Change in Heart Rate and Heart Rate Variability During Treatment for Depression in Patients With Coronary Heart Disease

ROBERT M. CARNEY, PHD, KENNETH E. FREEDLAND, PHD, PHYLLIS K. STEIN, PHD, JUDITH A. SKALA, RN, MA, PATRICIA HOFFMAN, PHD, AND ALLAN S. JAFFE, MD

Objective: Major depression is a common problem in patients with coronary heart disease (CHD) and is associated with an increased risk for cardiac morbidity and mortality. It is not known whether treating depression will improve medical prognosis in patients with CHD. Depression is also associated with elevated heart rate and reduced heart rate variability (HRV), which are known risk factors for cardiac morbidity and mortality that may explain the increased risk associated with depression. The purpose of this study was to determine whether treatment for depression with cognitive behavior therapy (CBT) is associated with decreased heart rate or increased HRV. **Methods:** Thirty depressed patients with stable CHD, classified as either mildly or moderately to severely depressed, received up to 16 sessions of CBT. The 24-hour heart rate and HRV were measured in these patients and in 22 medically comparable nondepressed controls before and after treatment of the depressed patients. **Results:** Average heart rate and daytime rMSSD (reflecting mostly parasympathetic activity) improved significantly in the severely depressed patients, but remained unchanged in the mildly depressed and the control patients. However, only rMSSD improved to a level comparable to the control patients. None of the remaining indices of HRV showed improvement. **Conclusions:** The results suggest that treating depression with CBT may reduce heart rate and increase short-term HRV. Thus, CBT may have a beneficial effect on a risk factor for mortality in depressed patients with coronary heart disease. A randomized, controlled study is needed to confirm these findings. **Key words:** depression, coronary heart disease, heart rate variability.

CHD = coronary heart disease; CBT = cognitive behavior therapy; MI = myocardial infarction; ENRICHD = enhancing recovery in coronary heart disease; HRV = heart rate variability; BDI = Beck Depression Inventory; SDNN = the standard deviation of N-to-N intervals, in msec; SDNNIDX = the average of standard deviations of N-to-N intervals for each 5-minute interval, in msec; rMSSD = the root mean square successive difference of N-to-N intervals, in msec; SSRI = selective serotonin reuptake inhibitor.

Depression is common in patients with CHD. Approximately one in five patients have major depression at the time of diagnostic cardiac catheterization (1–3) or after acute MI (4–7). Another one in five have some form of minor depression at these times (2, 5). Depression increases the risk that patients with newly diagnosed CHD will experience a cardiac event within 12 months (8, 9), and it is a risk factor for cardiac mortality and medical morbidity after an acute MI (7, 10–12). In some studies, as much as a four-fold adjusted relative risk of mortality has been reported among depressed compared with nondepressed post-MI patients (7).

The more severe forms of depression seem to be associated with a greater risk for cardiac events than are milder depressive disorders. For example, Barefoot and his colleagues (9) found that patients with documented coronary artery disease who had moderate to severe depression had an 84% greater risk for mortality than did nondepressed patients with coronary disease, vs. a 57% for patients with mild depression. Another study of 1551 participants from the Baltimore site in the Epidemiological Catchment Area (ECA) study who were free of heart disease in 1981, found that patients with a history of dysphoric mood had an odds ratio for MI of 2.1 (95% CI, 1.2–3.7), whereas those with a history of major depression had an odds ratio of 4.5 (95% CI, 1.7–12.4) (13). Thus, it seems that the risk of cardiac morbidity and mortality associated with depression exists along a continuum of severity, much like serum cholesterol or hypertension.

Whether this risk can be reduced in these patients by treating their depression is unknown. A large, multicenter clinical trial (the Enhancing Recovery in Coronary Heart Disease [ENRICHD] trial) currently is in progress, but the results are not expected to be available for several years.

