Psychophysiology, 48 (2011), 1604–1609. Wiley Periodicals, Inc. Printed in the USA.

DOI: 10.1111/j.1469-8986.2011.01232.x

The effect of major depression on postexercise cardiovascular recovery

JENNIFER L. GORDON,[a,b,c] BLAINE DITTO,[c] KIM L. LAVOIE,[a,b,d,e] ROXANNE PELLETIER,[a,b,e] TAVIS S. CAMPBELL,[a,f] ANDRÉ ARSENAULT,[a,b] AND SIMON L. BACON[a,b,d,g]

[a]Montreal Behavioural Medicine Centre, Montréal, Québec, Canada
[b]Research Centre, Montreal Heart Institute, Montréal, Québec, Canada
[c]Department of Psychology, McGill University, Montréal, Québec, Canada
[d]Research Centre, Hôpital du Sacré-Cœur, Montréal, Montréal, Québec, Canada
[e]Department of Psychology, University of Québec at Montréal, Montréal, Québec, Canada
[f]Department of Psychology, University of Calgary, Calgary, Alberta, Canada
[g]Department of Exercise Science, Concordia University, Montréal, Québec, Canada

Abstract

Major depressive disorder (MDD) is associated with increased cardiovascular (CV) mortality. Dysfunctional autonomic control of the CV system may represent a mechanism explaining this relationship. Poor CV recovery after exercise, indicative of dysfunctional autonomic control of the CV system, predicts CV events and death. This is the first study to examine the association between MDD and postexercise CV recovery. Some 886 patients underwent exercise stress tests. Heart rate (HR), systolic blood pressure, and diastolic blood pressure were measured at rest, peak exercise, 1 min, and 5 min after exercise. Patients with MDD had slower HR recovery ($p = .026$) 1 min after exercise than non-MDD patients. No other effects of MDD were found. MDD is accompanied by a dysregulation in autonomic control of exercise-related CV recovery, suggesting that depressed individuals have a slow parasympathetic recovery from exercise.

Descriptors: Depression, Heart rate (HR), Blood pressure (BP), Cardiovascular recovery, Exercise, Autonomic nervous system (ANS)

Major depressive disorder (MDD) is associated with both the development of cardiovascular disease (CVD) and poorer outcomes in patients with established CVD (Barth, Schumacher, & Herrmann-Lingen, 2004; Carney et al., 2008; Lavoie & Fleet, 2000; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002; Rozanski, Blumenthal, & Kaplan, 1999; Rutledge et al., 2006). For example, depressed individuals in a community sample were found to be twice as likely to have a myocardial infarction (MI) over a 17-year follow-up compared to nondepressed individuals (Barefoot & Schroll, 1996). In patients with established CVD, the impact of depression appears even more striking: In one study, patients who were depressed following an MI were over four times more likely to die in the following 5 years compared to nondepressed post-MI patients (Lesperance et al., 2002). However, the mechanisms underlying this relationship remain unclear.

Dysfunction of the autonomic nervous system (ANS) has been proposed as a potential mechanism linking MDD to CVD (Joynt, Whellan, & O'Connor, 2003). Whereas heart rate (HR) variability has long been used as a measure of autonomic dysfunction, HR recovery from exercise, the decrease in HR after exercise, has recently gained attention as an important complementary indicator of ANS imbalance (Hughes et al., 2006; Lahiri, Kannankeril, & Goldberger, 2008). Mounting evidence suggests that HR recovery is a powerful prognostic tool. For example, several studies have found slow HR recovery to be associated with a twofold increased mortality risk after adjusting for important covariates (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999; Jouven et al., 2005; Mora et al., 2003; Nishime, Cole, Blackstone, Pashkow, & Lauer, 2000), which is comparable to HR variability's prognostic power (Dekker et al., 2000; Kleiger, Miller, Bigger, & Moss, 1987; Nolan et al., 1998).

