DEPRESSION AND HEART RATE VARIABILITY IN PATIENTS
WITH CORONARY ARTERY DISEASE

DISSERTATION

Presented to the Graduate Council of the
University of North Texas in Partial
Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

Roger D. Saunders, B.A., M.A.

Denton, Texas

December, 1994
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Depression is an independent risk factor for morbidity and mortality in patients with coronary artery disease (CAD). Altered autonomic nervous system (ANS) activity, a common feature of depression, is also a risk factor for cardiac events in patients with CAD. Heart rate variability (HRV) reflects ANS activity, and reduced HRV predicts morbidity in cardiac populations. The purpose of this study was to determine whether differences in HRV exist between depressed and nondepressed patients with CAD. Twenty-one depressed inpatients, with angiographically documented CAD were retrospectively matched to 21 nondepressed CAD patients by sex, age, and smoking status. Demographic, medical, psychological interview data, and 24-hour ECG recordings were obtained. Depressed subjects had significantly lower HRV, or trends toward lower HRV, than nondepressed subjects, even after controlling for severity of CAD. Subject groups did not differ on left ventricular ejection fraction, history of myocardial infarction, or any other relevant medical variable assessed. These results suggest that depression is associated with decreased HRV in patients with
CAD, and may help to explain the increased rates of cardiac events observed in CAD patients with depression.
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CHAPTER I

INTRODUCTION

Atherosclerotic coronary artery disease (CAD) is the leading cause of death in the United States (Crawley, Walter, & Hurst, 1987), and traditional risk factors account for only about half of the incidence in middle-aged, American men (Blumenthal, Williams, Wallace, & Needles, 1987). Coronary artery disease may be silent but more commonly is associated with symptoms (e.g., myocardial infarction, angina pectoris, and sudden death) (Reiss & Eisenberg, 1992). For all too high a proportion of people developing clinical CAD, the first episode, sudden death, is the last, manifest before medical care can be brought to bear (Stamler, 1993). Epidemiologic studies have established associations between CAD and certain factors. The most important of these are hypercholesterolemia, cigarette smoking, abnormal glucose tolerance, obesity, sedentary living, psychosocial tensions, hypertension and diabetes mellitus (Crawley et al., 1987; Reiss & Eisenberg, 1992).

The sustained occurrence of CAD, accounting for one-third of all deaths in the United States, argues for further research that can more clearly identify physiological and
psychological parameters that contribute to the morbidity and mortality associated with CAD. Studies have demonstrated support for an association between adverse outcomes of CAD and an array of affective states, trait characteristics, social conditions, and life events. A quantitative review of 13 studies which investigated depression in relation to CAD, found the combined effect size for depression was as high as that found for Type A measures, and comparable to effect sizes for other major risk factors (Booth-Kewley & Friedman, 1987). According to these authors, the picture of the coronary-prone personality emerging from this meta-analysis does not appear to be limited to that of the workaholic, hurried, impatient individual. Rather it seems to be one of a person with one or more negative emotions, perhaps one who is depressed.

Studies also suggest that physicians have underestimated psychological morbidity and social disability in their patients (Mayou, Foster, & Williamson, 1978), and have been shown to be poor judges of psychological distress (Thompson, Stoudemire, Mitchell, & Grant, 1983). Kurosawa, Shimizu, Nishimatsu, Hirose, and Takano (1983), asserted that organic heart disease is the main object of the physicians' interest, and they seldom pay attention to the mental state of the patient. Additionally, physicians who treat patients with CAD may be inadequately trained to recognize depression. Not only do depressed CAD patients
experience the suffering and despair associated with clinical depression, but they are also more likely to be at risk for further morbidity and mortality due to their heart disease (Carney, Rich, Tevelde, Saini, & Clark, 1987a). Greater awareness of psychological morbidity in CAD patients has been recommended. At the same time, research is needed that can identify physiologic mediators which explain the increased morbidity and mortality associated with CAD in patients who also suffer from depression.

Major depression in cardiac patients was found to be predictive of major cardiac events, including myocardial infarction and bypass surgery, following diagnosis of CAD (Carney, Rich, Freedland, Saini, Tevelde, Simeone, & Clark, 1988a), and a five-fold greater risk of subsequent death than that found in nondepressed patients (Kennedy, Hofer, Cohen, Shindledecker, & Fisher, 1987). Elevated sympathetic nervous system activity, which accompanies affective disorders, has been implicated in promoting increased manifestations of CAD, lethal arrhythmias, and increased atherosclerosis, and thus may lead to a higher rate of mortality and morbidity (Carney et al., 1988b). Although a strong association has emerged, few studies have sought to identify specific physiological mediators that might be involved in this apparent harmful relationship between CAD and depression. Clinical depression in otherwise medically well psychiatric patients has been associated with
dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) and increased sympathetic activity (Esler, Turbott, Schwarz, Leonard, Bobik, Skews, & Jackman, 1982; Roy, Pickar, Linnoila, & Potter, 1985). Evidence for altered autonomic activity and HPA axis activity in clinically depressed medical patients, has included elevated levels of plasma cortisol, (Linkoski et al., 1985; and Rubin et al., 1987), plasma catecholamines, (Esler et al., 1982; Lake et al., 1982; Roy et al., 1985), and adrenocorticotropic hormone (ACTH) (Linkoski et al., 1985). Elevated resting heart rates, which are consistent with increased sympathetic and decreased parasympathetic activity, have also been observed in some depressed CAD patients populations (Carney, et al., 1988b; Dawson et al., 1977; Lahmeyer et al., 1987; Lake et al., 1982).