Although traditional treatments may be effective for depression in many patients with CHD (14), they may not reduce the risk for medical morbidity and mortality unless the underlying pathophysiological or behavioral mechanisms also improve. Post (15) has proposed that depression, even if it has been successfully treated, may have residual neurophysiological effects that never normalize and that even may worsen with

From the Departments of Psychiatry and Medicine (R.M.C., K.E.F., P.K.S., J.A.S., P.H.), Washington University School of Medicine, St. Louis, Missouri and Department of Medicine (A.S.J.), Mayo Clinic, Rochester Minnesota

Address reprint requests to: Robert M. Carney, PhD, Behavioral Medicine Center, Washington University School of Medicine, 4625 Lindell Blvd. Suite 420, St. Louis, MO 63108.

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recurrences. Some of these purportedly irreversible neurophysiological changes may be related to the increased risk for mortality in CHD patients.

We and others (16–18) have argued that altered autonomic tone associated with depression is a likely contributor to the increased risk of mortality in patients with CHD. Measuring heart rate and its HRV is one of the principal methods for assessing cardiac autonomic tone (19). Low HRV, reflecting high sympathetic and/or low vagal tone, has been shown to be a strong, independent predictor of mortality in patients with a recent acute MI (20), a history of MI (21), stable coronary disease (22), or congestive heart failure (23). Increased heart rate is also a predictor of cardiac mortality and morbidity in individuals without known CHD and in patients recovering from an acute MI (24–26).

Depression has been associated with increased heart rate (27–29) and reduced HRV in medically well psychiatric patients (30–32), although not all studies have found these effects (eg, 33). However, we and others (34–36) have found higher heart rate and lower HRV in depressed patients with stable coronary disease compared with medically nondepressed patients with stable coronary disease (35–38). This difference is especially pronounced with more severe depression (37). In our most recent study of medically stable CHD patients (ie, event-free for at least 6 months) (37), 47% of those who were moderately or severely depressed, 29% of those who were mildly depressed, and 13% of those who were not depressed, had a level of HRV previously shown to be associated with a 4.4 relative risk of mortality over 2 years in a comparable sample of CHD patients (39). The difference between the nondepressed and the moderately to severely depressed groups was statistically significant ($p = .02$). Thus, the patterns of heart rate and HRV seen in depressed patients may have prognostic importance, especially in patients with moderate to severe depression.

The purpose of this study was to determine whether treatment of depression in a group of medically stable patients with documented CHD is associated with a reduced 24-hour heart rate or increased HRV after 4 months of treatment. If so, the hypothesis that treatment of depression improves prognosis would be indirectly supported.

METHOD

Subjects

Medically stable patients with angiographically documented coronary artery disease were eligible to participate if they were ≤75 years old and had no history or current evidence of congestive heart failure, a recent (within 6 months) myocardial infarction, severe systemic illness, a noncardiac medical illness that could cause autonomic dysfunction (eg, uncontrolled diabetes or renal failure), a recent (within 6 months) coronary artery bypass surgery or angioplasty, cardiomyopathy, valvular heart disease other than mitral value prolapse, substance abuse, or a significant psychiatric disorder other than depression. Patients were excluded if they were scheduled for revascularization, not on a stable medication regimen, or receiving any medications that could affect cardiac autonomic tone, including beta blockers and tricyclic antidepressants. Some of the subjects in this study also participated in a larger cross-sectional study of HRV and depression. The baseline characteristics of the larger sample have been reported previously (37).

Both the depressed and nondepressed patients were recruited from cardiac rehabilitation centers and through newspaper advertisements. The depressed patients were offered free treatment for depression, and both the depressed and nondepressed subjects were paid $100 for their participation. Recruitment continued for 24 months, and depressed and nondepressed patients were enrolled concurrently throughout the recruitment phase of the study.

Procedure

Screening. Patients were initially screened to determine whether they met the medical inclusion or exclusion criteria. They then were scheduled to complete a psychodiagnostic interview.