To date, three studies (Hughes et al., 2006, 2008; von Kanel et al., 2009) have examined relations between depression and HR recovery following exercise, with mixed results. In the first study of 260 cardiac rehabilitation patients undergoing a treadmill exercise test, Hughes et al. (2006) found that Beck Depression

The authors thank Philippe Stébenne, Silvana Barone, Nadine Bekkouche, and Sandra Pelaez for help with data collection. Funding for the collection of data was provided by operating grants from the Heart and Stroke Foundation of Quebec and the Canadian Institutes of Health Research (CIHR: MOP79445 and MOP89965). Personal support was received for Gordon from the Canadian Hypertension Society (summer studentship), le Fonds de la recherche en santé du Québec (FRSQ; master's fellowship), and a Vanier Ph.D. fellowship. Salary support was received for Bacon and Lavoie (chercheur boursiers) from the FRSQ and from a CIHR New Investigator Award (Bacon).

Address correspondence to: Simon L. Bacon, Ph.D., Montreal Behavioural Medicine Centre, Department of Exercise Science, Concordia University, 7141 Sherbrooke St. West, Montréal, Québec, H4B 1R6, Canada. E-mail: simon.bacon@concordia.ca

PSYCHOPHYSIOLOGY

Inventory–II (BDI-II) scores were significantly negatively correlated with HR recovery 2 min after exercise. However, the results were somewhat difficult to interpret given the high rate of beta-blocker use (83%) and the fact that inclusion of exercise capacity eliminated the relationship between depression and HR recovery. This may indicate that poor HR recovery in depressed individuals is due partly to poorer physical fitness (Lavoie et al., 2004). However, these results were extended in another study of 188 patients with coronary artery disease but not taking beta blockers. Once again, BDI-II scores were predictive of poor HR recovery 1 min after an exercise stress test (Hughes et al., 2008). The relationship between depression and HR recovery remained even after adjustment for resting HR, peak HR, and total test time. On the other hand, a more recent study from another group found that depressive symptoms as measured using the Hospital Anxiety and Depression Scale did not predict 1-min postexercise HR recovery in patients (von Kanel et al., 2009).

These results are encouraging but raise a number of questions. For example, can the association between depression and HR recovery be replicated by another group? Are stronger results associated with higher levels of depression? Are results clearer using a structured clinical interview to diagnose depression as opposed to self-report questionnaires? Is the association between depression and HR recovery due solely to lower fitness as opposed to more general autonomic recovery following exercise? And finally, what are the effects, if any, of depression on the timing of HR recovery? The studies discussed above examined only immediate HR recovery (maximum 2 min after exercise). Although this is understandable, given the focus on parasympathetic activity in the development and progression of CVD, combined with research indicating that short-term HR recovery from exercise is mediated almost exclusively by parasympathetic reactivation, this ignores potential differences associated with depression later in the recovery period. Pharmacologic blockade studies using agents such as atropine and propranolol confirm that HR decrease during the first 30 s is produced almost exclusively by an increase in parasympathetic activity, but afterward the decrease in sympathetic activity becomes increasingly important (Imai et al., 1994). Mathematical models aimed at quantifying sympathetic and parasympathetic contributions to HR during the recovery period support this conclusion (Pierpont & Voth, 2004). As a result, it would be very informative to examine the relationship between depression and both early and a later-stage HR recovery from exercise.

Thus, the objectives of the current study were to (a) extend the current knowledge base by measuring depression with a structured diagnostic interview as well as a self-report questionnaire, (b) look at the association between clinical levels of depression as well as continuous variation in BDI-II scores and CV recovery, (c) control for the effects of a number of potential confounds, and (d) examine the relationship between depression on CV recovery to exercise at two time points to provide further information about the details of autonomic dysregulation. It was possible to accomplish these objectives in part due to the use of a significantly larger sample of patients than previous research.

