

# Depression, Anxiety, and the Cardiovascular System: The Cardiologist's Perspective

David S. Sheps, M.D., and David Sheffield, Ph.D.

Up to one fifth of patients with cardiovascular disease, including those who have experienced a myocardial infarction, may have concomitant major depression. Studies have suggested that the relative risk of major depression with cardiovascular disease ranges from 1.5 to 4.5. Further information is required to establish a dose-response relationship between depression and coronary artery disease (CAD); however, such a relationship has been shown between anxiety and CAD. Development of a conceptual model of the pathophysiologic actions of stress in CAD will assist in the understanding of this relationship. In patients with angiographic evidence of CAD, the presence of major depressive disorder was the best single predictor of cardiac events during the 12 months following diagnosis. Significantly, 6-month cumulative mortality following diagnosis of myocardial infarction has been shown to be higher in depressed patients than in nondepressed patients. A decrease in heart rate variability may mediate the deleterious effect of depression on post-myocardial infarction prognosis. Other factors such as mental stress and altered platelet function may also predispose depressed patients to a heightened risk of cardiac events. With an increased understanding of the relationship between depression and heightened risk of cardiovascular mortality, it is necessary to assess current overall treatment for cardiac patients. *(J Clin Psychiatry 2001;62[suppl 8]:12-16)*

Up to one fifth of patients with ischemic heart disease may have concomitant major depression.<sup>1-4</sup> Moreover, depression may also be considered a risk factor for developing cardiac disease.<sup>5-8</sup> With this in mind, it is useful to explore more fully the data that link depression and anxiety to cardiovascular disease and speculate on the underlying pathophysiologic mechanisms. A clearer understanding of the influence of depression on cardiovascular disease will focus our attention on the potential of antidepressant treatments to improve prognosis.

## EVIDENCE LINKING DEPRESSION AND ANXIETY TO CARDIOVASCULAR DISEASE

One way to examine the adequacy of the evidence relating depression and anxiety to cardiovascular disease is to use classic epidemiologic principles to assess causality.

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*From the Division of Cardiovascular Medicine, School of Medicine, University of Florida, Gainesville.*

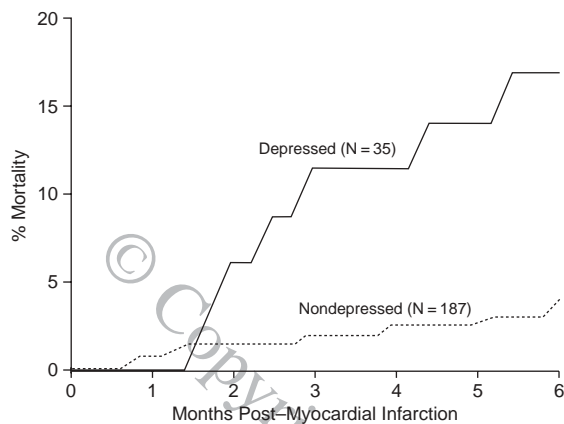
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*Reprint requests to: David S. Sheps, M.D., Division of Cardiovascular Medicine, School of Medicine, University of Florida, P.O. Box 100277, Gainesville, FL 32610-0277.*

The main criteria used for assessment are strength of association (risk ratio), dose-response relationships, consistency of association, and temporally correct association. Some current studies relating depression to coronary artery disease (CAD) have methodological weaknesses that make assessing the strength of the association inconclusive. For example, when psychiatric diagnostic instruments that have not been modified are used to determine the prevalence of depression, they may not have the same validity for patients with CAD as they do in the general population. Excluding some patients because of the severity of their cardiovascular disease and measuring depressive symptoms at different times after hospital admission also reduce the validity of the analysis. However, some of the studies of the link between cardiovascular disease and depression are relatively well controlled, are prospective in design, use structured clinical interviews with diagnostic instruments, include other risk factors for CAD in their analysis, and control for demographic factors.<sup>6-15</sup> In these studies, the relative risk of major depression or depressive symptoms for cardiovascular disease or cardiovascular disease-related death ranges from 1.5 to 4.5. These relative risks are quite high for epidemiologic studies, so it would seem that the strength of the association is quite reasonable and impressive in magnitude. Therefore, there are good data to support the criterion of strength of association between the risk factor of depression and CAD.



Figure 2. Six-Month Cumulative Mortality in Depressed and Nondepressed Post-Myocardial Infarction Patients<sup>a</sup>



<sup>a</sup>Reprinted from Frasure-Smith et al.,<sup>1</sup> with permission.