Psychiatric Interview. A modified version of the National Institute of Mental Health Diagnostic Interview Schedule (40) was administered to determine the presence of depression and to identify other psychiatric disorders. The interview was modified to assess the duration of current depressive symptoms. The interviewer had extensive training and prior experience with psychiatric interviewing. The diagnosis of major depression, as defined by the current edition of the American Psychiatric Association *Diagnostic and Statistical Manual* (DSM-IV) (41), was derived from the interview. The DSM-IV criteria were also used to classify patients after treatment as remitted, partially remitted, or not remitted.

Severity of Depression. The BDI, a 21-item questionnaire (41), was administered to assess the subject's self-reported severity of depression. BDI scores between 10 and 19 were classified indicating mild to low moderate depression, and scores of 20 or higher as high moderate to severe depression (42).

HRV Measurement. Twenty-four-hour ambulatory electrocardiogram (ECG) recordings were obtained on an outpatient basis using Marquette Series 8500 Holter monitors (GE Marquette Medical Systems, Milwaukee, WI) and analyzed on a Marquette SXP Laser Holter scanner (software version 5.8) using standard techniques to accurately label beats and artifacts. Patients were excluded from further analysis if they were not in predominantly regular sinus rhythm or if they had sustained atrial arrhythmias such as atrial fibrillation or greater than 10% ectopic complexes. Beat-stream files, representing the time and classification of each QRS (electrocardiographic wave complex or interval) complex, were transferred to a Sun SPARCstation computer (Sun Microsystems, Inc., Mt. View, CA) for heart rate variability analysis using validated techniques (43, 44).

Time Domain HRV Indices. HRV can be described either by frequency or time domain indices. To be consistent with our previous studies (35–37), 24-hour time domain indices of HRV were computed, including average heart rate (reflecting normal-to-normal intervals in beats/min), SDNN (the SD of normal-to-normal intervals, in msaq), SDNNIDX (the average of the SD of normal-to-normal intervals for each 5-minute interval, in ms), and rMSSD (the root mean square successive difference of normal-to-normal intervals, in ms). These indices were selected because they are thought to com-

pletely sample the different domains of HRV. SDNN reflects all sources of variability including circadian effects and is primarily determined by long-term HRV. RMSSD primarily reflects parasympathetically mediated short-term changes in heart rate, and SDNNIDX reflects intermediate variability, a mixture of parasympathetic and sympathetic influences (45). Based on the results of recent studies suggesting that daytime HRV may be more predictive of cardiac events than 24-hour HRV (46), we also computed daytime (8:00 AM to 8:00 PM) and nighttime (12:00 AM to 6:00 AM) HRV indices.

Exercise. Subjects were asked to provide a detailed description of their exercise routines and other physical activities. Their responses were then classified as: 0) no regular exercise; 1) limited exercise, not sufficiently aerobic; 2) aerobic exercise lasting 20 minutes or longer, 1 to 2 times per week; 3) aerobic exercise lasting 20 minutes or longer, 3 to 6 times per week; or 4) aerobic exercise lasting 20 minutes or longer on a daily basis.

Cognitive Behavior Therapy. Patients were seen by one of two licensed clinical psychologists with training and experience in cognitive behavior therapy. The intervention was conducted following the guidelines of two treatment manuals. The first, *Cognitive Therapy of Depression* (42), presents the cognitive model of depression and the core CBT protocol. It has been used in most previous outcome studies of CBT for depression. The second, *Cognitive Therapy for Cardiac Patients* (47) provides guidelines for adapting CBT for use with depressed cardiac patients.

The patients were seen for up to 16 sessions of individual outpatient CBT. In most cases, the treatment sessions were held weekly and limited to 50 minutes. The frequency of sessions was increased temporarily to twice a week if the patient was severely depressed, judged by the therapist to be at increased risk for suicide, or currently coping with a major life crisis. Therapeutic telephone contacts between sessions were permitted as clinically indicated.