Method

Participants

This research was a secondary analysis of the Mechanisms and Outcomes of Silent Myocardial Ischemia (MOSMI) study, a longitudinal study aimed at examining the risk factors for silent (painless) ischemia and the impact of silent ischemia on cardiovascular outcomes. Patients were eligible for this study if they had been referred for an exercise stress test using single photon emission computed tomography (SPECT) imaging in the Department of Nuclear Medicine of the Montreal Heart Institute. Patients are most often referred for an exercise stress test either as a screening procedure because their doctor judges them to be at high risk for a cardiac event (e.g., family history, dyslipidimia, or atypical chest pain) or because the patient complains of symptoms of ischemia (e.g., chest pain, fatigue, or increased breathlessness during exercise). A total of 905 patients were recruited. Although there were no age, sex, or race restrictions for inclusion, patients were excluded if they were unable to understand French or English fluently enough to reliably answer questions during the medical and psychiatric interviews. The study also required that participants be excluded if they were pregnant or nursing, suffering from a serious non-CV comorbid condition (e.g., chronic obstructive pulmonary disease, cancer), a pain disorder other than angina, used a nonsteroidal anti-inflammatory agent (NSAID) in the last week, or used an analgesic on the day of the exercise test. Written consent was obtained from all participants. The MOSMI study was approved by the Human Ethics Committee of the Montreal Heart Institute. Of this sample, 886 individuals, the focus of these analyses, had interview, questionnaire, and exercise data.

Procedure

Overview. Participants underwent a two-day protocol SPECT rest–stress test during which HR and blood pressure (BP) were measured at rest, at peak exercise, and 1 min and 5 min after exercise. After completing the stress test, they were administered a structured, psychiatric diagnostic interview, the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spitzer et al., 1994). The PRIME-MD contains modules for the assessment of mood and anxiety disorders. Finally, participants completed a sociodemographic and medical history questionnaire including details regarding medication usage and depressive symptoms.

Depressive symptoms. The BDI-II (Beck, Steer, & Brown, 1996) was used to measure depressive symptoms. This widely used questionnaire consists of 21 items scored from 0 to 3, with higher numbers indicating greater symptom severity. According to a meta-analysis of 165 studies, the BDI-II has an internal consistency of .837 (.007) and a test–retest reliability of .690 (.009; Yin & Fan, 2000). The BDI-II has been shown to have good sensitivity (.82–.90) and specificity (.84–.89) in diabetic patients, a population similar to that used in this study (Lustman, Clouse, Griffith, Carney, & Freedland, 1997).

Assessment of major depression. The PRIME-MD (Spitzer et al., 1994) is a structured psychiatric diagnostic interview designed to detect some of the most common disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV; American Psychiatric Association, 1994). For the present study, a trained research assistant administered the mood and anxiety disorders modules of the electronic version of the PRIME-MD, which assess major and minor depressive disorder, dysthymia, and bipolar disorder as well as panic disorder, generalized anxiety disorder, and other anxiety disorders. Though the PRIME-MD takes between 10 and 20 min to administer, it

has been shown to be of comparable reliability, sensitivity, and specificity to longer structured interviews such as the Structured Clinical Interview for DSM (Spitzer et al., 1994). It has been used successfully in previous studies (Douglas, Taylor, & O'Malley, 2004; Miller, Stetler, Carney, Freedland, & Banks, 2002) assessing the prevalence of psychiatric disorders in CVD patients.

Exercise stress test. The exercise stress test was conducted using a treadmill and followed the modified Bruce protocol (Okin, Ameisen, & Kligfield, 1986). Like the standard Bruce protocol, the speed and incline of the treadmill increases at 3-min intervals. However, the first two stages of the modified protocol begin with a lower workload than the standard test, beginning at a speed of 1.7 mph and 0% grade, then increasing to a 5% grade but remaining at the same speed. The third stage of the modified protocol corresponds to the first stage of the standard protocol. These modifications are meant to adapt the test to elderly and sedentary patients. Participants' HR, systolic BP (SBP), and diastolic BP (DBP) were measured before, every 2 min during, and 1 min and 5 min after the exercise. BP was measured by an experienced technician using a manual sphygmomanometer (Welch Allyn Tycos-767 series, Skaneateles Falls, NY). HR was recorded during the test using a standard 12-lead electrocardiogram configuration (Marquette Medical Systems Inc., Milwaukee, WI). The test ended when patients reached self-reported fatigue, when they had reached at least 85% of their maximum HR, or when they showed signs of malignant arrhythmias, severe hypertension (SBP > 240 mmHg) or hypotension (20 mmHg decline in SBP).

