Depression, Heart Rate Variability, and Acute Myocardial Infarction

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Background—Clinical depression is associated with an increased risk for mortality in patients with a recent myocardial infarction (MI). Reduced heart rate variability (HRV) has been suggested as a possible explanation for this association. The purpose of this study was to determine if depression is associated with reduced HRV in patients with a recent MI.

Methods and Results—Three hundred eighty acute MI patients with depression and 424 acute MI patients without depression were recruited. All underwent 24-hour ambulatory electrocardiographic monitoring after hospital discharge. In univariate analyses, 4 indices of HRV were significantly lower in patients with depression than in patients without depression. Variables associated with HRV were then compared between patients with and without depression, and potential confounds were identified. These variables (age, sex, diabetes, and present cigarette smoking) were entered into an analysis of covariance model, followed by depression status. In the final model, all but one HRV index (high-frequency power) remained significantly lower in patients with depression than in patients without depression.

Conclusions—We conclude that greater autonomic dysfunction, as reflected by decreased HRV, is a plausible mechanism linking depression to increased cardiac mortality in post-MI patients. (Circulation. 2001;104:2024-2028.)

Key Words: depression ■ myocardial infarction ■ heart rate variability

Depression is a risk factor for cardiac morbidity and mortality in patients with coronary heart disease (CHD), especially after acute myocardial infarction (MI).1–5 Major depression is associated with a 4-fold increase in the risk of mortality during the first 6 months after acute MI, and its prognostic significance is comparable to that of left ventricular dysfunction and history of MI.6

Little is known about how depression contributes to this increased risk, although factors such as increased platelet aggregation and poor adherence to cardiac treatment regimens have been suggested.1,6 However, altered cardiac autonomic tone remains one of the most plausible explanations.1,6 Increased sympathetic or decreased parasympathetic nervous system activity predisposes patients with CHD to ventricular tachycardia, ventricular fibrillation, and sudden cardiac death.7,8 Elevated sympathetic nervous system activity and dysregulation of the hypothalamic pituitary-adrenal axis have been found in medically healthy patients with major depression, as indicated by elevated plasma and urinary catecholamines and their metabolites9–12 and by elevated plasma and urinary cortisol.10 Thus, altered autonomic tone may account for the effect of depression on cardiac mortality.

Heart rate variability (HRV) analysis is a widely used method for studying cardiac autonomic modulation.13 Low HRV reflects excessive sympathetic or inadequate parasympathetic tone13 and is a strong, independent predictor of post-MI mortality.14–16

Mean 24-hour HRV has been found to be lower in depressed than in medically similar nondepressed patients with stable CHD,17–19 suggesting a possible mechanism linking depression to cardiac mortality. However, these studies were limited by small sample sizes and lack of adjustment for all known confounders. The purpose of this study was to determine whether the effects of depression on HRV are still apparent after adjusting for all known confounders in a large sample of post-MI patients.

Subjects
The subjects were patients who had been screened for the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial. Details of the methods of the ENRICHD study have been reported previously.20 Briefly, patients with a recent (≤28 days) acute MI who were depressed or socially isolated were randomly assigned to usual care or a cognitive-behavioral intervention. The aim was to determine the effects of treating depression and social isolation on reinfarction and mortality.

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All patients admitted between October 1997, and January 2000, to the coronary care units at 4 ENRICHED clinical sites (Washington University, St Louis, Mo; Duke University, Durham, NC; Harvard University, Boston, Mass; and Yale University, New Haven, Conn) were screened for eligibility. MI was documented by cardiac enzymes with chest pain compatible with acute MI, characteristic evolutionary ST-T changes, or new Q waves. Patients were excluded from ENRICHED and from the present study if they (1) had other life-threatening medical illnesses, cognitive impairment, severe psychiatric disorder, active suicidal ideation, alcoholism, or other present substance abuse other than tobacco use; (2) were physically unable to complete the interview or the ENRICHED intervention; (3) were presently taking tricyclic or monoamine oxidase inhibitor antidepressants; (4) lived too far away to participate in weekly intervention sessions; or (5) refused to participate. Patients with atrial fibrillation, atrial flutter, or an implanted pacemaker were also excluded from the present study but not from ENRICHED.

