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Depression and heart rate variability in patients with coronary heart disease

ABSTRACT

Depression is common in patients with coronary heart disease (CHD) and is a risk factor for cardiac morbidity and mortality in these patients. Depression is associated with autonomic nervous system dysfunction, which may at least partially explain this increased risk. Low heart rate variability (HRV), which reflects excessive sympathetic and/or inadequate parasympathetic modulation of heart rate, is a strong predictor of mortality in patients with CHD. Most studies—both in patients with stable CHD and in patients with a recent acute coronary event—have found HRV to be lower in depressed patients than in their nondepressed counterparts. This manuscript provides an overview of this literature and concludes that HRV may account for a substantial part of the risk associated with depression in CHD.

Depression is a common psychiatric disorder in patients with coronary heart disease (CHD). Whereas the lifetime prevalence of major depression in the United States is estimated to be about 16%,[1] with an annual rate of about 7%, approximately 20% of patients with CHD have major depression at any point in time.[2–5] About the same proportion have minor depression.[3] During the 12 months following an acute coronary event, as many as 30% of patients may develop major depression;[6] the prevalence of minor depression during this 12-month period has not been reported but is also estimated to be about 30%. Thus, up to 60% of patients with an acute coronary event experience symptoms of depression within the 12 months following the event.

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In addition to being highly comorbid with CHD, depression is also a significant risk factor for cardiac morbidity and mortality in patients with CHD. This risk is present from the time of initial diagnosis of CHD by cardiac catheterization and angiography[7,8] as well as after an acute myocardial infarction (MI),[6,9–11] an episode of unstable angina,[12] or coronary artery bypass graft surgery.[13–15] A recent meta-analysis of more than 20 studies of depression following acute MI found that major depression more than doubles the risk of mortality in the months following the acute event.[16] Another meta-analysis found that just having symptoms of depression at various times in the course of CHD doubles the risk of death, and that clinical depression is associated with an even higher risk.[17]

Depression has been associated with many behavioral and biological abnormalities that could help explain the increased mortality risk in depressed patients with cardiac disease, including reduced adherence to treatment regimens, increased prevalence of smoking and diabetes, platelet dysfunction and coagulant processes, inflammatory processes, and alterations in hypothalamic-pituitary-adrenal axis and autonomic nervous system (ANS) function.[18,19] Any or all of these might contribute to the increased risk for cardiac morbidity and mortality in depressed patients. Of all these possibilities, however, ANS dysfunction probably has received the most attention.[20] Excessive sympathetic or reduced parasympathetic nervous system activity in patients with CHD may promote myocardial ischemia, ventricular tachycardia, ventricular fibrillation, and even sudden cardiac death.[21–23]

Studies dating back to the 1960s have found plasma and urinary catecholamine levels and resting heart rate (HR)to be elevated in medically well psychiatric patients with major depression compared with nondepressed controls.[24–30] Studies of patients with CHD have also found elevated resting and 24-hour HRs in depressed compared with nondepressed patients.[31,32] Additional evidence of ANS dysfunction in depressed CHD patients includes increased HR response to orthostatic

challenge;[32] increased QT interval variability, reflecting abnormal ventricular repolarization;[33] abnormal HR response to ventricular arrhythmias (turbulence);[34] and an increased incidence of ventricular tachycardia.[35] All of these factors have been related to ANS dysfunction, and all are predictors of mortality in cardiac patients.

Many, though not all, studies of medically well depressed psychiatric patients have also found reduced HR variability (HRV), reflecting abnormal ANS modulation of HR. Low HRV is an excellent predictor of cardiac-related mortality[36–39] and thus may further help to explain the relationship of depression to increased risk of mortality.

MEASUREMENT OF HEART RATE VARIABILITY

Analysis of HRV is a widely used method for studying cardiac autonomic modulation of HR.[36] Low HRV generally reflects excessive sympathetic and/or inadequate parasympathetic modulation of HR[36] and is a strong predictor of mortality in patients with CHD.[37–39]

Three methods of deriving HRV

In large prognostic or epidemiologic studies, HRV is usually measured over a 24-hour period and is derived from electrocardiographic (ECG) data by one of three methods: time domain analysis, frequency domain analysis, and nonlinear statistical models.

Time domain indices are based on descriptive statistical analyses of the HR time series. These include the standard deviation of all normal-to-normal intervals (SDNN) and the root mean square of successive N-N differences (rMSSD).

Frequency domain indices. Fast Fourier transforms and spectral analyses of ECG data are used to characterize HRV in the frequency domain. Frequency domain indices are defined by specific frequency ranges:

- Ultra low frequency (ULF; < 0.0033 Hz)
- Very low frequency (VLF; 0.0033 to 0.04 Hz)
- Low frequency (LF; 0.04 to 0.15 Hz)
- High frequency (HF; 0.15 to 0.4 Hz).

