Low Heart Rate Variability and the Effect of Depression on Post–Myocardial Infarction Mortality

Robert M. Carney, PhD; James A. Blumenthal, PhD; Kenneth E. Freedland, PhD; Phyllis K. Stein, PhD; William B. Howells, MS; Lisa F. Berkman, PhD; Lana L. Watkins, PhD; Susan M. Czajkowski, PhD; Junichiro Hayano, MD; Peter P. Domitrovich, PhD; Allan S. Jaffe, MD

Background: Depression is associated with an increased risk for mortality after acute myocardial infarction (MI). The purpose of this study was to determine whether low heart rate variability (HRV) mediates the effect of depression on mortality.

Methods: Twenty-four–hour ambulatory electrocardiograms were obtained from 311 depressed patients with a recent acute MI who were enrolled in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial and from 367 nondepressed patients who met the ENRICHD medical inclusion criteria. Standard HRV indexes were extracted from the recordings.

Results: The log of very low-frequency (LnVLF) power, an index of HRV derived from power spectral analysis of the electrocardiogram signal (0.0033–0.04 Hz [in milliseconds squared]), was lower in the depressed than in the nondepressed patients (P<.001). There were 47 deaths (6.1%) during a 30-month follow-up. After adjusting for potential confounders, the depressed patients remained at higher risk for all-cause mortality compared with the nondepressed patients (hazard ratio, 2.8; 95% confidence interval [CI], 1.4–5.4; P<.003). When LnVLF power was entered into the model, the hazard ratio for depression dropped to 2.1 (95% CI, 1.1–4.2; P=.03). The proportion of the risk for depression attributable to LnVLF power was 0.27 (95% CI, 0.23–0.31; P<.001).

Conclusions: Low HRV partially mediates the effect of depression on survival after acute MI. This finding helps to clarify the physiological mechanisms underlying depression’s role as a risk factor for mortality in patients with coronary heart disease. It also raises the possibility that treatments that improve both depression and HRV might also improve survival in these patients.

Arch Intern Med. 2005;165:1486-1491
Patients admitted between October 1997 and January 2000 to the coronary care units of 4 of the 8 ENRICHD clinical trial sites (Washington University, St Louis, Mo; Duke University, Durham, NC; Harvard University, Boston, Mass; and Yale University, New Haven, Conn) for an acute MI were screened for eligibility within 28 days following hospital admission. Myocardial infarction was documented by cardiac enzyme levels combined with chest pain compatible with acute MI, characteristic evolutionary ST-T segment changes, or new Q waves. The methods of the ENRICHD study13,14 and of this ancillary study12,15 have been reported previously. Patients were excluded from this study if they (1) had other life-threatening medical illnesses, cognitive impairment, or other major psychiatric disorders; (2) were too ill or logistically unable to participate; (3) were currently taking tricyclic or monoamine oxidase inhibitor antidepressants, as these agents are known to lower HRV; or (4) refused to participate.

Patients were included in the depressed group if they scored a 10 or higher on the Beck Depression Inventory16 and met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for major or minor depression or dysthymia.7 However, to enroll patients as soon as possible after the index MI, patients with a prior episode of major depression were eligible for enrollment if they met the symptom criteria for a major or minor depressive episode for at least 7 (instead of the usual 14) days.14

Patients were eligible for enrollment in the present study as nondepressed controls if they were otherwise eligible for ENRICHD but did not meet the ENRICHD criteria for depression or low social support,14 had no prior episodes of major depression, and scored a 10 or lower on the Beck Depression Inventory. The first eligible nondepressed patient was enrolled following enrollment of each depressed patient. If a depressed patient could not be identified on a given day, the first eligible nondepressed patient was enrolled.

A total of 358 depressed patients who were enrolled in the ENRICHD study and 408 patients with an acute MI who were free of depression but otherwise eligible for the ENRICHD study and 408 patients with an acute MI who were screened for eligibility within 28 days following hospital admission. Myocardial infarction was documented by cardiac enzyme levels combined with chest pain compatible with acute MI, characteristic evolutionary ST-T segment changes, or new Q waves. The methods of the ENRICHD study13,14 and of this ancillary study12,15 have been reported previously. Patients were excluded from this study if they (1) had other life-threatening medical illnesses, cognitive impairment, or other major psychiatric disorders; (2) were too ill or logistically unable to participate; (3) were currently taking tricyclic or monoamine oxidase inhibitor antidepressants, as these agents are known to lower HRV; or (4) refused to participate.