Procedures

Dementia Screening

The Orientation Memory Concentration Test21 was used to screen for cognitive impairment. Patients with a score ≤10 were excluded.

Depression Assessment

Patients not excluded by the above criteria were eligible if they met the ENRICHED modified Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria22 for major or minor depression or dysthymia or the ENRICHED criteria for social isolation.20 The modified DSM-IV criteria for major and minor depression allowed patients with the required number of depression symptoms to be eligible if the symptoms were present at least 7 (instead of 14) days, provided that there was at least one prior episode of major depression.

Depression Interview and Structured Hamilton (DISH)

The DISH23 is a semistructured interview developed for the ENRICHED study to diagnose present depressive episodes according to the DSM-IV criteria24 and to screen for other psychiatric disorders. There is a high level of diagnostic agreement between DISH interviews administered by trained research nurses and SCID interviews administered by trained clinicians (weighted κ=0.86).23 Patients meeting the modified DSM-IV criteria for either major or minor depression or dysthymia were classified as “depressed” and eligible for participation in the study.

Beck Depression Inventory (BDI)

The BDI25 is a 21-item measure of the self-reported severity of depression symptoms. BDI scores can range from 0 to 64; the standard BDI cutoff for depression is a score of 10 or higher.26

Enrollment

Subjects With Depression

All patients with depression meeting the above criteria who were enrolled in either arm of ENRICHED were eligible for participation in this study if their BDI score was 10 or higher. The HRV data were acquired after randomization but (in the intervention arm) before treatment was initiated.

Control Subjects Without Depression

Patients who were otherwise eligible for ENRICHED but who did not meet the ENRICHED depression or social isolation criteria,26 had no previous episodes of major depression, and scored 9 or below on the BDI were eligible for enrollment in this study as control subjects without depression. Enrollment of controls continued throughout the recruitment period but was capped at 120% of the sample with depression.

Medical Assessments

Medical Information

Medical records were reviewed to ascertain the patient’s history of coronary disease and revascularization and present medications, medical comorbidity, and CHD risk factors, including smoking, diabetes mellitus, and obesity. An echocardiogram was obtained if no estimate of left ventricular function was available.

Ambulatory Electrocardiographic (AECG) Monitoring

To assure standardization of AECG recordings, Marquette Model 8500 monitors were used at all sites. The monitor continuously records 2 analog data channels and a 32-Hz digital timing signal channel that is also used for marking patient events. The electrodes were configured for recording heart rate, heart rate variability, arrhythmias, and ST segment depression. In each case, a 12-lead ECG was obtained to check AECG signal quality.

The tapes were scanned at the HRV core laboratory at Washington University on a Marquette XSP Laser scanner with software version 5.8 (Marquette Electronics) using standard procedures. The labeled beat file was exported to a Sun workstation (Sun Microsystems) for HRV analysis.

Heart Rate Variability Analysis

Spectral analysis yields a set of frequency domain indices by partitioning the heart rate variance into spectral components and quantifying their power. The following indices were calculated: ultra low frequency (ULF) (1.15×10^{-6} to 0.00335 Hz) in ms², which reflects circadian and other long-term variations in heart rhythm; very low frequency (VLF) power (0.0033 to 0.04 Hz) in ms², which, in addition to sympathetic and parasympathetic inputs, may be influenced by the thermoregulatory, peripheral vasoconstrictor, and renin-angiotensin systems25–27; low frequency (LF) power (0.04 to 0.15 Hz) in ms², which reflects both sympathetic and parasympathetic tone and is strongly associated with blood pressure regulation27; and high-frequency (HF) power (0.15 to 0.40 Hz) in ms², which is modulated by respiration and, in medically healthy persons, primarily reflects vagal tone.27 The spectral HRV analysis methods have been described previously.28 Briefly, the sequence of normal-to-normal intervals was resampled and filtered to generate a uniformly spaced time series. Missing or noisy segments were replaced by linear interpolation from the surrounding signal. The average normal-to-normal interval was subtracted from the time series and fast Fourier transformed to extract the frequency components underlying the cyclic activity in the time series. Measurement of ultra-low and very-low-frequency power was based on en bloc analysis of the entire 24-hour recording.28 Other power indices express the average of 5-minute segments in which ≥80% of the beats are normal.