These indices are usually log-transformed to produce approximately normal distributions. Efferent vagal activity is largely responsible for the HF component, whereas LF power seems to reflect both sympathetic and parasympathetic activity.[36] There is less certainly about the contributions to ULF.[36] While not completely understood, VLF power is known to be unaffected by beta-blockade but nearly abolished by atropine, suggesting that the parasympathetic nervous system is the predominant determinant of VLF.[40]

Nonlinear statistical models. HRV has also been characterized by nonlinear mathematical models, such as those based on chaos theory and fractals. Nonlinear methods quantify the structure of the HR time series, including its regularity and self-similarity. These indices include the short-term fractal scaling exponent and approximate entropy.

HEART RATE VARIABILITY AND DEPRESSION IN CHD

Some studies have assessed HRV and depression following acute MI,[41–45] whereas others have focused on HRV in medically stable patients with CHD.[46–49] Most of the studies have used frequency domain indices to calculate HRV.

HRV in post-MI patients with depression

In the largest study of depressed post-MI patients published to date,[41] 24-hour HRV levels were compared between 380 patients with a recent MI who had either major or minor depression and 425 post-MI patients who were not depressed. In univariate analyses, the four frequency domain indices of HRV (ULF, VLF, LF, and HF) were significantly lower in the depressed than in the nondepressed patients. After adjustment for possible confounders, all the indices except HF remained significantly lower in depressed patients than in nondepressed patients.

HRV in depressed patients with stable coronary disease

Most[46–48] but not all[49] studies have also found HRV to be lower in depressed than in nondepressed patients with stable CHD. The one exception was reported by Gehi et al,[49] who assessed participants from the Heart and Soul Study cohort who had stable CHD at the time HRV was determined. Of the 873 outpatients with stable CHD who received 24-hour ambulatory ECG monitoring, 195 were found to have major depression. No differences between depressed and nondepressed patients were found on any time domain or frequency domain measure of HRV. This is the largest study to date of medically stable CHD patients assessed for depression and HRV, but its results differ from those of most smaller studies. The authors noted that although there was no difference in HRV between depressed and nondepressed patients, HRV in the nondepressed patients was similar to that in depressed patients in other samples.[50] They speculated that the participants in their study, who were largely recruited from a Veterans Affairs hospital, may have been sicker than most participants in other studies and that this might have obscured depression-related differences in HRV.[50]

What is the clinical significance of HRV differences?

When evaluating differences in HRV between depressed and nondepressed patients, it is important to look past statistical comparisons and consider the clinical significance of these differences—ie, whether they are large enough to affect clinical outcomes or to be responsible

for the depressed patients' increased risk of death.

In the Cardiac Arrhythmia Pilot Study, HRV was assessed 1 year after acute MI in 331 patients.[51] All measured indices of HRV were strong predictors of mortality. Patients with VLF power of less than 600 ms^2 (natural logarithm of VLF power [LnVLF] < 6.4) were found to have a 4.4 relative risk of death over the next 2 years.[51] In a study of a similar group of medically stable (ie, event-free for ⩾ 6 months) patients with CHD,[48] 47% of those who were moderately to severely depressed, 29% of those who were mildly depressed, and 13% of those who were not depressed had VLF power below this cutpoint.

In the Multicenter Post-Infarction Program study, which evaluated patients in the immediate post–acute MI period, an LnVLF less than 5.2 was associated with a relative risk of 4.7 for cardiac mortality over the next 2.5 years.[37] In our own study of post-MI patients, 7% of the nondepressed participants and 16% of the depressed participants had VLF power below this value, a difference that was significant even after adjusting for covariates ($P = .006$).[41] Thus, mean 24-hour HRV is low enough in depressed patients with medically stable CHD and in those with recent acute MI to have prognostic significance.

How much of depression's effect is due to low HRV?

In an attempt to determine whether low HRV accounts for at least part of the effect of depression on mortality, a statistical mediation model was applied to data collected in a follow-up study of the 311 depressed patients with recent acute MI described above,[41] who were enrolled in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial,[52] and 367 patients who met the ENRICHD medical inclusion criteria but were without depression.[53] VLF was selected as the index of HRV for this study because of its prognostic importance in post-MI patients. As noted earlier, VLF was significantly lower in the depressed patients.[41] During a median follow-up of 24 months, there were 47 deaths within the overall study population of 766 patients (6.1%).[53] Consistent with earlier studies, the depressed patients were at higher risk for all-cause mortality, even after adjusting for potential confounders (hazard ratio = 2.8; 95% confidence interval [CI], 1.4 to 5.4; $P < .003$). When the LnVLF was entered into the model, the hazard ratio for depression dropped to 2.1 (95% CI, 1.1 to 4.2; $P = .03$), indicating that the LnVLF accounted for about one-quarter of the total mortality risk. Thus, the study results suggest that low HRV at least partially mediates the effect of depression on survival after acute MI.