All patients completed at least eight sessions. Patients received fewer than 16 sessions of CBT if they reported no significant depressive symptoms, were judged by their therapist to be in full remission, and were found to be in remission on a diagnostic interview before the 16th session.

Follow-up. Both the depressed and the nondepressed patients were scheduled to complete the diagnostic interview and the Beck Depression Inventory approximately 4 months after the initial assessment (Time 2). As during the initial visit (Time1), the patients were fitted with a Holter monitor after the psychological assessment. The monitor was removed the next day.

Statistical Analyses

We hypothesized that decreases in heart rate and increases in HRV occur in both mildly and severely depressed patients in conjunction with treatment, with a greater effect in the severely depressed group. Heart rate, HRV, and exercise were analyzed using repeated measures analysis of variance. Because pre- and postdifferences in the depressed groups were hypothesized, *t* tests for paired samples were used to compare mean heart rate and HRV at Times 1 and 2 within each group. The Student-Newman-Keuls test was used for post-hoc comparisons between groups. Chi-square and Fisher exact test were used to test univariate associations between categorical variables. Alpha was set at 0.05 per comparison; SAS 6.12 was used for all analyses.

RESULTS

Thirty-seven depressed and 26 nondepressed patients met all of the inclusion criteria and were admitted to the study. At Time 1, one depressed patient was excluded because of sustained atrial fibrillation, and a second depressed patient and one nondepressed patient had more than 10% ectopic complexes. Five of the depressed and three of the nondepressed patients did not complete the assessments at Time 2. Of these, one of the depressed and one nondepressed patient had begun taking a beta blocker, and a tricyclic antidepressant was prescribed for one depressed patient. Two of the depressed and one of the nondepressed patients did not return for the assessments at Time 2 because of illness, one of the depressed patients moved from the area, and one of the nondepressed patients refused to return for reassessment. Thus, data were collected at both Time 1 and 2 on 30 depressed and 22 nondepressed subjects. Eighteen of the depressed patients were categorized as having mild depression, and 12 had moderate to severe depression. Comparisons of demographic and selected medical variables are presented in Table 1. There were no significant differences among the three groups on any

TABLE 1. Medical and Demographic Characteristics

Characteristic[a]	Severely Depressed (N = 12)	Mildly Depressed (N = 18)	Nondepressed (N = 22)	p	Post hoc Tests
Age (years)	59.2 ± 9.5	60.9 ± 6.3	62.7 ± 8.5	.22	
Beck Depression Inventory (BDI)	27.9 ± 6.8	15.2 ± 3.6	2.6 ± 2.3	.00	1>2> 3
Female	50% (6)	44% (8)	32% (7)	.53	
Hypertension	54% (7)	56% (10)	59% (10)	.96	
History of MI	67% (8)	56% (10)	56% (12)	.65	
Diabetes	25% (3)	33% (6)	27% (6)	.87	
Cigarette smoker	17% (2)	11% (2)	9% (2)	.63	
History of depression	83% (10)	67% (12)	18% (4)	.01	
Body mass index (BMI)	30.0 ± 6.6	27.0 ± 4.1	29.4 ± 6.5	.65	

[a] Continuous variables are reported as means ± SD; categorical variables are listed as column-wise percentage (cell size).

of these variables, except for history of major depression, which was more common in both of the depressed groups than in the nondepressed control group.

Patients were reassessed an average of 17.4 ± 2.2 weeks after the initial assessment. The results of the depression treatment are presented in Table 2. The treatment was quite effective, with only two (11%) of the mildly and one (8%) of the moderate to severely depressed patients remaining depressed at the conclusion of treatment.

