

Association of Depression With Reduced Heart Rate Variability in Coronary Artery Disease

Robert M. Carney, PhD, Roger D. Saunders, PhD, Kenneth E. Freedland, PhD, Phyllis Stein, PhD, Michael W. Rich, MD, and Allan S. Jaffe, MD

Decreased heart rate (HR) variability is an independent risk factor for mortality in cardiac populations. Clinical depression has also been associated with adverse outcomes in patients with coronary artery disease (CAD). This study tests the hypothesis that depressed patients with CAD have decreased HR variability compared with nondepressed CAD patients. Nineteen patients with angiographically documented CAD and either major or minor depression were compared with a sample of nondepressed CAD patients according to age, sex, and

smoking status. All patients underwent 24-hour Holter monitoring, and the standard deviation of all normal-to-normal intervals was used as the primary index of HR variability. HR variability was significantly lower in depressed than nondepressed patients (90 ± 35 vs 117 ± 26 ms; $p \leq 0.01$), even after adjusting for relevant covariates. Thus, decreased HR variability may help explain the increased risk for cardiac mortality and morbidity in depressed CAD patients.

(Am J Cardiol 1995;76:562-564)

Psychoiatric depression is associated with increased morbidity and mortality in patients with coronary artery disease (CAD).¹⁻⁹ Recent studies have found that depressed psychiatric patients have reduced heart rate (HR) variability, reflecting altered autonomic tone.^{10,11} Decreased HR variability predicts mortality after myocardial infarction¹² and in patients with heart failure.¹³ In an earlier study, we found a trend toward lower HR variability during 24-hour ambulatory electrocardiographic monitoring in a small group of depressed patients with CAD, compared with an unselected group of nondepressed CAD patients.¹⁴ Depressed patients with CAD tend to be younger, are more likely to be women, and are more likely to smoke than nondepressed patients¹⁵; these factors are known to affect HR variability.¹⁶⁻¹⁸ Accordingly, the present study tests the hypothesis that HR variability is lower in depressed patients with CAD than in nondepressed CAD patients matched for age, sex, and smoking status.

METHODS

Subject pool: Patients at Barnes and Jewish Hospitals, St. Louis, Missouri, undergoing elective coronary arteriography for diagnostic evaluation of CAD, were eligible to participate if they: (1) were aged ≤ 75 years; (2) had no history of significant arrhythmias, congestive heart failure, a recent (within 4 weeks) myocardial infarction, or other severe systemic illness, coronary artery bypass surgery or angioplasty; cardiomyopathy or valvular heart disease other than mitral valve prolapse; and (3) had $\geq 50\%$ stenosis in ≥ 1 major coronary artery.

From the Departments of Psychiatry and Medicine, Washington University School of Medicine, St. Louis, Missouri. This study was supported by Grant RO1 HL42427-03 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received March 27, 1995; revised manuscript received and accepted June 21, 1995.

Address for reprints: Robert M. Carney, PhD, Department of Psychiatry, Washington University School of Medicine, 216 South Kingshighway, St. Louis, Missouri 63110.

The first 100 patients meeting these criteria who gave informed consent formed the subject pool for this study.

Medical assessments: Left heart catheterization, hemodynamics, and left ventricular and selective coronary angiography were performed according to standard techniques. Coronary arteriograms and left ventriculograms were interpreted independently by experienced angiographers who were blinded to the results of the psychiatric interview and Holter monitoring. CAD was defined as a $\geq 50\%$ reduction in the luminal diameter of ≥ 1 major coronary artery or branch. Left ventricular ejection fraction was calculated by the area-length method. Standardized data forms were used to abstract other pertinent medical information from hospital records.

Psychiatric interview: A modified version of the National Institute of Mental Health Diagnostic Interview Schedule¹⁹ was administered on the day of catheterization to determine the presence of psychiatric disorders. It was modified to assess the chronicity of current depressive symptoms. The interviewers had extensive training and prior experience with psychiatric interviews and were blinded to HR variability data. Diagnoses of major or minor depression, as defined by the current American Psychiatric Association Diagnostic and Statistical Manual (DSM-IV),²⁰ were derived from the interview data.