Data Analysis

Missing data were handled using missing at random assumptions following Rubin's rules (Rubin, 1987). The PROC MI method of multivariate imputation in SAS V 9.2 (SAS Institute, Cary, NC) was used to generate five copies of the data set. These were analyzed independently, each with missing values imputed. PROC MIANALYZE was used to average estimates of the variables to give a single mean estimate and adjusted standard error according to Harrell's guidelines (Harrell, 2001). As such all analyses included 886 participants.

Cardiovascular recovery was defined as the difference between the SBP, DBP, and HR measured at peak exercise and the same variable at 1 and 5 min after exercise. Given the time pressures of a busy hospital unit and demand for the equipment, there was significantly more missing data in the 5-min postexercise values than the 1-min values (21% vs. 0%). As a result, separate analyses were conducted examining the relationship between depression and HR recovery at 1 and 5 min. Two sets of General Linear Models were conducted for each CV measure (SBP, DBP and HR), the first examining the effects of MDD on the CV recovery variables measured at 1 min after exercise and the second assessing the effects of MDD on the variables 5 min after exercise. All models included age, sex, CVD history (i.e., having had a previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or cerebrovascular event), BP medication prescription and on-the-day usage, anxiolytic prescription, and antidepressant prescription as covariates. CV reactivity (defined as the difference between the baseline and peak level) of the given variable and exercise capacity in metabolic equivalents of task (METs) were also included as covariates to adjust for the likelihood that depressed patients would fatigue more quickly than nondepressed patients and therefore achieve lower maximal HR and BP, as previous research has shown (Lavoie et al., 2004).

Results

Participant Characteristics

Characteristics of the 886 participants are presented in Table 1. The sample included 610 (68.8%) men and had a mean age of 60 +/− 10 years. Fifty-one participants met diagnostic criteria for MDD, making the overall rate 5.8%. Interestingly, similar to Hughes et al. (2006), people with MDD had significantly lower exercise capacity in terms of metabolic equivalents ($F = 6.80$, $p = .009$). Patients with MDD did not differ from non-MDD patients in terms of their reasons for stopping the stress test, with shortness of breath being the most common reason for stopping in both groups (61.1% in MDD patients, 62.0% in non-MDD patients) and fatigue being the second most common reason (36.0% for MDD patients, 33.1% for non-MDD patients).

1-Min Recovery Analyses

There was a significant effect of MDD on 1-minute HR recovery, β (*SEM*) = −.70 (1.67), $p = .026$, such that patients with MDD had slower HR recovery compared to those without MDD (Figure 1). However, there was no significant effect of MDD on SBP, β (*SEM*) = −1.31 (2.26), $p = .561$, or DBP recovery, β (*SEM*) = −0.31 (1.01), $p = .764$. When similar analyses tested the effect of BDI-II score on CV recovery, no significant results were found. Covariates significantly predicting 1-min recovery included reactivity (predicting SBP, DBP, and HR recovery), age (SBP, HR), anxiolytic prescription (SBP), and exercise capacity (HR).

5-Min Recovery Analyses

There was no significant effect of MDD on 5-min HR recovery, β (*SEM*) = −0.15 (1.31), $p = .910$, SBP recovery, β (*SEM*) = 1.56 (2.86), $p = .590$, or DBP recovery, β (*SEM*) = 2.06 (1.48), $p = .182$. No significant results were found when the main effect of BDI-II score on CV recovery was tested. Covariates significantly predicting 5-min recovery included reactivity (SBP, DBP, and HR), age (SBP), CVD status (SBP), sex (HR), anxiolytic prescription (HR), and exercise capacity (HR).