Two severely depressed and one mildly depressed patient were taking SSRI antidepressants at the time of the study. They were receiving the drug for at least 3 months before beginning our treatment, and all were continued on the drug through the posttreatment assessment. Although the drug may have helped to relieve their depression, they still met the diagnostic criteria for a major depressive episode as baseline. Furthermore, because they were taking the drug continuously throughout the study period, the effects were unlikely to contribute to the change in heart rate or HRV, so they were retained in the study.

Analyses of mean heart rate, HRV, and exercise activity are presented in Tables 3–7. The group X time interaction was significant only for daytime heart rate. However, because pre- and postdifferences in the depressed groups were hypothesized, *t* tests for paired samples were used to compare mean heart rate and HRV at Times 1 and 2 within each group.

TABLE 2. Depression Outcomes

	Depressed		
	Not (N = 22)	Mildly (N = 18)	Severely (N = 12)
Beck Depression Inventory (BDI)			
Pre-	2.6 ± 2.3	15.2 ± 3.6	27.9 ± 6.8
Post-	2.8 ± 2.9	5.5 ± 3.6	10.2 ± 6.6
Posttreatment depression diagnosis			
Full remission		5 (28%)	3 (25%)
Partial remission		10 (56%)	8 (67%)
Unremitted		2 (11%)	1 (8%)

Average Heart Rate

At Time 1, 24 four-hour (p = .006), daytime (p = .001), and nighttime (p = .009) mean heart rates were higher in the severely depressed compared with the nondepressed group. At Time 2, daytime (p = .02) heart rate was higher in the severely and mildly depressed groups compared with the nondepressed controls, and there was a trend for 24 hour (p = .06) and nighttime (p = .06) heart rate to be higher in the severely depressed patients compared with the mildly depressed and nondepressed controls. After treatment, there was a significant reduction in 24 hour (p = .01), daytime (p = .01), and nighttime (p = .02) heart rate in the severely depressed patients, but no significant changes in either the nondepressed or the mildly depressed groups.

TABLE 3. Average Heart Rate

Measurement Period	Time						p
	Pretest			Posttest			
	SNK[a]	Mean	SD	SNK[a]	Mean	SD	
24 Hour[b]							
Nondepressed	A	73.2	8.5	A	72.4	8.6	.54
Mildly depressed	A, B	78.2	9.5	A	79.3	10.1	.58
Severely depressed	A	84.6	8.6	A	79.8	11.4	.01
Day time[c]							
Nondepressed	A	76.7	8.6	A	75.5	8.5	.41
Mildly depressed	A	82.8	9.7	B	83.7	10.5	.77
Severely depressed	B	89.5	8.4	B	83.9	11.3	.01
Night time[d]							
Nondepressed	A	64.5	8.3	A	64.0	9.6	.56
Mildly depressed	A, B	69.1	9.6	A	69.5	12.5	.91
Severely depressed	B	74.8	8.9	A	71.9	10.4	.02

[a] SNK = Student-Newman-Keuls test.
Groups sharing the same letter do not differ significantly at the specified time.
[b] Groups: Pre, p = .006; Post, p = .06; Time, p = .13; Group X Time, p = .07.
[c] Groups: Pre, p = .001; Post, p = .02; Time, p = .06; Group X Time, p = .05.
[d] Groups: Pre, p = .009; Post, p = .37; Time, p = .37; Group X Time, p = .57.

TABLE 4. SDNN

Measurement Period	Time						*p*
	Pretest			Posttest			
	SNK[a]	Mean	SD	SNK[a]	Mean	SD	
24 Hour[b]							
Nondepressed	A	115.9	21.8	A	116.9	24.8	.82
Mildly depressed	A	115.3	29.9	A	115.6	31.1	.97
Severely depressed	A	103.4	17.4	A	98.9	18.6	.23
Day time[c]							
Nondepressed	A	99.0	26.4	A	103.3	19.5	.36
Mildly depressed	A	97.1	29.5	A, B	95.7	36.0	.83
Severely depressed	A	86.3	20.5	B	80.6	21.3	.19
Night time[d]							
Nondepressed	A	90.3	27.6	A	86.4	23.7	.73
Mildly depressed	A	87.5	29.8	A	85.6	35.0	.74
Severely depressed	A	71.7	19.1	A	73.1	15.8	.75