Ambulatory monitoring: A 24-hour electrocardiogram was recorded from a Delmar Avionics 559 Holter monitor during the day after catheterization. It was obtained before rather than after hospital discharge, to minimize the potential confound between depression and physical activity level. Consequently, physical exertion and exertion-related electrocardiographic events were minimized in both depressed and nondepressed patients. The electrocardiograms were analyzed on a Marquette SXP scanner, running software version 5.7 (Marquette Electronics, Inc., Milwaukee, Wisconsin). All supraventricular and ventricular ectopic beats were excluded from the analysis.

Heart rate variability: The standard deviation of all normal RR intervals (SDNN) is the most widely used

TABLE I Demographics and Medical Characteristics by Matched Pair Group			
	Depressed Patients (n = 19)	Nondepressed Patients (n = 19)	p Value
Age (yr)	58.4 ± 9.7	59.5 ± 9.1	0.70
Men	12 (63)	12 (63)	1.00
Current smoker	9 (47)	6 (32)	0.32
History of myocardial infarction	9 (47)	7 (37)	0.51
Number of vessels with ≥50% stenosis	2.2 ± 0.9	1.8 ± 1.0	0.21
Number of vessels with ≥75% stenosis	1.8 ± 1.0	1.1 ± 0.9	0.02
Left ventricular ejection fraction	60.1 ± 17.1	63.6 ± 14.1	0.53
Diabetes mellitus	7 (37)	5 (26)	0.49
Values are expressed as mean ± SD or number (%).			

index of HR variability. It reflects all of the time-domain HR variability, and it is an independent predictor of mortality after myocardial infarction.¹² It was therefore selected as the primary measure of HR variability for this study. Other time-domain indexes of HR variability were computed for exploratory analyses, including 2 measures of short-term variability that reflect primarily vagal influences (pNN50, the proportion of adjacent cycles differing by >50 ms, and rMSSD, the root-mean-square of successive differences), an index of intermediate-term variability (SDNNIDX, the average of the standard deviations of all normal-to-normal intervals calculated for each 5-minute interval), and an additional index of long-term variability reflecting circadian and other rhythms (the standard deviation of the 5-minute averages of all normal RR intervals). Because Holter monitors lacked timing tracks to calibrate the tape speed, frequency-domain indexes were not analyzed.

Subjects: Major depression was diagnosed in 9 patients and minor depression was diagnosed in 10. These patients were matched with 19 nondepressed patients according to age, sex, and smoking status. Matches were made by research personnel who were blinded to all other data.

Data analysis: Chi-square and Fisher's exact tests were used to test univariate associations between categorical variables. Two-tailed paired *t* tests were used for univariate comparisons of continuous variables. Analysis of covariance was used to control for significant covariates. Alpha was set at 0.05 per comparison.

RESULTS

Medical and demographic comparisons of depressed and nondepressed patients are presented in Table I. Subjects were evenly matched for age and sex, but there were more current smokers among depressed than nondepressed patients, and some pairs could not be matched on smoking status. However, the difference was not statistically significant. Depressed and nondepressed patients had a similar number of vessels with ≥50% stenosis, but depressed patients had significantly more vessels with ≥75% stenosis. There were no other significant medical or demographic differences. No patient in either group was taking β blockers at the time of the study, and

TABLE II Exploratory Time-Domain Index of Heart Rate Variability by Matched Pair Group			
HRV Index	Depressed Patients (n = 19)	Nondepressed Patients (n = 19)	p Value
SDANN (ms)	74 ± 32	94 ± 17	0.02
SDNNIDX (ms)	46 ± 19	58 ± 26	0.12
pNN50 (ms)	11 ± 1	18 ± 17	0.12
rMSSD (ms)	31 ± 14	42 ± 25	0.11
Values are expressed as mean ± SD. HRV = heart rate variability; pNN50 = proportion of adjacent cycles differing by >50 ms; rMSSD = root-mean-square of successive differences; SDANN = standard deviation of the 5-minute averages of all normal RR intervals; SDNNIDX = average of the standard deviations of all normal RR intervals for each 5-minute segment.			

there were no differences with respect to any other cardiac medications.