Analytic Strategy and Statistical Analyses

The HRV distributions were tested for normality and, as expected, were significantly skewed. They were then log transformed to produce normalized distributions. ANOVA was used to determine whether there were HRV differences between the groups with major depression, minor depression, and no depression. The plan was to combine the major and minor depression groups for the remaining analyses if planned contrasts revealed no differences on any HRV index between these two groups. χ² tests, two-tailed r tests, and Pearson correlations were used to determine whether the demographic and medical variables that have been associated with HRV in previous studies were significantly associated both with HRV and with depression in this study. The variables included sex, age, β-blockade, diabetes, left ventricular ejection fraction, blood pressure, present smoking, and post-MI coronary bypass surgery.29 α was set at 0.10 per comparison for these univariate tests. Variables that emerged from these analyses as potential covariates because they were associated both with HRV and with depression were then entered into separate multiple regression analyses for each log-transformed HRV index. Backward elimination with P<0.05 to remove was used to drop redundant covariates (if any). All retained variables were then used as covariates in ANCOVA models testing the effects of depression on each of the log-transformed HRV indices, with α set at 0.05 per comparison.
Sixty-two patients met the modified ENRICHD were included in the present sample. One hundred depression and social isolation but otherwise eligible for ENRICHD study, and 411 acute MI inpatients free of technical difficulties, leaving 307 (86%) usable tapes from

Although all 4 log-transformed indices of 24-hour HRV were significantly lower in patients with major and minor depression than in the patients without depression, there were no differences between patients with major and minor depression (Table 1.) Consequently, these groups were combined for the following analyses.

Fewer patients with depression were married (57%) than were patients without depression (77%) (P<0.001), and fewer belonged to a racial or ethnic minority group (21%) compared with the patients without depression (29%) (P<0.05). Neither variable was significantly associated with any log-transformed HRV index.

The potential demographic and medical covariates are reported by group in Table 2. The groups differed with respect to age, sex, diabetes, and present cigarette smoking. Consistent with the findings of previous studies, these variables were also related to one or more of the log-transformed HRV indices (Table 3). All 4 variables were retained in the multiple regression analyses and were therefore entered as covariates in the analyses of the effects of depression on each log HRV index. After adjustment for these covariates, depression remained significantly associated with every index except for HF power (Table 4).

To determine the relationship between the severity of depression and HRV, correlations coefficients between BDI scores and each covariate-adjusted index of HRV were calculated: LnULF, r = −0.12, P<0.003; LnVLF, r = −0.16, P<0.0001; LnLF, r = −0.13, P<0.001; and LnHF, r = −0.07, P<0.07.

## Discussion

All 4 log-transformed frequency domain indices of HRV (ULF, VLF, LF, and HF) were significantly lower in post-MI patients with depression than in post-MI patients without depression, and there were no differences in HRV between patients with major versus minor depression. With the exception of HF, the differences between the patients with and without depression remained significant after adjusting for medical and demographic confounds. All of the medical and demographic variables selected as potential covariates, on the

### TABLE 1. Unadjusted HRV in Patients With Major, Minor, or No Depression

<table>
<thead>
<tr>
<th>HRV Index</th>
<th>No Depression (n=365)</th>
<th>Minor Depression (n=170)</th>
<th>Major Depression (n=135)</th>
<th>P*</th>
<th>P†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnULF</td>
<td>8.86±0.75</td>
<td>8.64±0.82</td>
<td>8.61±0.87</td>
<td>0.0009</td>
<td>0.0002</td>
<td>0.80</td>
</tr>
<tr>
<td>lnVLF</td>
<td>6.87±0.98</td>
<td>6.50±1.05</td>
<td>6.44±1.33</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.67</td>
</tr>
<tr>
<td>lnLF</td>
<td>5.65±1.19</td>
<td>5.29±1.23</td>
<td>5.27±1.53</td>
<td>0.001</td>
<td>0.0002</td>
<td>0.90</td>
</tr>
<tr>
<td>lnHF</td>
<td>4.79±1.16</td>
<td>4.47±1.18</td>
<td>4.65±1.33</td>
<td>0.01</td>
<td>0.01</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Results are reported as mean±SD. lnULF indicates log of ultra-low-frequency power (1.15×10−15 to 0.00335 Hz) in ms²; lnVLF, log of very-low-frequency power (0.0033 to 0.04 Hz) in ms²; lnLF, log of low-frequency power (0.04 to 0.15 Hz) in ms²; and lnHF, log of high-frequency power (0.15 to 0.40 Hz) in ms².