### EFFECT OF DEPRESSION AND ANXIETY ON PROGNOSIS AFTER MYOCARDIAL INFARCTION

One of the earliest studies looking at the relationship between depression and CAD was published by Carney and colleagues<sup>2</sup> in 1987. They studied 50 patients in whom coronary angioplasty had shown evidence of CAD. Patients were assessed by the Beck Depression Inventory<sup>26</sup> and a semistructured interview for depression (DSM-III criteria), in addition to the State-Trait Anxiety Inventory.<sup>27</sup> Twenty-six percent of patients screened met criteria for major depression. Patients taking  $\beta$ -blockers did not differ from other patients with regard to presence or absence of major depressive illness or severity of depression. Univariate correlations for the presence of any cardiac event with risk factors and medications were analyzed. The strongest univariate correlations were left ventricular ejection fraction, severity of CAD, and major depressive disorder (R values, 0.3–0.4). The presence of major depressive disorder was the best single predictor of cardiac events during the first 12 months following diagnostic coronary angiography. The impact of major depressive disorder was at least equivalent to that of left ventricular dysfunction and history of previous myocardial infarction.

Subsequently, many studies have been published looking at the relationship between depression and CAD events in patients with either stable CAD or recent myocardial infarction.<sup>1,28</sup> For example, Frasure-Smith et al.<sup>1</sup> studied 222 patients hospitalized with myocardial infarction (Figure 2). The diagnosis of depression was made using the Diagnostic Interview Schedule,<sup>29</sup> and the prevalence of major depression in this study was 16%. The 6-month cumulative mortality was significantly higher in the depressed patients than in the nondepressed patients, as shown in Figure 2.

### POSSIBLE MECHANISMS OF THE ADVERSE IMPACT OF DEPRESSION AND ANXIETY IN PATIENTS WITH CORONARY ARTERY DISEASE

As described in the earlier discussion of the pathophysiologic model, there is evidence to suggest that increased sympathetic tone may mediate the adverse prognosis associated with phobic anxiety and depression in patients with CAD. Kawachi et al.<sup>30</sup> published their findings from the Normative Aging Study, in which 581 men, free of CAD and diabetes, were enrolled. These men were aged 47 to 56 years on entry. Heart rate variability was measured with paced deep breathing. The standard deviation of the heart rate and the maximum minus the minimum heart rate over 1 minute were determined. Heart rate variability is defined as the standard deviation of successive intervals between 2 consecutive R waves on an electrocardiogram, in normal sinus rhythm; it reflects the balance between sympathetic and parasympathetic input on the heart. A high degree of heart rate variability is observed in normal hearts, whereas patients with severe CAD or heart failure can have significantly decreased heart rate variability.

After adjusting for age, men reporting higher levels of phobic anxiety had a higher resting heart rate ( $p = .025$ ). After adjusting for age, mean heart rate, and body mass index, men reporting higher levels of phobic anxiety had lower heart rate variability ( $p = .03$ ). These data suggest that phobic anxiety is associated with altered cardiac autonomic control and hence might predispose to increased risk of sudden cardiac death. It was, however, unclear whether phobic anxiety caused diminished heart rate variability or vice versa. Moreover, the investigators could not rule out the presence of subclinical CAD during their study. Assessments of heart rate variability were made from short-lasting electrocardiographic (ECG) records, whereas many previous studies have used 24 hours of electrocardiographic recordings. In addition, a high score on the Crown-Crisp Index does not necessarily imply a clinical diagnosis of anxiety disorder. Nevertheless, the findings are quite interesting and provocative.

The risk of subsequent cardiac events for patients with heart disease has been shown in numerous studies to be related to decreased heart rate variability and/or increased sympathetic tone. Reduced high-frequency heart rate variability has been observed in depressed patients when compared with nondepressed patients. In patients with confirmed CAD, diminished heart rate variability during 24-hour Holter monitoring was more common in depressed patients than in matched nondepressed patients. A decrease in high-frequency heart rate variability reflects decreased parasympathetic tone, possibly predisposing to ventricular arrhythmias, increased platelet stickiness, and, perhaps, excessive cardiovascular mortality.

We have also studied changes in heart rate variability during daily life in patients with CAD but without clinical

depression.<sup>31</sup> The study tested the hypothesis that those CAD patients with higher depression scores but without clinical depression have lower heart rate variability during daily life. We studied 33 men and 9 women aged 46 to 79 years with CAD and exercise-induced ischemia. The standard deviation of normal RR intervals (SDNN) and average heart rate were obtained from 24-hour ambulatory ECG monitoring. Patients were grouped by median split of the Minnesota Multiphasic Personality Inventory-Depression (MMPI-D)<sup>32</sup> score. It is important to point out that none of our patients was clinically depressed, although they were not formally analyzed by diagnostic instruments for this purpose. Our results showed that SDNN was lower and average heart rate was higher in patients with higher depression scores ( $p = .009$  and  $p = .003$ , respectively). These relationships remained substantially unaltered after statistically adjusting for gender. Average heart rate and SDNN were the only demographic or clinical factors that varied between the groups. We concluded that, in comparison with patients with lower depression scores, patients with higher depression scores had lower heart rate variability during daily life. We attributed these findings to the established relationship between depression and survival risk in patients with CAD. Our study is clinically important because it shows the same type of relationship between a tendency towards depression, as indicated by a high MMPI-D score, and abnormalities in heart rate variability in a population that is not obviously clinically depressed.