Patients were included in the depressed group if they scored a 10 or higher on the Beck Depression Inventory16 and met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for major or minor depression or dysthymia. However, to enroll patients as soon as possible after the index MI, patients with a prior episode of major depression were eligible for enrollment if they met the symptom criteria for a major or minor depressive episode for at least 7 (instead of the usual 14) days.14

Patients were eligible for enrollment in the present study as nondepressed controls if they were otherwise eligible for ENRICHD but did not meet the ENRICHD criteria for depression or low social support,14 had no prior episodes of major depression, and scored a 10 or lower on the Beck Depression Inventory. The first eligible nondepressed patient was enrolled following enrollment of each depressed patient. If a depressed patient could not be identified on a given day, the first eligible nondepressed patient was enrolled.

A total of 358 depressed patients who were enrolled in the ENRICHD study and 408 patients with an acute MI who were free of depression but otherwise eligible for the ENRICHD study were enrolled in the present study. Of the 358 patients enrolled in the ENRICHD study, 163 met the criteria for major depression and 195 met the criteria for minor depression or dysthymia. More detailed accounts of recruitment, enrollment, and the demographic and medical characteristics of the participants in the present and in the ENRICHD study have been previously reported.12,13

PROCEDURES

Ambulatory Electrocardiographic Monitoring

To ensure standardization of ambulatory electrocardiographic (ECG) recordings, the same model ambulatory ECG recorder (Marquette model 8500; Marquette Electronics Inc, Milwaukee, Wis) was used across sites. The Marquette Holter continuously records 2 analog data channels in addition to a 32-Hz digital timing signal channel that records patient events. Signal quality was checked with a 12-lead ECG prior to each 24-hour recording.

The tapes were scanned at the HRV core laboratory at Washington University on a Marquette SXP laser scanner with software version 5.8 (Marquette Electronics) using standard Holter analysis procedures. The longest and shortest true normal-to-normal intervals were identified and carefully edited for each recording. The labeled beat-to-beat file was exported to a Sun workstation (Sun Microsystems, Palo Alto, Calif) for HRV analysis.

HRV Analysis

Very low-frequency (VLF) power (0.0033-0.04 Hz [in milliseconds squared]) was chosen a priori as the index of HRV for this study. The methods used for spectral analysis have been described previously.18 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 frequency components underlying the cyclic activity in the time series were extracted by fast Fourier transformation. Measurement of VLF power was based on en bloc analysis of the entire 24-hour recording.18

Follow-up

Patients were scheduled for follow-up assessments at 6 months after enrollment and annually thereafter for up to 30 months. The major end point for this ancillary study was all-cause mortality. Death certificates were obtained to confirm all reported deaths.

STATISTICAL ANALYSES

Baron and Kenny19 proposed a framework for testing mediational hypotheses (Figure 1 and Figure 2), which is sup-
RESULTS

In the present study, 160 of the depressed patients were randomized to the ENRICHD intervention and 182 were randomized to usual care. Consistent with the primary results of the ENRICHD clinical trial,21 there were no differences in the rates of death between these 2 arms (log rank, P=.66). Thus, treatment arm assignment was dropped from the remaining analyses.

Ambulatory ECGs with at least 18 hours of usable data (5-minute segments with at least 80% normal-to-normal intervals) were available for 311 (87%) of the 358 depressed patients included in the ENRICHD study and by 367 (90%) of the 408 nondepressed patients included in the present study (P>.05). The demographic and medical characteristics of patients who had or did not have an ECG suitable for HRV analysis are presented in Table 1. The patients who were excluded from the HRV analyses had higher Beck Depression Inventory scores and were more likely to be in Killip class III or IV and to have had coronary artery bypass graft surgery compared with those who were included.

Comparisons between depressed and nondepressed patients on medical and demographic variables have been reported previously.12 Briefly, the depressed patients were slightly younger (mean±SD age, 57±12 vs 61±11 years) and were more likely to be female (50% vs 32%), to have diabetes mellitus (35% vs 22%), and to be a current cigarette smoker (41% vs 24%) compared with nondepressed patients.