*P value for the omnibus F test. †P value for major/minor depression vs no depression. ‡P value for major depression vs minor depression.

#### TABLE 2. Medical and Demographic Characteristics by Depression Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Depressed (n=307)</th>
<th>Not Depressed (n=366)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.1±12.3</td>
<td>60.9±11.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>17.2±7.4</td>
<td>3.9±2.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>49.5</td>
<td>32.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.0±19.3</td>
<td>121.7±19.3</td>
<td>0.86</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>22.3</td>
<td>19.3</td>
<td>0.95</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>34.5</td>
<td>22.1</td>
<td>0.0003</td>
</tr>
<tr>
<td>Present cigarette smoker, %</td>
<td>40.7</td>
<td>23.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>45.8±13.3</td>
<td>46.8±11.7</td>
<td>0.39</td>
</tr>
<tr>
<td>β Blockade, %</td>
<td>85.2</td>
<td>80.0</td>
<td>0.47</td>
</tr>
<tr>
<td>Hypertensive (&gt;140/90 mm Hg), %</td>
<td>22.1</td>
<td>20.2</td>
<td>0.54</td>
</tr>
<tr>
<td>CABG, %</td>
<td>15.4</td>
<td>12.6</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Continuous variables are reported as mean±SD; categorical variables are listed as column-wise percentage.
pathetic modulation of HR, and VLF remained significantly suggests that VLF power may also largely reflect parasym-
thetic activity to these HRV indices cannot be precisely
specified. The group with depression showed decreased ULF,LF, and VLF but not HF power after covariate adjustment.
ULF, LF, and VLF power all are influenced by both sympa-
thetic and parasympathetic systems, whereas HF is largely
thought to reflect parasympathetic modulation. However,
most of the evidence for the role of parasympathetic modu-
lation in HF power comes from studies of healthy humans
and animals. In many cardiac patients, HF power is con-
founded by nonrespiratory sinus arrhythmia, which exag-
gerates the magnitude of HF but does not reflect vagal
activity to these HRV indices cannot be precisely

The relative contributions of sympathetic and parasympa-
thetic activity to these HRV indices cannot be precisely
specifed. The group with depression showed decreased ULF,LF, and VLF but not HF power after covariate adjustment.
ULF, LF, and VLF power all are influenced by both sympa-
thetic and parasympathetic systems, whereas HF is largely
thought to reflect parasympathetic modulation. However,
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lation in HF power comes from studies of healthy humans
and animals. In many cardiac patients, HF power is con-
founded by nonrespiratory sinus arrhythmia, which exag-
gerates the magnitude of HF but does not reflect vagal
activity to these HRV indices cannot be precisely

basis of previously established associations with HRV in
post-MI patients, were significantly and independently asso-
ciated with at least one index of HRV in this sample. This
suggests that the subjects in this study were similar to the
ones in earlier studies of HRV in post-MI patients.

The correlations between HRV and the severity of depres-
sion as measured by the BDI, although significant, were
lower in this study than in an earlier study of medically stable
CHD patients. However, that study assessed HRV in pa-
tients who were event-free for at least 6 months, whereas the
patients in the present study had a recent acute MI. All indices
of HRV were lower in the present than in the earlier study.
Furthermore, the patients in the earlier study had a wider
range of BDI scores than these patients. Thus, the ranges of
HRV indices and the BDI scores were more restricted in
this study, and this may have contributed to lower correla-
tions between HRV and depression.