Discussion

The primary purpose of this study was to assess the relationship between diagnosed MDD and postexercise HR and BP recovery 1 and 5 min after exercise. We hypothesized that patients with MDD would have slower HR and BP recovery compared to patients without MDD at both time points. This hypothesis was partially supported, as MDD was associated with slower HR recovery 1 min after exercise. This suggests that poor autonomic control of the CV system may be a mechanism explaining depressed patients' increased risk of developing CVD. However, our finding that BDI-II scores were not predictive of recovery suggests that subclinical levels of depression are not as reliably associated with ANS dysfunction. This may explain some of the

Table 1. *Participant Characteristics*

	Nondepressed	Depressed	*p* value	Data missing (%)
Demographics				
n	835	51		
Sex (% women)[a]	30.4	43.1	.057	0
Age (years)[a]	60.5 ± 9.8	56.0 ± 9.7	.002	0
Caucasian (%)	95.9	95.1	.807	16
High school diploma (%)	53.5	43.1	.149	0
BDI-II score	8.0 ± 6.4	19.0 ± 9.7	<.001	16
Exercise capacity (METS)	8.3 ± 1.7	7.6 ± 1.4	.014	1
% of max HR reached	88.4	83.3	.006	1
CVD risk factors and events				
Body mass index	27.5 ± 4.3	28.9 ± 5.6	.046	14
Current smoker (%)	17.2	33.3	.021	15
CVD (%)	33.4	35.3	.783	0
Hypertension (%)	61.3	66.0	.524	9
Hypercholesterolemia (%)	61.8	59.6	.764	10
Past MI (%)	22.6	20.0	.708	24
PCI (%)	24.7	33.3	.228	25
CABG (%)	14.1	10.3	.504	26
Stroke (%)	2.5	3.2	.801	38
Medication usage				
Anxiolytics (%)[a]	15.1	17.6	.622	0
Antidepressants (%)[a]	5.9	19.6	<.0001	0
Ace inhibitors (%)	21.7	27.7	.338	10
Beta blockers (%)	29.9	29.8	.985	10
ARBs (%)	15.2	10.6	.399	10
Antihypertensives (%)[a]	52.4	48.9	.646	10
Antihypertensive on-the-day usage (%)[a]	44.3	41.1	.662	0
Statins (%)	50.7	46.8	.609	10

Note: BDI: Beck Depression Inventory; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery; ARB: angiotensin receptor blockers.
[a]Included in multiple imputation analyses.

variance in previous studies examining the relation between depression and exercise recovery.

Although a full explanation of the finding that MDD was associated with slower HR recovery at 1 min but not 5 min after exercise awaits further research, this may be due to the relative contributions of parasympathetic and sympathetic activity to recovery. For example, Imai et al. (1994) found that whereas atropine but not propranolol influenced the immediate decrease in heart rate upon cessation of exercise, propranolol had a greater impact on the degree of heart rate recovery several minutes later. As a result, the findings suggest that in the present sample MDD was associated more with parasympathetic than sympathetic dysregulation. Previous studies have found depression to be linked to parasympathetic dysregulation, as indicated by high-frequency heart rate variability (Hughes & Stoney, 2000; Stein et al., 2000) as well as sympathetic activity as indicated by elevated plasma and urinary catecholamines (Esler et al., 1982; Lake et al., 1982; Roy, Pickar, De Jong, Karoum, & Linnoila, 1988).

A competing explanation for the delayed HR recovery among patients with MDD may relate to depressed individuals' well-known tendency to ruminate (Nolen-Hoeksema, 2000). Studies have found that increased rumination following an emotionally laden task is associated with reduced cardiovascular recovery (Glynn, Christenfeld, & Gerin, 2002). Considering that a test