As expected, the distribution of VLF power was skewed and therefore was log transformed and standardized. The depressed patients had significantly lower LnVLF power, both in unadjusted mean±SD of the unstandardized measures (6.5±1.2 for depressed vs 6.9±1.0 for nondepressed patients) and after adjustment for the ENRICHD risk score (β coefficient, −0.37; 95% confidence interval

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ECG (n = 678)</th>
<th>No Ambulatory ECG (n = 88)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.22 ± 11.57</td>
<td>58.65 ± 12.47</td>
<td>.66</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>10.07 ± 8.58</td>
<td>12.47 ± 10.56</td>
<td>.02</td>
</tr>
<tr>
<td>Women</td>
<td>40.0</td>
<td>37.5</td>
<td>.66</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>24.2</td>
<td>25.0</td>
<td>.87</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.82 ± 5.49</td>
<td>29.61 ± 5.26</td>
<td>.20</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.91 ± 19.18</td>
<td>120.94 ± 17.04</td>
<td>.37</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28.2</td>
<td>19.5</td>
<td>.09</td>
</tr>
<tr>
<td>Cigarette smoker (ever)</td>
<td>72.0</td>
<td>70.1</td>
<td>.76</td>
</tr>
<tr>
<td>LVEF</td>
<td>48.2 ± 12.5</td>
<td>47.3 ± 11.7</td>
<td>.47</td>
</tr>
<tr>
<td>Killip class III or IV</td>
<td>4.7</td>
<td>9.8</td>
<td>.05</td>
</tr>
<tr>
<td>Non Q-wave AMI</td>
<td>65.5</td>
<td>66.3</td>
<td>.88</td>
</tr>
<tr>
<td>Anterior wall AMI</td>
<td>32.3</td>
<td>27.6</td>
<td>.38</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.15 ± 0.81</td>
<td>1.07 ± 0.73</td>
<td>.42</td>
</tr>
<tr>
<td>Prior AMI</td>
<td>21.1</td>
<td>21.2</td>
<td>.99</td>
</tr>
<tr>
<td>Prior coronary bypass</td>
<td>10.0</td>
<td>18.2</td>
<td>.02</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>30.6</td>
<td>34.9</td>
<td>.42</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>83.1</td>
<td>75.6</td>
<td>.09</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>49.0</td>
<td>43.0</td>
<td>.30</td>
</tr>
<tr>
<td>Aspirin</td>
<td>90.0</td>
<td>90.5</td>
<td>.87</td>
</tr>
<tr>
<td>Coronary bypass post-AMI</td>
<td>13.5</td>
<td>15.1</td>
<td>.68</td>
</tr>
<tr>
<td>Coronary angioplasty &lt;24 h</td>
<td>63.2</td>
<td>57.5</td>
<td>.30</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ECG, electrocardiogram; LVEF, left ventricular ejection fraction.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Continuous variables are reported as mean ± SD and categorical variables are listed as percentage of subjects with the characteristic unless otherwise specified.
Depression is associated with lower LnVLF power and with decreased survival in this series of post-MI patients, even after adjusting for potential confounders. Adding LnVLF power to the risk score–adjusted depression model significantly reduces, but does not eliminate, the effect of depression on survival. Thus, these results show that the effect of depression on survival is partially mediated by low HRV. The identification of this mechanistic pathway suggests that depression’s association with mortality is unlikely to be spurious. Thus, this finding provides further support for the role of depression as a risk factor for mortality after acute MI.

Surprisingly, the effects of both depression and HRV on survival were weaker in the first 12 months following acute MI than after 1 year. This finding is inconsistent with some of the earlier studies of depression in which the effects on survival were evident within weeks after acute MI. In response to acute MI, HRV drops precipitously and then makes a gradual recovery. There is some evidence that untreated depression may be associated with slower HRV recovery. Furthermore, depression is a chronic, recurring problem that may potentially affect the course and outcome of coronary heart disease for months or years after an MI. It is possible that the early negative effects of depression and low HRV are offset by the protective effects of the aggressive strategies for treating acute MI and for minimizing early post-MI risk that have been widely implemented over the past 15 years. In any case, both depression and HRV were less predictive of survival both depression and HRV were less predictive of survival in the first year after acute MI than in the second and third years.