[a] SNK = Student-Newman-Keuls test.
Groups sharing the same letter do not differ significantly at the specified time.
[b] Groups: Pre, $p = .35$; Post, $p = .16$; Time, $p = .78$; Group X Time, $p = .83$.
[c] Groups: Pre, $p = .37$; Post, $p = .06$; Time, $p = .78$; Group X Time, $p = .44$.
[d] Groups: Pre, $p = .16$; Post, $p = .37$; Time, $p = .65$; Group X Time, $p = .80$.

TABLE 5. SDNNIDX

Measurement Period	Time						*p*
	Pretest			Posttest			
	SNK[a]	Mean	SD	SNK[a]	Mean	SD	
24 Hour[b]							
Nondepressed	A	45.1	12.9	A	42.3	12.6	.98
Mildly depressed	A, B	41.6	14.1	A	41.6	16.7	.24
Severely depressed	B	33.5	10.3	A	36.4	13.3	.11
Day time[c]							
Nondepressed	A	42.1	13.4	A	40.9	9.7	.56
Mildly depressed	A	40.2	14.7	A	40.0	15.1	.94
Severely depressed	B	30.8	9.1	A	35.3	13.6	.07
Night time[d]							
Nondepressed	A	56.2	23.5	A	48.9	19.0	.02
Mildly depressed	A, B	46.1	17.3	A	45.5	23.0	.88
Severely depressed	B	35.9	12.9	A	37.7	13.8	.49

[a] SNK = Student-Newman-Keuls test.
Groups sharing the same letter do not differ significantly at the specified time.
[b] Groups: Pre, $p = .06$; Post, $p = .57$; Time, $p = .97$; Group X Time, $p = .21$.
[c] Groups: Pre, $p = .05$; Post, $p = .44$; Time, $p = .40$; Group X Time, $p = .18$.
[d] Groups: Pre, $p = .02$; Post, $p = .30$; Time, $p = .34$; Group X Time, $p = .16$.

SDNN

There were no differences among the groups for 24 hours, daytime, or nighttime SDNN at Time 1, but there was a trend for more severely depressed patients to have a lower daytime SDNN at Time 2 compared with the nondepressed patients ($p = .06$). There were no significant changes between Times 1 and 2 in any group.

SDNNIDX

There was a trend for severely depressed patients to have lower 24-hour SDNNIDX at Time 1 than nondepressed patients ($p = .06$), and this difference was significant both during the day ($p = .05$) and night ($p = .02$). There was also a trend ($p = .07$) for an increase in SDNNIDX from Time 1 to Time 2 during the day among the severely depressed patients, and

TABLE 6. rMSSD

Measurement Period	Time						*p*
	Pretest			Posttest			
	SNK[a]	Mean	SD	SNK[a]	Mean	SD	
24 Hour[b]							
Nondepressed	A	22.8	7.2	A	22.3	7.3	.74
Mildly depressed	A	21.6	8.7	A	21.4	10.7	.93
Severely depressed	A	17.2	5.3	A	19.4	5.3	.10
Day time[c]							
Nondepressed	A	18.6	7.3	A	19.9	6.3	.35
Mildly depressed	A	19.6	7.6	A	19.1	8.1	.74
Severely depressed	A	15.2	3.7	A	19.6	6.0	.01
Night time[d]							
Nondepressed	A	31.4	14.8	A	28.0	13.4	.11
Mildly depressed	A	25.7	13.0	A	25.4	17.5	.76
Severely depressed	A	20.3	8.3	A	20.9	6.5	.78

[a] SNK = Student-Newman-Keuls test.
Groups sharing the same letter do not differ significantly at the specified time.
[b] Groups: Pre, $p = .14$; Post, $p = .67$; Time, $p = .63$; Group X Time, $p = .57$.
[c] Groups: Pre, $p = .19$; Post, $p = .92$; Time, $p = .05$; Group X Time, $p = .08$.
[d] Groups: Pre, $p = .06$; Post, $p = .38$; Time, $p = .55$; Group X Time, $p = .57$.

