Depression, the Autonomic Nervous System, and Coronary Heart Disease

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Depression is a risk factor for medical morbidity and mortality in patients with coronary heart disease (CHD). Dysregulation of the autonomic nervous system (ANS) may explain why depressed patients are at increased risk. Studies of medically well, depressed psychiatric patients have found elevated levels of plasma catecholamines and other markers of altered ANS function compared with controls. Studies of depressed patients with CHD have also uncovered evidence of ANS dysfunction, including elevated heart rate, low heart rate variability, exaggerated heart rate responses to physical stressors, high variability in ventricular repolarization, and low baroreceptor sensitivity. All of these indicators of ANS dysfunction have been associated with increased risks of mortality and cardiac morbidity in patients with CHD. Further research is needed to determine whether ANS dysfunction mediates the effects of depression on the course and outcome of CHD, and to develop clinical interventions that improve cardiovascular autonomic regulation while relieving depression in patients with CHD. **Key words:** autonomic nervous system, coronary disease, depression, depressive disorder, mortality, myocardial infarction.

ANS = autonomic nervous system; **CHD** = coronary heart disease; **HRV** = heart rate variability; **MI** = myocardial infarction; **NE** = norepinephrine; **SNS** = sympathetic nervous system.

INTRODUCTION

Depression has significant adverse effects on the course and outcome of coronary heart disease (CHD). Depressed patients are twice as likely as nondepressed patients to have a major cardiac event within 12 months of the diagnosis of coronary artery disease (1), and they are significantly more likely to die in the years following the diagnosis (2). Depression also increases the risk of dying after an acute myocardial infarction (3–10), an episode of unstable angina (11), or coronary artery bypass graft surgery (12–14). Although some studies have failed to find a relationship between depression and mortality in patients after myocardial infarction (MI; 15,16), most have found depression to be a significant risk factor for mortality and/or cardiac morbidity (17).

Although the relationship between depression and cardiac events is well established, the mechanisms underlying this relationship remain unclear. Dysregulation of the autonomic nervous system (ANS) is one of the most plausible candidates (18–21). Reduced parasympathetic and increased sympathetic nervous system (SNS) activity can lower the threshold for myocardial ischemia, ventricular tachycardia, ventricular fibrillation, and sudden cardiac death in patients with CHD (22–24). Furthermore, coronary artery disease is a chronic inflammatory process that is triggered by injury to the vascular endothelium (25,26), and high levels of circulating catecholamines may contribute to recurrent endothelial injury (26). Elevated catecholamines may also promote procoagulant processes by potentiating platelet activation through direct agonist effects, by increasing hemodynamic stress on vascular walls, or by inhibiting vascular eicosanoid synthesis (27,28). Both inflammatory and platelet coagulant processes associated with depression are described in detail elsewhere in this issue (29,30). This review focuses on studies that have found evidence of altered ANS regulation in depressed CHD patients.

CATECHOLAMINE LEVELS IN DEPRESSED PATIENTS

Some of the earliest evidence of ANS dysregulation in depression was found in studies of medically well patients with major depressive disorder. These studies found elevated levels of plasma and urinary catecholamines, primarily norepinephrine (NE), in depressed patients compared with controls (31–37).

Because the concentration of plasma NE generally parallels the level of activity of the SNS, elevated NE in depressed patients suggests that SNS activity is increased. However, the interpretation of plasma NE concentration is complex. When plasma NE is sampled from antecubital venous blood, it reflects local sympathetic activity in the forearm, but it may or may not reflect cardiac or total body sympathetic activity levels (38). Moreover, high levels of circulating NE could result from increased NE release because of sympathetic hyperactivity, diminished NE clearance, or both (39). These complexities make it difficult to interpret elevations in plasma or urinary NE in human studies. It is possible to obtain better estimates of systemic sympathetic activity by employing arterialized venous sampling and plasma NE kinetic techniques that rely on dilution of radiolabeled NE and mathematical modeling to provide estimates of postganglionic NE release and NE clearance (40). Using this approach, Veith et al. (37) demonstrated that the elevated levels of circulating plasma NE in medically healthy patients with major depression are a result of increased total body sympathetic activity.

HEART RATE AND HEART RATE VARIABILITY

Resting heart rate has been studied in depressed patients along with measures of catecholamine levels or other markers of autonomic function. Most of these studies have found higher heart rates in depressed patients than in nondepressed controls (33,35–37,41,42), consistent with altered cardiac ANS function. Elevated resting heart rate is a risk factor for sudden cardiac death, even in the general population (43–45).

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It also increases the risk for progression of atherosclerosis (47,48), ventricular arrhythmias (23), myocardial ischemia (46), and plaque disruption in acute coronary syndromes (49) in individuals with CHD. Mean 24-hour heart rate has been found to be higher in depressed than nondepressed patients with CHD, with differences ranging from 5 to 11 bpm (49–53).