To conduct a conservative test of our hypothesis, we selected just 1 measure of HRV, LnVLF power, from among the 5 standard frequency domain indexes. We
chose LnVLF power because it is strongly related to both depression and survival in patients with a recent acute MI. We subsequently examined other frequency domain HRV indexes in an exploratory analysis. None of them accounted for more of the depression-mortality relationship than did LnVLF.

Very low-frequency power reflects changes in heart rate at a cycle length of 20 seconds to 5 minutes. The underlying physiology of VLF power is only partially understood. However, there is evidence that VLF power reflects not only cardiovascular autonomic modulation but also thermoregulatory activity and blood pressure modulation by the renin-angiotensin-aldosterone system. Support for the effect of the renin-angiotensin-aldosterone system on VLF power comes from animal studies, as well as from a study of post-MI patients, which found angiotensin-converting enzyme inhibition to be associated with increased VLF power. Taylor and colleagues recently investigated the relative contributions of these systems to VLF power in young, healthy subjects. Very low-frequency power was unaffected by β-blockade but was nearly abolished by atropine. No evidence was found for any contribution by the thermoregulatory system. Their results suggest that although the renin-angiotensin-aldosterone system does contribute to VLF power, the dominant determinant is the parasympathetic nervous system.

There is evidence that tricyclic antidepressants and monoamine oxidase inhibitors lower HRV and that they increase the risk of cardiovascular mortality in patients with coronary heart disease. Although it is not known whether their effect on HRV contributes to the heighted risk of death, both classes of antidepressants are known to be unsafe for patients with left bundle branch block. As a result, they are generally not recommended for use in patients with coronary heart disease.

Selective serotonin reuptake inhibitors, on the other hand, do not seem to have significant cardiotoxic effects and they do not decrease HRV. However, it is not clear whether they actually improve HRV during the initial course of depression treatment. There is preliminary evidence that HRV may increase as depression improves following cognitive behavior therapy, a form of psychotherapy. However, there is little evidence that HRV completely normalizes in response to any depression treatment. If depression treatments fail to improve HRV or to modify other pathways linking depression to cardiac mortality, it may be difficult to improve survival in post-MI patients by treating depression. This may explain the failure of the ENRICHD clinical trial intervention to improve survival. More research is needed to determine the effect of treating depression on HRV, as well as on other potential pathways linking depression to increased risk for mortality.

The finding that HRV only partially mediates the effect of depression on survival suggests that other mediators also participate in this relationship. That depression does not become a significant risk factor for mortality until after about 12 months following acute MI may be because of a decline over time in patient adherence to medical treatment. Other possible mechanisms underlying the relationship of depression to mortality have been considered in detail elsewhere, including the procoagulant and proinflammatory processes that have been associated with both depression and coronary heart disease. A limitation of this study is that the results may not generalize to all post-MI patients because patients who were too sick or debilitated to participate in the ENRICHD trial intervention were excluded. Furthermore, patients were excluded from this study if only less than 18 hours of usable data could be extracted from the 24-hour ambulatory ECG. As a result, patients were excluded if they had more than 20% ectopic beats, had undetectable QRS complex onset, or were in atrial fibrillation or flutter at the time of the ECG monitoring. The excluded patients had higher Beck Depression Inventory scores, were more likely to be in Killip class III or IV, and were more likely to have had prior coronary artery bypass graft surgery compared with the patients with analyzable ECG recordings.

In conclusion, low HRV, as measured by LnVLF power, partially mediates the effect of depression on survival following an acute MI. Other factors associated with depression may also increase the risk for mortality. More research is needed to identify these mechanisms as well as treatments for depression that will improve both depression and survival following acute MI.

Accepted for Publication: October 20, 2004.
Correspondence: Robert M. Carney, PhD, Behavioral Medicine Center, 4625 Lindell Blvd, Suite 420, St Louis, MO 63108 (carneyr@bmc.wustl.edu).
Funding/Support: This research was supported in part by grant 2 RO-1 HL 58946 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md
Acknowledgment: We thank Diane Catellier, DrPH, for her contributions to this study.

REFERENCES