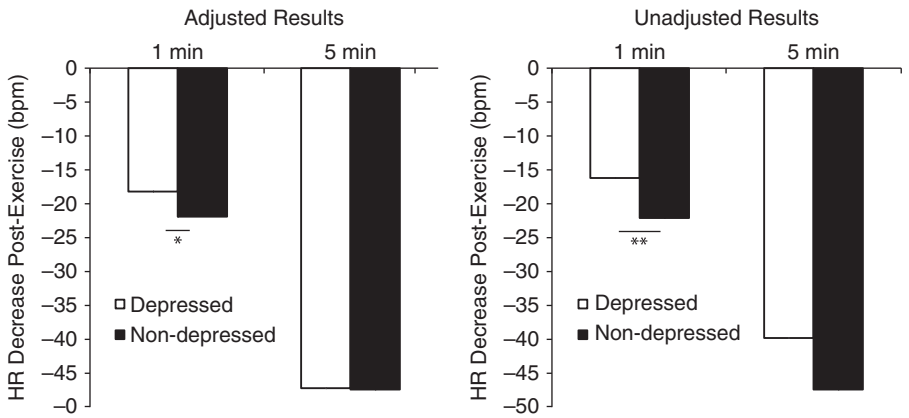

Figure 1. Heart rate recovery at 1 and 5 min according to depression status. bpm: beats per minute. $N = 886$. *$p = .026$, **$p < .0001$.

screening for the presence of CVD would likely be emotionally laden for most patients, depressed patients' reduced early CV recovery could, in fact, be attributed to increased rumination over the stress test compared to their nondepressed counterparts. Future research examining the relationship between depression and CV recovery should assess posttask rumination to explore this possibility.

The adjusted difference of 3.7 beats per minute (bpm) 1 min after exercise between depressed and nondepressed participants may have clinical significance. For example, Shetler et al. (2001) followed 2,193 men who underwent a similar treadmill test for 7 years. They found that individuals who died during the follow-up period had a 2.9 bpm smaller decrease in HR 1 min following exercise compared to survivors, independent of a number of characteristics. Regardless of whether or not the samples are entirely comparable, this suggests that the difference in HR change observed in the present study is potentially important.

The study had several strengths, including a large sample size and clinical assessment of MDD. Also, while corroborating previous findings indicating poorer fitness in many depressed individuals (Lavoie et al., 2004; Marchionni et al., 2000; Ruo, Rumsfeld, Pipkin, & Whooley, 2004), by statistically adjusting for exercise capacity, the results indicate that the association between MDD and HR recovery is unlikely to be solely due to differences in fitness. In this respect, the results are consistent with Hughes et al.'s (2008) second study.

As far as additional limitations, the study was purely cross-sectional, making it impossible to infer causal relationships. As well, although the results are adjusted for recent beta-blocker and psychotropic use, statistical adjustments are limited in that they only control for the average effect of these medications, whereas the effects of these medications vary widely across individuals. The fact that there are patients with and without MDD taking antidepressants may also complicate the interpretation of the diagnostic categories. However, when the interaction between MDD status and antidepressant use was tested, it was found to be nonsignificant, suggesting that current symptoms of depression are associated with poor HR recovery regardless of antidepressant treatment. Furthermore, the overall percentage of individuals with MDD in the present sample (5.8%) was somewhat lower than might be expected based on rates observed in other samples of CVD patients (Herrmann, Brand-Driehorst, Buss, & Ruger, 2000). Although this may limit the study's generalizability to CVD patients with more typical rates of MDD, several points must be considered. First, the sex ratio of MDD in the current study (8.2% in women vs. 4.7% in men) was consistent with the typical 2:1 ratio (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). Second, clinical interviews tend to produce more stringent diagnoses and can lower rates of observed psychopathology. Although self-report instruments such as the BDI are often used with CVD patients, interviews are probably better able to distinguish symptoms such as lack of energy and sleep problems that are due to CVD rather than depression. Finally, there may be local differences in rates of depression.

In conclusion, the present findings suggest that MDD is associated with slower HR recovery from exercise. Postexercise recovery is an informative, important characteristic reflecting autonomic regulation and risk for cardiovascular disease.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed). Washington, DC: Author.

Barefoot, J. C., & Schroll, M. (1996). Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*, *93*, 1976–1980.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine*, *66*, 802–813.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory–II*. San Antonio, TX: Psychological Corporation.

