating the relationship between depression and HR recovery, consisted of bivariate correlations and hierarchical multiple linear regression analyses. Age was included in the regression models as a control variable because increasing age is associated with reductions in parasympathetic cardiac control (46). Resting and maximum HR were also included as covariates. The potential contribution of total exercise time to HR recovery was evaluated as an estimate of physical fitness. The relationships among depression, HR

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TABLE 2. Beck Depression Inventory Score, Resting Heart Rate, Maximum HR, HR Recovery, and Total Exercise Time(s): Correlations and Descriptive Statistics (N = 188)

	BDI	Resting HR		Peak HR		HR Recovery		Exercise Time(s)	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
BDI	—	0.07	.38	−0.02	.78	−0.15	.04	−0.11	.12
Resting HR				0.40	.001	−0.32	.001	−0.14	.05
Peak HR				—		0.00	.96	0.38	.001
HR recovery						—		0.22	.002
M	6.67	79.3		138.0		24.0		464.26	
SD	5.7	13.7		18.3		3.0		178.6	
Range	0–34	43–123		89–187		2–71		157–1178	

HR recovery is transformed in correlation analyses.
BDI = Beck Depression Inventory; HR = heart rate; HRR = heart rate recovery; M = mean; SD = 1 standard deviation.

recovery, and HRV from AECG were explored in correlation and regression analyses.

RESULTS

Sample characteristics are presented in Table 1 for the sample as a whole. Table 2 summarizes BDI scores and HR variables. BDI scores ranged from 0 to 34 (M = 6.36, interquartile range = 2.5–8.5) and 18% had scores ≥10, suggesting the possibility of clinically significant depression. Total exercise time ranged from 157 to 1178 seconds (M = 4635.2, SD = 179.8). HR recovery at 1-minute postexercise averaged 23.9 seconds (SD = 13.0).

Correlations

Univariate correlation analyses are presented in Table 2. Depression scores were not associated with total exercise time ($r = -0.12$, $p = .12$), nor were they associated with resting or peak HR. Depression scores were negatively correlated with HR recovery ($r = -0.15$, $p = .04$).

Regression Analyses

Hierarchical multiple linear regression analyses were performed to further evaluate the relationship between depressive symptoms and HR recovery. The first step regressed HR recovery on age, resting HR, and maximum HR. The resulting equation accounted for 15.6% of the variance in HR recovery (adjusted $R^2 = 0.14$, $F(4,182) = 8.46$, $p < .001$). Significant effects were found for age ($\beta = -0.19$) and resting HR ($\beta = -0.39$). When BDI scores were added in the second step, the model accounted for 18.3% of the variance in HR recovery (adjusted $R^2 = 0.16$, $F(5,181) = 8.1$, $p < .001$), and BDI scores explained 2.6% of the variance in HR recovery ($\Delta R^2 = 0.026$, $F(1,181) = 5.18$, $p = .02$). In an alternate model, when total exercise time was added to the model including age, resting HR, and peak HR, total exercise time did not explain additional variability in HR recovery ($\Delta R^2 = 0.01$, $F(1,181) = 2.14$, $p = .15$). When BDI score was added to this model, it explained an additional 2.3% of the variability in HR recovery ($\Delta R^2 = 0.023$, $F(1,180) = 5.15$, $p = .02$). Thus, the prior inclusion of total exercise time did not eliminate the relationship between depressive symptoms and HR recovery. The final model including age, resting HR, peak HR, total exercise time, and BDI score explained a total of 19% of the variability in HR recovery (adjusted $R^2 = 0.16$, $F(6,180) = 7.02$, $p < .001$). These results were not appreciably altered by controlling for current smoking status, diabetes, or history of myocardial infarction, nor were they altered by excluding the individuals taking antidepressants.

Relationship of Depressive Symptoms and HR Recovery With HRV

Table 3 reports correlations in the 163 participants with complete data for both HRV and HR recovery measures. Regression analyses followed the same procedures as above. In the first step, age was entered as a control variable. In the second step, depression score (or HR recovery value) was added to evaluate the additional variance explained. After controlling for age, depression symptoms were related to ULF ($\Delta R^2 = 0.038$, $F(1,160) = 6.4$, $p = .01$) and HF ($\Delta R^2 =$

TABLE 3. HR Recovery, Total Exercise Time(s), and HRV: Correlations and Descriptive Statistics (N = 163)

HRV (ln ms²)	ULF		VLF		LF		HF		Ratio	
	r	*p*	*r*	*p*	*r*	*p*	*R*	*p*	*R*	*p*
BDI	−0.17	.025	−0.10	.20	−0.09	.23	−0.15	.053	0.09	.27
HR recovery	0.31	.001	0.34	.001	0.24	.002	0.18	.02	−0.03	.67
Exercise time(s)	0.21	.006	0.23	.003	0.14	.08	0.04	.58	0.05	.53

HR recovery is transformed in correlation analyses. HRV is log transformed, with the exception of the HRV ratio.
BDI = Beck Depression Inventory; HR = heart rate; HRR = heart rate recovery; M = mean; SD = 1 standard deviation.