TABLE 7. Exercise Rating Scale

Group	*N*	Time						*p*
		Pretest			Posttest			
		SNK[a]	Mean	SD	SNK[a]	Mean	SD	
Depressed								
No	22	A	2.3	1.4	A	2.2	1.4	.82
Mildly	18	A	2.1	1.5	A	2.0	1.5	.68
Severely	12	A	2.0	1.5	A	2.2	1.5	.78

[a] SNK = Student-Newman-Keuls test. Groups sharing the same letter do not differ significantly at the specified time.

there was a significant decrease in SDNNIDX among the nondepressed patients at night ($p = .02$).

rMSSD

There were no differences among the groups at either Times 1 or 2 in 24-hour or daytime rMSSD, but there was a trend for severely depressed patients to have lower rMSSD at night compared with the nondepressed patients ($p = .06$). Daytime rMSSD increased significantly in the severely depressed group ($p = .01$) between Times 1 and 2.

Exercise Rating Scale

There were no differences between the groups at Time 1 or 2 on self-reported exercise. There were also no changes in reported exercise between Times 1 and 2.

DISCUSSION

Cognitive-behavioral treatment of depression in patients with CHD was associated with a decrease in heart rate and an increase in short-term HRV. Thus, these results suggest that CBT may improve prognosis in depressed CHD patients. However, the study did not include an untreated depressed control group. Although the untreated, nondepressed group was intended to control for heart rate and HRV changes over time in CHD patients, it is possible that these may improve in depressed patients without treatment, although there is little evidence that HRV spontaneously improves in medically stable cardiac patients (48). Nevertheless, this remains a logical possibility. On the other hand, it is also possible that heart rate and HRV gradually worsen in untreated depressed patients. If so, the absence of change in some of the HRV indices for the treated depressed group would represent a beneficial effect of treatment, and this would not be detected in the absence of an untreated depressed control group. In any case, the design of the study, and in particular, the absence of an untreated depressed group, requires that the results be interpreted with caution.

Average heart rate was higher, and SDNNIDX, which reflects a mixture of sympathetic and parasympathetic influences, was significantly lower, in the severely depressed patients compared with the nonde-

pressed controls during the day, night, and the total 24 hours of recording at Time 1. In addition, rMSSD, which primarily reflects parasympathetic activity, tended to be lower at night in the severely depressed patients compared with those with mild depression and the nondepressed controls. After treatment, average heart rates for day time, night time, and 24 hours had decreased to values similar to those seen in the mildly depressed subjects. Furthermore, treatment was associated with a significant increase in daytime rMSSD and a trend toward increased 24-hour rMSSD. Nighttime rMSSD was unchanged. Consistent with the increase in daytime rMSSD, daytime values for SDNNIDX also showed a trend toward improvement. Correlations between changes in heart rate and daytime rMSSD and BDI scores were in the predicted direction, but were not significant. Only daytime rMSSD improved to the level observed in nondepressed patients. Mean heart rate was still higher in the severely depressed patients compared with the nondepressed controls. Furthermore, none of the other indicators of HRV showed improvement.

Taken together, these results suggest that treatment of depression with CBT may have significant effects on heart rate, but the effects on heart rate variability are limited to short-term HRV. Although the magnitude of these effects are smaller, the results are similar to those found when beta -blockers are administered to healthy adults (49) or to patients with coronary artery disease (50). Beta blockade, which directly reduces sympathetic tone, decreases mean heart rate, especially during the daytime, and increases rMSSD without any significant change in longer-term HRV. Thus, CBT may reduce sympathetic predominance and/or may improve vagal tone during the day in patients with moderate to severe depression. Although the effects on heart rate are modest, if they can be replicated in a controlled trial, they might nevertheless have prognostic significance.