Depression is associated with exaggerated heart rate responses to physical and psychological stressors in medically well subjects (54–58), and it increases cardiovascular reactivity to physical stressors in patients with CHD (52). In one study, heart rate was measured at rest and during orthostatic challenge in 50 depressed and 39 medically comparable nondepressed patients with CHD. NE did not differ between the depressed patients and the controls, but this may have been a result of a measurement artifact (52). Resting heart rate did differ between the groups, with a mean of 69.9 bpm ± 10.4 bpm in the depressed and 63.6 bpm ± 10.2 bpm in the nondepressed groups ($p = .005$). The changes from supine heart rate at 2, 5, and 10 minutes after standing were significantly greater in the depressed patients than the nondepressed controls ($p = .02$, .004, and .02, respectively), with depressed patients having a mean maximum change in heart rate of 11.9 bpm ± 6.8 bpm, compared with 7.9 bpm ± 6.8 bpm among the nondepressed controls. These differences remained significant even after adjusting for covariates. Thus, depressed patients with CHD have higher 24-hour heart rates and higher heart rate responses to physical stressors than nondepressed patients. To our knowledge, heart rate responses to psychological stressors have not yet been studied in depressed patients with CHD.

Heart rate variability (HRV) is one of the most widely used methods for measuring cardiac autonomic activity in humans (59). Beat-to-beat variability in the heart's rhythm is determined primarily by ANS modulation of the intrinsic cardiac pacemakers. HRV, then, reflects the balance between the sympathetic and parasympathetic regulatory control of the heartbeat; low HRV suggests excessive cardiac sympathetic modulation, inadequate cardiac parasympathetic modulation, or both (59). Low HRV also predicts mortality in patients with a recent MI (60–63) or with stable coronary disease (64).

Many studies have found HRV to be lower in depressed psychiatric patients compared with controls (65–67), although some have not (e.g., 68). There is more consistent evidence that HRV is lower in depressed than nondepressed patients with stable coronary disease (53,69,70) or with a recent history of acute MI (71).

In addition to statistical significance, it is important to consider the clinical significance of differences between depressed patients and controls for any putative mechanism. Unless the difference is large enough to affect clinical outcomes, it is unlikely to be responsible for the depressed patients' increased risk for mortality. The Cardiac Arrhythmia Pilot Study assessed HRV 1 year after an acute MI (62). All of the measured indices of HRV were strong predictors of mortality. Patients with a log(n) of very low frequency power <6.4 had a 4.4 relative risk of mortality over the next 2 years. In a recent study of a similar group of medically stable (i.e., event-free for at least 6 months) CHD patients, 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 very low frequency power below this cut-point (53). In the Multicenter Post Infarction Project study (61), log(n) of very low frequency power <5.2 was associated with a relative risk of 4.7 for cardiac mortality over the 2.5 years after the acute MI. In our study of post-MI patients, 7% of the nondepressed patients and 16% of the depressed patients had very low frequency power below this value, a difference that was significant even after adjusting for covariates ($p = .006$; 10). Thus, mean 24-hour HRV is low enough in depressed patients with medically stable CHD and after an acute MI to have prognostic significance.

Low HRV has consistently been found in studies of depressed CHD patients, but in only approximately half of the studies of medically well depressed patients. Furthermore, although several HRV indices are highly predictive of cardiac mortality, the relative contributions of the sympathetic and parasympathetic nervous systems and other physiological processes remain unclear. HRV clearly has the potential to explain much of the effect of depression on cardiac mortality, but more work is needed to delineate the underlying physiological processes.

Ventricular tachycardia can be precipitated by cardiac autonomic imbalance (23,24), as reflected by lower HRV, and this is the arrhythmia that usually precedes ventricular fibrillation and sudden cardiac death (72,73). One study found that depressed patients with stable coronary artery disease and preserved ventricular function had more frequent and longer runs of ventricular tachycardia than medically comparable nondepressed patients (74). Twenty-three percent of the depressed patients in this study and 3.5% of the nondepressed patients with stable CHD had episodes of ventricular tachycardia ($p < .008$). Depression remained a significant predictor of ventricular tachycardia even after controlling for potential confounds ($p < .01$). The relative risk for ventricular tachycardia among the depressed patients was 8.2 (95% confidence limits, 2.1–31.7). Research is needed to determine whether the increased prevalence of ventricular tachycardia in depressed patients, especially those with poor left ventricular function, explains the increased risk for sudden cardiac death in these patients (17).