Carney, R. M., Freedland, K. E., Steinmeyer, B., Blumenthal, J. A., Berkman, L. F., Watkins, L. L., & Jaffe, A. S. (2008). Depression and five year survival following acute myocardial infarction: A prospective study. *Journal of Affective Disorders*, *109*, 133–138.

Cole, C. R., Blackstone, E. H., Pashkow, F. J., Snader, C. E., & Lauer, M. S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *New England Journal of Medicine*, *341*, 1351–1357.

Dekker, J. M., Crow, R. S., Folsom, A. R., Hannan, P. J., Liao, D., Swenne, C. A., & Schouten, E. G. (2000). Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: The ARIC Study. Atherosclerosis Risk In Communities. *Circulation*, *102*, 1239–1244.

Douglas, K. M., Taylor, A. J., & O'Malley, P. G. (2004). Relationship between depression and C-reactive protein in a screening population. *Psychosomatic Medicine*, *66*, 679–683.

Esler, M., Turbott, J., Schwarz, R., Leonard, P., Bobik, A., Skews, H., & Jackman, G. (1982). The peripheral kinetics of norepinephrine in depressive illness. *Archives of General Psychiatry*, *39*, 295–300.

Glynn, L. M., Christenfeld, N., & Gerin, W. (2002). The role of rumination in recovery from reactivity: Cardiovascular consequences of emotional states. *Psychosomatic Medicine*, *64*, 714–726.

Harrell, F. E. (2001). *Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis*. New York: Springer.

Herrmann, C., Brand-Driehorst, S., Buss, U., & Ruger, U. (2000). Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. *Journal of Psychosomatic Research*, *48*, 455–462.

Hughes, J. W., Casey, E., Luyster, F., Doe, V. H., Waechter, D., Rosneck, J., & Josephson, R. (2006). Depression symptoms predict heart rate recovery after treadmill stress testing. *American Heart Journal*, *151*, 1122.e1–6.

Hughes, J. W., & Stoney, C. M. (2000). Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosomatic Medicine*, *62*, 796–803.

Hughes, J. W., York, K. M., Li, Q., Freedland, K. E., Carney, R. M., & Sheps, D. S. (2008). Depressive symptoms predict heart rate recovery after exercise treadmill testing in patients with coronary artery disease: Results from the Psychophysiological Investigation of Myocardial Ischemia study. *Psychosomatic Medicine*, *70*, 456–460.

Imai, K., Sato, H., Hori, M., Kusuoka, H., Ozaki, H., Yokoyama, H., & Kamada, T. (1994). Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *Journal of the American College of Cardiology*, *24*, 1529–1535.

Jouven, X., Empana, J. P., Schwartz, P. J., Desnos, M., Courbon, D., & Ducimetiere, P. (2005). Heart-rate profile during exercise as a predictor of sudden death. *New England Journal of Medicine*, *352*, 1951–1958.

Joynt, K. E., Whellan, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: Mechanisms of interaction. *Biological Psychiatry*, *54*, 248–261.

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders*, *29*, 85–96.

Kleiger, R. E., Miller, J. P., Bigger, J. T. Jr., & Moss, A. J. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *American Journal of Cardiology*, *59*, 256–262.

Lahiri, M. K., Kannankeril, P. J., & Goldberger, J. J. (2008). Assessment of autonomic function in cardiovascular disease: Physiological basis and prognostic implications. *Journal of the American College of Cardiology*, *51*, 1725–1733.

Lake, C. R., Pickar, D., Ziegler, M. G., Lipper, S., Slater, S., & Murphy, D. L. (1982). High plasma norepinephrine levels in patients with major affective disorder. *American Journal of Psychiatry*, *139*, 1315–1318.

Lavoie, K. L., & Fleet, R. P. (2000). The impact of depression on the course and outcome of coronary artery disease: Review for cardiologists. *Canadian Journal of Cardiology*, *16*, 653–662.

Lavoie, K. L., Fleet, R. P., Lesperance, F., Arsenault, A., Laurin, C., Frasure-Smith, N., & Bacon, S. L. (2004). Are exercise stress tests appropriate for assessing myocardial ischemia in patients with major depressive disorder? *American Heart Journal*, *148*, 621–627.