However, the finding that patients with major and minor
depression had comparably low HRV is consistent with the
relationship between depression and mortality in post-MI
patients. Frasure-Smith et al reported that patients without
major depression who had a BDI score ≥10 had about the
same mortality rate in the 18 months after an acute MI as
patients with major depression and a BDI ≥10. Thus, patients
with even a few depressive symptoms were at the same risk
of dying as were patients with major depression. To be

### Table 3. Twenty-Four Hour HRV by Medical and Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>InULF</th>
<th>InVLF</th>
<th>InLF</th>
<th>InHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n=673)</td>
<td>( r = -0.06 )</td>
<td>( r = -0.13 )</td>
<td>( r = -0.18 )</td>
<td>( r = -0.09 )</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n=404)</td>
<td>8.59±0.77</td>
<td>6.37±1.12</td>
<td>5.16±1.33</td>
<td>4.61±1.28</td>
</tr>
<tr>
<td>Male (n=269)</td>
<td>8.86±0.80</td>
<td>6.90±1.02</td>
<td>5.70±1.21</td>
<td>4.73±1.15</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=486)</td>
<td>8.90±0.76</td>
<td>6.93±0.90</td>
<td>5.78±1.08</td>
<td>4.86±1.14</td>
</tr>
<tr>
<td>Yes (n=187)</td>
<td>8.38±0.78</td>
<td>6.06±1.27</td>
<td>4.72±1.46</td>
<td>4.21±1.24</td>
</tr>
<tr>
<td>Present Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=462)</td>
<td>8.79±0.81</td>
<td>6.68±1.15</td>
<td>5.45±1.33</td>
<td>4.70±1.22</td>
</tr>
<tr>
<td>Yes (n=211)</td>
<td>8.68±0.78</td>
<td>6.73±0.95</td>
<td>5.57±1.18</td>
<td>4.63±1.18</td>
</tr>
</tbody>
</table>

**Note:** InULF indicates log of ultra-low-frequency power (1.15×10⁻⁵ to 0.00335 Hz) in ms²; lnVLF, log of very-low-frequency power (0.0033 to 0.04 Hz) in ms²; lnLF, log of low-frequency power (0.04 to 0.15 Hz) in ms²; lnHF, log of high-frequency power (0.15 to 0.40 Hz) in ms². Continuous variables are reported as mean±SD.

### Table 4. Adjusted HRV in Patients With and Without Depression*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depressed</th>
<th>Not Depressed</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>InULF</td>
<td>8.52±0.05</td>
<td>8.66±0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>InVLF</td>
<td>6.32±0.06</td>
<td>6.59±0.065</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>InLF</td>
<td>5.09±0.07</td>
<td>5.34±0.08</td>
<td>0.009</td>
</tr>
<tr>
<td>InHF</td>
<td>4.41±0.07</td>
<td>4.58±0.08</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Note:** InULF indicates log of ultra-low-frequency power (1.15×10⁻⁵ to 0.00335 Hz) in ms²; lnVLF, log of very-low-frequency power (0.0033 to 0.04 Hz) in ms²; lnLF, log of low-frequency power (0.04 to 0.15 Hz) in ms²; lnHF, log of high-frequency power (0.15 to 0.40 Hz) in ms². Continuous variables are reported as mean±SEM.

*Adjusted for age, sex, diabetes status, and present smoking status.
enrolled in the present study, patients with either major or minor depression also had to have a BDI ≥10. Our patients with minor depression are therefore similar to the depressed patients without major depression in the Frasure-Smith et al11 study. It is possible that any form of depression after an acute MI lowers HRV and increases mortality risk.32 Additional research is needed to examine this possibility.

A limitation of this study is that the sample with depression consisted of participants in a clinical trial. Furthermore, the sample without depression met all of the eligibility criteria for the clinical trial except for depression or social isolation. Patients who were too sick or debilitated to participate in the depression intervention were not enrolled. Therefore, the patients in this study are not fully representative of the post-MI population.

Our results raise the question of whether treating depression might increase HRV and thereby reduce the risk of mortality. There is some evidence that treating depression with cognitive-behavioral psychotherapy33 or selective serotonin reuptake inhibitors34 may increase HRV in patients with stable CHD. However, we must await the results of clinical trials such as ENRICHD to determine whether treating depression can improve medical outcomes in post-MI patients.

In conclusion, after adjusting for confounders, 24-hour HRV indexes that are known to predict mortality are significantly lower in patients with depression than in patients without depression with a recent MI. Lower HRV, reflecting more severe autonomic dysfunction, is thus a plausible explanation for the increased risk of cardiac mortality that has been documented in post-MI patients with depression. Although it has not yet been shown that treatment of post-MI depression will improve survival, identification and treatment of depression will improve quality of life and should be a part of routine care for post-MI patients.

Acknowledgments
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