OTHER EVIDENCE FOR CARDIAC AUTONOMIC DYSFUNCTION IN DEPRESSION

Baroreflex Dysfunction

Less is known about the effects of depression on two other parameters reflecting cardiac ANS modulation: baroreflex function and ventricular repolarization. The arterial baroreflex is modulated by the ANS and by other mechanisms involved in cardiovascular regulation. Like low HRV, impaired baroreflex sensitivity predicts cardiac events, including ventricular arrhythmias (75) and sudden cardiac death (76). Watkins and Grossman (77) found that depression was associated with a

reduction in baroreflex control of heart rate in patients with CHD. A more recent study from this group failed to find evidence for lower baroreflex control in post-MI patients with depression, but they did find an association with anxiety (78). Pitzalis et al. (79), on the other hand, found reduced baroreflex function in a group of unmedicated post-MI patients with depression, but not in anxious patients or in depressed patients receiving β-blockers. Approximately 80% of the depressed patients in the second Watkins et al. study were taking β-blockers at the time of study (78), which may explain why this group did not find an lower baroreflex control of heart rate in their depressed patients. Thus, it is possible that the SNS may contribute to reduced baroreflex sensitivity in depressed CHD patients, and this may increase their risk for cardiac events. Clearly, more research is needed to determine the relationship of depression to baroreflex dysfunction and cardiac events.

Ventricular Repolarization

The QT interval is the electrocardiographic representation of ventricular repolarization time. Variability in the QT interval reflects beat-to-beat fluctuations in myocardial recovery time, and increased variability is a significant predictor of arrhythmic events and sudden cardiac death (80–83). Postural challenge and isoproterenol infusion have been shown to increase QT interval variability (84), which suggests that ventricular repolarization is modulated, at least in part, by the SNS.

In the only study to date of depressed cardiac patients, QT variability was found to be significantly higher in the depressed patients than in a group of age-matched and gender-matched nondepressed CHD patients during two of eight sampling periods over 24 hours of ambulatory monitoring (85). Sudden cardiac death has been shown to have a circadian pattern, with the peak incidence occurring in the early morning hours (86). The difference in QT variability between depressed and nondepressed patients was greatest during the early morning, just after 6:00 AM. This may reflect a greater increased risk for arrhythmias and sudden death for depressed patients during this normally high-risk time. Thus, depression may increase the risk of mortality after an acute MI by contributing to dysregulation of ventricular repolarization.

EFFECTS OF TREATING DEPRESSION ON CARDIAC AUTONOMIC FUNCTION

A number of studies have examined the effects of various treatments for depression on heart rate and HRV. Tricyclic antidepressants tend to increase heart rate and decrease HRV, presumably because of their anticholinergic side effects (87–89), and they are generally not recommended for treatment of depression in patients with heart disease. The selective serotonin reuptake inhibitors appear to have no significant cardiotoxic side effects and are recommended for treating depression in these patients. In a preliminary study among healthy volunteers, short-term sertraline administration suppressed circulating plasma NE appearance, which is compatible with a reduction in total body SNE activity (90). However, whereas some studies have shown that treatment of depression with selective serotonin reuptake inhibitors improves HRV (91–93), others have found only temporary or no improvement (94–96).

To our knowledge, there is only one study that assessed whether heart rate or HRV improves following a psychotherapeutic intervention for depression. Fifty patients with stable CHD and comorbid major depression were given as many as 16 sessions of cognitive behavior therapy, a recognized psychotherapeutic treatment for depression (51). After completing treatment, 90% of the depressed patients were in full or partial remission. The mean 24-hour heart rate dropped 5 bpm in the depressed patients over the course of treatment, compared with less than 1 bpm in a group of nondepressed controls. There was also a significant increase in an index of HRV (rMSSD) that reflects primarily parasympathetic modulation, and a trend ($p = .07$) toward an increase in an index of HRV (SDNNIDX) that reflects a mixture of sympathetic and parasympathetic influences.

The clinical significance of these changes is difficult to estimate. However, heart rate reduction is one of the best predictors of improved survival in patients receiving β-blockers, in both short-term and long-term intervention trials. Reduction in heart rate and the percent reduction in mortality and nonfatal reinfarction correlated at approximately 0.60 across the major β-blocker post-MI intervention trials (97). On average, heart rate decreased by approximately 11 bpm among patients randomized to β-blockers in the major trials (97). The mean heart rate of the severely depressed patients receiving the psychotherapeutic intervention decreased by approximately 5 bpm between the pretreatment and posttreatment assessments, or nearly half of the reduction that is typically achieved by giving patients β-blockers. These results, although intriguing, await replication. However, the implications for treating depression and possibly improving cardiac prognosis are clear. More studies are needed to evaluate the effects of depression treatment on cardiac autonomic function, cardiac morbidity, and mortality.

SUMMARY AND CONCLUSIONS

It is not yet certain that altered ANS activity is responsible for the increased risk of mortality and medical morbidity associated with depression in patients with CHD. Nevertheless, there is considerable evidence of autonomic cardiovascular dysregulation in depressed patients. Furthermore, many indicators of cardiovascular autonomic dysregulation, including elevated resting and 24-hour heart rates, increased heart rate responses to physical stressors, reduced HRV and baroreceptor sensitivity, and high variability in ventricular repolarization, have been associated with increased mortality and cardiac morbidity, especially in vulnerable populations such as post-MI patients. More studies are needed to determine whether these factors mediate the increased risk of mortality in depressed patients with CHD, and to identify clinical interventions that can improve them.

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