Lesperance, F., Frasure-Smith, N., Talajic, M., & Bourassa, M. G. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*, *105*, 1049–1053.

Lustman, P. J., Clouse, R. E., Griffith, L. S., Carney, R. M., & Freedland, K. E. (1997). Screening for depression in diabetes using the Beck Depression Inventory. *Psychosomatic Medicine*, *59*, 24–31.

Marchionni, N., Fattirolli, F., Fumagalli, S., Oldridge, N. B., Del Lungo, F., Bonechi, F., & Masotti, G. (2000). Determinants of exercise tolerance after acute myocardial infarction in older persons. *Journal of the American Geriatrics Society*, *48*, 146–153.

Miller, G. E., Stetler, C. A., Carney, R. M., Freedland, K. E., & Banks, W. A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *American Journal of Cardiology*, *90*, 1279–1283.

Mora, S., Redberg, R. F., Cui, Y., Whiteman, M. K., Flaws, J. A., Sharrett, A. R., & Blumenthal, R. S. (2003). Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: A 20-year follow-up of the lipid research clinics prevalence study. *JAMA*, *290*, 1600–1607.

Nishime, E. O., Cole, C. R., Blackstone, E. H., Pashkow, F. J., & Lauer, M. S. (2000). Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*, *284*, 1392–1398.

Nolan, J., Batin, P. D., Andrews, R., Lindsay, S. J., Brooksby, P., Mullen, M., & Fox, K. A. A. (1998). Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*, *98*, 1510–1516.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology*, *109*, 504–511.

Okin, P. M., Ameisen, O., & Kligfield, P. (1986). A modified treadmill exercise protocol for computer-assisted analysis of the ST segment/heart rate slope: Methods and reproducibility. *Electrocardiology*, *19*, 311–318.

Pierpont, G. L., & Voth, E. J. (2004). Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. *American Journal of Cardiology*, *94*, 64–68.

Roy, A., Pickar, D., De Jong, J., Karoum, F., & Linnoila, M. (1988). Norepinephrine and its metabolites in cerebrospinal fluid, plasma, and urine. Relationship to hypothalamic-pituitary-adrenal axis function in depression. *Archives of General Psychiatry*, *45*, 849–857.

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation*, *99*, 2192–2217.

Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys*. New York: Wiley.

Ruo, B., Rumsfeld, J. S., Pipkin, S., & Whooley, M. A. (2004). Relation between depressive symptoms and treadmill exercise capacity in the Heart and Soul Study. *American Journal of Cardiology*, *94*, 96–99.

Rutledge, T., Reis, S. E., Olson, M., Owens, J., Kelsey, S. F., Pepine, C. J., & Merz, C. N. (2006). Depression is associated with cardiac symptoms, mortality risk, and hospitalization among women with suspected coronary disease: The NHLBI-sponsored WISE study. *Psychosomatic Medicine*, *68*, 217–223.

Shetler, K., Marcus, R., Froelicher, V. F., Vora, S., Kalisetti, D., Prakash, M., & Myers, J. (2001). Heart rate recovery: Validation and methodologic issues. *Journal of the American College of Cardiology*, *38*, 1980–1987.

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy, F. V., Hahn, S. R., & Johnson, J. G. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA*, *272*, 1749–1756.

Stein, P. K., Carney, R. M., Freedland, K. E., Skala, J. A., Jaffe, A. S., Kleiger, R. E., & Rottman, J. N. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research*, *48*, 493–500.

von Kanel, R., Saner, H., Kohls, S., Barth, J., Znoj, H., Saner, G., & Schmid, J. (2009). Relation of heart rate recovery to psychological distress and quality of life in patients with chronic heart failure. *European Journal of Cardiovascular Prevention and Rehabilitation*, *16*, 645–650.

Yin, P., & Fan, X. (2000). Assessing the reliability of Beck Depression Inventory scores: Reliability generalization across studies. *Educational and Psychological Measurement*, *60*, 201–223.

(Received November 7, 2010; Accepted May 24, 2011)