### MYOCARDIAL ISCHEMIA IN RESPONSE TO MENTAL STRESS

Recently, several studies have shown that, in the laboratory, patients with CAD respond to acute psychological stress with myocardial ischemia. Most of the studies have included patients with documented CAD. Fifty percent of patients with documented CAD and positive exercise tests have evidence of psychological stress-induced ischemia, detected in the laboratory using radionuclide techniques. Several investigators, including Jiang and colleagues,<sup>33</sup> have shown that these responses in the laboratory are associated with abnormally high event rates on follow-up. During a 5-year period, Jiang and colleagues<sup>33</sup> followed up 126 patients with CAD. Psychological stress-induced ischemia at baseline was associated with significantly higher rates of subsequent fatal and nonfatal cardiac events, independent of age, baseline left ventricular ejection fraction, and previous myocardial infarction. This study suggested that the relationship between psychological stress and adverse cardiac events is mediated by myocardial ischemia. Using a similar protocol to that of Jiang et al.,<sup>33</sup> we observed the same relationship in the Psychophysiological Investigations in Myocardial Ischemia (PIMI) population.<sup>34</sup>

Some similarities exist between the acute psychological stress response and the chronic responses previously described for patients with depression and anxiety. The relationship between heart rate variability and ischemic responses to mental stress was reported in the PIMI population.<sup>35</sup> Heart rate variability was measured prior to and during a Stroop mental stress task in 147 cardiac patients enrolled in the PIMI study. All patients had documented CAD and ECG evidence of ischemia during exercise. Forty-seven patients showed radionuclide or ECG evidence of ischemia due to mental stress during the Stroop mental stress task. Analysis of heart rate variability measures provided evidence of altered autonomic responses in patients showing mental stress ischemia. During the Stroop task, patients with mental stress ischemia had decreases in high-frequency and low-frequency power compared with patients without mental stress ischemia. These data suggest that ischemic responses to mental stress were associated with increased sympathetic activation and/or vagal withdrawal. Thus, the increased risk associated with low heart rate variability in cardiac patients may be due in part to psychological stress and associated changes in cardiac autonomic balance. Furthermore, acute stressors in the laboratory and chronic stressors such as depression and anxiety may have similar pathophysiologic mechanisms in predisposing patients to risk and may in fact be additive.

### ALTERED PLATELET FUNCTION

Platelet mechanisms linking depression and heart disease are supported by associations between cerebrovascular disease and depression. The Established Populations for Epidemiologic Studies of the Elderly prospective study assessed 10,294 persons who were 65 years and older. Stroke rates were 2.3 to 2.7 times higher in persons designated as "high" compared with "low" on depressive symptoms.<sup>36</sup>

The actions of platelets are thought to be central in the development of atherosclerosis and in the precipitation of sudden death or other acute coronary syndromes. Platelets have receptors for catecholamine and serotonin (5-HT). Increased levels of catecholamines, such as those found in depression, could initiate platelet responses, including aggregation and precipitation of an acute coronary syndrome. When platelets aggregate, they also release granules that may contain chemotactic and mitogenic factors, inducing the migration of leukocytes and other factors such as platelet factor 4,  $\beta$ -thromboglobulin, and 5-HT. These other factors stimulate and attract other platelets and cause increased vasoconstriction. Abnormalities of platelet function such as increased intracellular free calcium, increased 5-HT<sub>2</sub> receptor binding density, and decreased serotonin transporter sites have been described in depressed patients. All



of these abnormalities could predispose the depressed patient to increased platelet aggregation.

### IMPACT OF DEPRESSION AND ANXIETY ON THE MANAGEMENT OF THE CARDIOVASCULAR PATIENT

Firm data on how we should manage depression and anxiety in the cardiovascular patient are somewhat lacking. What we can say is that most depression and anxiety disorders remain undiagnosed in primary care and cardiac patients. Furthermore, it is likely that these disorders influence patient compliance with physician-prescribed medication and advice that might lead to healthy behaviors such as adherence to diet and exercise and could certainly affect patient outcome. Controlled clinical trials are ongoing to assess the influence of treatment of depressive disorders in the post-myocardial infarction patient and its impact on survival. These trials include drug treatment with sertraline (SADHART) and cognitive-behavioral therapy (ENRICHED). Results of these trials should be available within several years. The most important areas for future research clearly lie in further elucidating mechanisms explaining the increased risk for patients with depression and anxiety concomitant with cardiovascular disease.

*Drug names:* dexamethasone (Decadron and others), sertraline (Zoloft).

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