SDNN was significantly lower in depressed (90 ± 35 ms) than nondepressed patients (117 ± 26 ms; *p* < 0.01). After controlling for the number of vessels with ≥75% stenosis, depression was retained in the model (*p* = 0.04). Covariate-adjusted least-squares mean SDNNs for depressed and nondepressed groups were 92 and 115 ms, respectively.

Mean HR was determined by averaging all normal RR cycle intervals. Depressed patients had a mean normal RR interval of 973 ± 160 ms compared with 936 ± 231 ms for nondepressed patients (*p* = 0.37).

All of the secondary indexes of HR variability were lower in depressed than in nondepressed patients, but only 1 index (the standard deviation of the 5-minute averages of all normal RR intervals) was significantly lower. These data are presented in Table II.

DISCUSSION

During 24 hours of Holter monitoring, depressed patients with CAD had significantly lower HR variability, as measured by SDNN, than did nondepressed matched controls. Decreased SDNN is an independent risk factor for mortality in postmyocardial infarction patients.¹² A second index of long-term HR variability (the standard deviation of the 5-minute averages of all normal RR intervals) was also significantly lower in depressed patients, and this index predicts mortality in patients with heart failure.¹³

Although depressed and nondepressed patients differed with respect to the number of vessels with ≥75% stenosis, HR variability remained significantly lower in depressed patients after adjusting for this difference. Reduced long-term HR variability may reflect increased sympathetic or decreased vagal tone in these patients. Although there were no significant differences in the indexes of intermediate- or short-term HR variability, the differences did approach significance. A larger sample may be required to detect any real difference in short-term variability.

Decreased HR variability in depressed patients, reflecting dysregulation of the autonomic nervous system, may help to explain the increased risks for mortality and morbidity that have been observed in depressed CAD patients. Decreased HR variability as a result of a reduction in vagal tone has been found to predispose to ven-

tricular fibrillation in experimental myocardial infarction in animal models.²¹ Although the patients in this study were medically stable at the time of assessment, during subsequent critical stages of their illness, such as the period after an acute myocardial infarction, reduced HR variability could place them at increased risk for further cardiac morbidity or mortality.

The clinical significance of these findings can be appreciated by comparing them with findings of studies on the prognostic significance of reduced HR variability. In a study of patients with congestive heart failure,¹³ for example, having a standard deviation of 5-minute averages ≤ 55 ms was a significant independent risk factor for mortality. In the present study, 5 of the depressed patients (26%) and none of the nondepressed patients were below 55 ms.

Although the indexes reflecting short-term HR variability only approached significance, the results of this study are generally consistent with those of Dalack and Roose¹⁰ and Rechlin et al¹¹ who reported decreased high-frequency variability in medically well, depressed psychiatric patients compared with normal controls. In contrast to their findings, Yeragani et al²² reported no difference in HR variability between depressed psychiatric patients and normal controls. However, there are several important differences between the study of Yeragani et al and the present study: The patients in their study were medically well and considerably younger than those in our sample. Furthermore, HR variability was measured by electrocardiogram during an orthostatic challenge for a total of approximately 6 minutes, a protocol that did not capture long-term variability. The present study utilized 24-hour Holter electrocardiographic monitoring of hospital inpatients whose physical activity was minimal. Although the implications of the different methods for measuring HR variability in depressed patients do deserve further investigation, the present study sought to measure and quantify HR variability in ways that were consistent with previous studies of its prognostic significance.

In conclusion, the results of this study support the hypothesis that depression is associated with altered cardiac autonomic tone in patients with CAD. Whether such alterations actually explain the increased morbidity and mortality seen in depressed CAD patients remains to be determined. Previous studies have shown that depression is also associated with reduced adherence to prescribed cardiac medications,²³ and that depressed CAD patients are more likely to be current smokers and to have hypertension than nondepressed CAD patients.¹⁵

Prospective studies are needed to determine the relative importance of these candidate mechanisms on prognosis in depressed CAD patients, and to determine whether effective treatment of depression can reduce morbidity and mortality.

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