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0.024, $F(1,159) = 3.93$, $p = .04$). Depression scores were not related to the VLF or LF components of HRV or the LF/HF ratio. After controlling for age, HR recovery predicted 9.4% of the variability in ULF, 11.1% of the variability in VLF, 4.9% of the variability in LF and 3.3% of the variability in HF (F values >4.0, p values $<.05$). In contrast, HR recovery was not related to the LF/HF ratio ($F = 0.4$, $p = .52$).

DISCUSSION

Here, we report that depressive symptoms are associated with HR recovery, after controlling for age, resting HR, and peak HR. Although these associations were not large, these results are similar to those reported by Hughes et al. (39), and extend the findings to a group of patients who were not taking beta-blockers. Specifically, beta blockers had been withdrawn for five half-lives from those patients prescribed beta blockers. However, it is possible that were residual effects of beta blocker usage or possibly HR rebound due to withdrawal. Nevertheless, these findings suggest that the relationship between depressive symptoms and HR recovery is not merely due to an association of depression severity with beta blocker usage or a failure of patients with more depressive symptoms to achieve an adequate chronotropic response. Although the magnitude of the relationship was not very strong, with depression scores accounting for about 2.6% of the variability in HR recovery, depressive symptoms were as powerful a predictor of HR recovery as were age and total exercise time.

Controlling for the length of time that patients exercised during the ETT did not eliminate the relationship between depressive symptoms and HR recovery. It was expected that total exercise time, as an estimate of physical fitness (44,45), would help to explain the relationship between depressive symptoms and HR recovery. However, in this sample, depressive symptoms were not associated with total exercise time, which contrasts with other reports that higher depression scores were associated with lower estimated METS (39,47). These results suggest that mechanisms besides reduced physical activity (48,49) and poor physical fitness are involved in the relationship between depressive symptoms and HR recovery.

We also found that depressive symptoms were associated with two HRV indices from two 24-hour Holter monitoring periods, which is similar to the typical finding that depressive symptoms are associated with lower HRV (16–19). For example, Carney et al. (23) recently reported that clinical depression was associated with lower HRV, and also that HRV accounts for 27% of the variance in risk of mortality associated with depression. Our findings are not completely consistent, as depression was associated with ULF and HF, but not VLF or LF. This may be due to the restricted range of depressive symptoms in our sample and the relatively small sample. Specifically, among the 166 individuals for whom HRV data were available, only 26 had BDI scores of 10 or greater. Because the study employed a relatively small sample, it may have been underpowered to detect a relationship between depression and HRV.

Considered together with our finding that depressive symptoms are related to HR recovery, it is also possible that HR recovery is more a more sensitive indicator of the relationship between depression and ANS functioning than VLF and HF in some contexts (e.g., in patients who show evidence of myocardial ischemia on an exercise treadmill test while off medications). Studies with larger samples and a broader range of depressive symptoms are needed to evaluate the relative strengths of association among depression, HRV, and HR recovery.

We found that HR recovery is associated with the ULF, VLF, LF, and HF components of HRV but not with the ratio of LF to HF. One other study found that HR recovery at 1 minute was positively correlated with LF and uncorrelated with HF among elderly men (50), but to our knowledge, there are no other published reports on the relationship between HR recovery and HRV indices from 24-hour monitoring. Although more research is necessary, these results imply that HR recovery and HRV are complementary measures. HR recovery from ETT is easily obtained from routine assessments of cardiac patients (e.g., at enrollment in cardiac rehabilitation), and thus may be a convenient, inexpensive, and valuable measure to employ in studies of depression and autonomic functioning among cardiac patients.

CONCLUSION

The results of this study suggest that depressive symptoms are associated with ANS dysfunction as indicated by prolonged HR recovery after ETT, when controlling for age and gender. HR recovery may be a particularly sensitive marker of ANS dysregulation among patients with depressive symptoms.

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