Heart rate has been found to be a significant, independent predictor of cardiac events, including sudden cardiac death (24–26). Heart rate reduction has been shown to be one of the best predictors of beta-blocker efficacy in both acute and long-term intervention trials of acute myocardial infarction (51). In a review of the major beta blocker post-MI intervention trials, Kjekshus (51) found a correlation between reduction in heart rate and reduction in mortality and nonfatal reinfarctions of $r = 0.60$ and $r = 0.59$, respectively. He further noted that the clinical trials reported a mean heart rate reduction of 10.7 beats/minute in patients receiving a beta blocker. The mean heart rate of the severely depressed patients was reduced by nearly 5 beats/minute during the 24 hours of measurement. Although not as impressive as the effect of beta blockade on heart rate, this 5-beat/minute reduction resulted from a psychotherapeutic intervention, not from cardiac medications.

There have not yet been any controlled studies of the effects of CBT on depression in patients with CHD. However, the effect of CBT on depression in this uncontrolled study was quite striking. Depression was successfully treated in 16 of the 18 patients classified as having mild depression and in 11of 12 patients classified as having moderate to severe depression, with both groups showing significant reductions in BDI scores after treatment. By comparison, there was virtually no change in BDI scores among the nondepressed patients. This suggests that CBT may be an effective treatment for depression in these patients.

Although the results of this study do not prove that treating depression with CBT will reduce the risk associated with depression in CHD patients, they do demonstrate a measurable physiologic improvement which could have a significant benefit. Other treatments for depression have been studied in relation to their effect on heart rate and HRV. Electroconvulsive therapy has been associated with *decreases* both in total HRV and in the amplitude of respiratory sinus arrhythmia (which primarily reflects vagal activity) (52). Several studies have found that the tricyclic antidepressants increase heart rate and reduce HRV, presumably because of their anticholinergic side effects (53–55). However, the HRV effect of another class of antidepressants, the SSRIs, is less clear. Roose et al. (56) treated a group of depressed CHD patients with either paroxetine or nortriptyline for 6 weeks. Both groups responded equally well in terms of improvement of depression. Whereas the nortriptyline-treated patients showed a decrease in 24-hour HRV at weeks 2 and 6, the patients treated with paroxetine demonstrated an increase in 24-hour HRV at week 2. However, HRV returned to pretreatment levels in these patients by week 6. On the other hand, using a variety of SSRIs, two other studies have documented an increase in HRV after depression treatment (57, 58). Unfortunately, neither study included a control group, and both involved small numbers of patients. Thus, the effect of treating depression with SSRIs on HRV remains uncertain.

There are at least two possible explanations for the failure of heart rate and HRV to normalize completely to the level of the nondepressed post-MI patients after successful treatment of depression in the present study. First, both may eventually normalize, but perhaps the patients in this study were not followed long enough to detect the effect. Second, it is possible that heart rate and HRV *never* return to normal once there

has been an episode of major depression. Clearly, future studies should include long-term HRV follow-up assessments.

Finally, additional limitations of the study must be acknowledged. First, the results of the study may not extend to patients receiving beta blockers or to patients with any of the other study exclusions. Second, for various reasons, 11 patients were not reassessed at Time 2. If they had been included, the results of the study might have differed.

In summary, CBT was associated with a significant decrease in 24-hour heart rate and an increase in daytime rMSSD, a measure of short-term HRV. A randomized, controlled study is needed to confirm these findings. Although we do not know that lowering heart rate or increasing HRV in depressed CHD patients will lead to an improved prognosis, the results of this study suggest that treatment with CBT may have a beneficial effect on a risk factor for mortality in these patients.

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