A role for premature ventricular contractions

In one of the first prognostic studies of depression following acute MI, Frasure-Smith et al reported an interaction between depression and premature ventricular contractions (VPCs) on subsequent mortality.[6] Specifically, they found that depressed patients who had 10 or more VPCs per hour after an MI were at considerably higher risk of death than were either depressed post-MI patients without VPCs or nondepressed post-MI patients with 10 or more VPCs per hour. One interpretation of these data is that depressed patients may be at greater risk for death due to an abnormal response to VPCs or other arrhythmias.

HR turbulence analysis is a method for quantifying HR response to VPCs. In most individuals, when a VPC occurs, HR first accelerates and then decelerates. HR responses that differ from this pattern have been found to be even better predictors of post-MI mortality than more traditional measures of HRV in these patients.[54,55]

A total of 498 patients from the study reported above[53] were found to have VPCs during 24-hour ambulatory monitoring.[34] Of these patients, 260 had normal HR turbulence, 152 had equivocal HR turbulence, and 86 had abnormal HR turbulence. The depressed patients were more likely than their nondepressed counterparts to have abnormal HR turbulence (risk factor–adjusted odds ratio [OR] = 1.8; 95% CI, 1.0 to 3.0; $P = .03$). The patients were followed for a median of 24 months. Consistent with earlier studies, depressed patients had worse survival (OR for death = 2.4; 95% CI, 1.2 to 4.6; $P = .02$) than the nondepressed patients. When HR turbulence was added to the statistical model, the adjusted hazard ratio for depression decreased to 1.9 (95% CI, 0.9 to 3.8; $P = .08$). When the LnVLF was added to this model, the adjusted hazard ratio decreased further, to 1.6 (95% CI, 0.8 to 3.4; $P = .18$). Thus, the combination of VLF and HR response to VPCs explained about half of the effect of depression on survival in these patients.

Causality not proven, but further study warranted

Obviously, these results do not prove that there is a causal relationship between depression, low HRV, and mortality. However, they are consistent with the interpretation that HRV, especially when combined with measures of HR response to VPCs, may account for a significant proportion of depression's association with mortality following an MI. Future studies of these risk markers should explore their potential interrelationships to clarify how they may jointly contribute to the risk of death in patients with depression.

RELATIONSHIP AMONG HRV AND OTHER POSSIBLE BIOLOGICAL PATHWAYS

As discussed earlier, other biological pathways that may link depression to increased mortality have

been reported. The two that have received the most support are proinflammatory and procoagulant processes.[18,19] Studies of medically healthy depressed psychiatric patients and of depressed CHD patients have found depression to be associated with higher levels of the inflammatory risk markers interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor–alpha (TNF-α) and with inflammatory-procoagulant markers such as fibrinogen,[56–60] as well as with platelet activation. Low HRV and elevations in proinflammatory or procoagulant markers generally have been described as though they are independent pathways. However, both inflammatory and coagulant responses can be modulated by ANS activity,[61,62] and a cholinergic anti-inflammatory pathway was recently proposed in which there is vagal efferent inhibition of proinflammatory cytokine release, thereby reducing systemic inflammation.[62,63] Low HRV, reflecting reduced vagal activity, should therefore be associated with higher levels of both proinflammatory and procoagulant markers. Recent studies have found a relationship between HRV activity and increased markers of inflammation in other high-risk patients, including those with heart failure[64,65] and with acute coronary syndrome.[66]

In a recent study of 44 patients with major depression, moderate negative correlations were found between fibrinogen and four measures of HRV.[67] IL-6 was also negatively correlated with one measure of HRV (total power) and was marginally related to two others (VLF and LF power). On the other hand, neither CRP nor TNF-α was significantly related to any measure of HRV. The finding that fibrinogen and IL-6 are moderately related to HRV suggests a link between these factors in depressed CHD patients. Thus, these risk markers, which are commonly found in patients with depression, may be related and contribute to the increased mortality associated with depression. This possibility should be investigated in larger mechanistic studies of depression and cardiac morbidity and mortality.

SUMMARY AND FUTURE DIRECTIONS

Low HRV and other markers of cardiac ANS dysfunction in depressed patients are likely to contribute to the elevated risk associated with depression in patients with CHD. More work is needed to clarify the physiologic and behavioral mechanisms underlying depression's role as a risk factor for mortality in patients with CHD. Work is also needed to identify treatments that improve both depression and HRV, and to determine whether such treatments might also improve survival in these patients.[68]

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