Heart rate variability (HRV), usually determined from a 24-hour ambulatory electrocardiogram, provides the technical basis for the statistical analysis of interbeat intervals and frequency oscillations. This analysis can provide measures of both sympathetic and parasympathetic cardiac activity, and have demonstrated the ability to predict mortality in various clinical populations (Kleiger, Miller, Bigger, & Moss, 1987). For example, in post myocardial infarction populations, decreased HRV predicted both arrhythmic events and mortality with greater sensitivity and specificity than conventional measures such as left
ventricular ejection fraction (Bigger et al., 1992; Farrell et al., 1991). Three previously published studies have been found which utilized HRV measures with depressed and nondepressed patient controls (Carney et al., 1988b; Dalack & Roose, 1990; Yeragani et al., 1991). Yeragani et al., (1991) reported no significant difference in any of the heart rate variability measures between depressed patients and normal controls. Carney et al., (1988b) did report a non-significant trend toward decreased HRV in their depressed group. Dalack and Roose (1990), reported that with a cut-off of 2.5 msec., using the HRV time domain measure pNN50 (the percent of successive normal beat to normal beat intervals that vary by more than 50 milliseconds), HRV was found to be markedly diminished in depressed patients compared to normal controls. What has become germane to the course of these investigations, is that several important control variables which are known to affect cardiac autonomic activity, such as age, sex, smoking status, and drug usage were not incorporated into the designs.

The present study investigates HRV as a potential mediating determinant in the adverse role of psychological depression in patients with CAD, and utilizes a matched groups design to control for potentially important covariates.
Depression in General Medical and Cardiac Populations

Major depression (MD) has been identified as the most common psychiatric diagnosis among medical populations. (Hall, Popkin, Devaul, Faillace, & Stickney, 1980; Maguire & Granville-Grossman, 1968). Prevalence rates for MD in general medical practice have ranged from 5% (Porter, 1970) to 32% (Glass, Allen, Uhelenhath, Kimball, & Borinstein, 1978). An earlier study of the severity of depressive symptomology, as measured by the Beck Depression Inventory (BDI) (Beck, Ward, & Mendelson, 1968), showed 18% of patients in a general medical population had scores greater than 13 (mild mood disturbance), with 14% scoring greater than 30 (moderate to severe depression) (Schwab, 1967).

Reported prevalence rates for clinically significant depression and MD among cardiac patients have varied. Clinically significant depression has been investigated in several cardiac populations. In one such study, Hackett, Cassem, and Wishnie (1968), observed 50 patients on a coronary care unit and determined 58% to be depressed or exhibited behavior consistent with depressed affect. In a study of 400 patients with coronary heart disease (CAD), 27% were found to be experiencing moderate, 14% severe, and 8% gross depression, characterized by ideas of hopeless dependency, egocentricity and profound intellectual disintegration (Wynn, 1967). Wynn had argued that only the most robust personality is not depressed after a myocardial
infarction, but that usually the degree of depression is not deep, and it should not cause significant long-term disability. Cay, Vetter, Philip, and Dugard, (1972), noted that 65% of post myocardial infarction patients showed evidence of emotional upset, of which 58% reporting, retrospectively, that their depression and anxiety was present before they were admitted. In a more recent study, Kurosawa, Shimizu, Nishimatsu, Hirose, and Takano, (1983) administered a psychiatric interview to 163 acute myocardial infarction patients three days after admission to a critical care unit, and found 63.8% showed some mental disorder; of which 26% were found to be in an anxious state, and 18.4%, a depressive state. The investigators also observed that those with lesser mental severities tended to show an anxious state, whereas those showing greater severities tended to express a depressive state.

More recent research designs have included refined methods of interviewing which have provided for a DSM-III-based diagnosis of major depression. Schleifer et al., (1989) found a prevalence rate for major depression of 18% among patients interviewed 8 to 10 days after infarction. Although the effect was not statistically significant, these depressed patients showed a trend toward an increased rate of re-hospitalization and reinfarction. An additional 27% of patients met criteria for minor depression by Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robins,
1978). In a St. Louis population of 50 cardiac catheterization patients found to have demonstrable CAD, 18% were again found to have MD by DSM-III criteria (Carney, Rich, Tevelda, Saini, Clark, & Jaffe, 1987b). Although there was a relationship between depression status and smoking, depression was not related to the extent of CAD, age, or use of beta blockers. Another important finding of this study was that of the patients who met criteria for depression, 78% had not been diagnosed or treated for their depression. These rates compare to 3.2% (six-month prevalence rate) (Henderson & Pollard, 1992) and 2.35% (one year prevalence rate) (Eaton et al., 1989), for major depression in two St. Louis non-medical, general population samples.

Outside of the consistent body of information which demonstrates an association between major depression and CAD, little data are available concerning which depressive symptoms are more likely to be experienced by CAD patients, with or without depression. Freedland et al., (1992), found fatigue to be common in both depressed and nondepressed cardiac patients. Anda et al. (1993) found that both depressed affect and hopelessness were associated with an increased risk for incidence of CAD itself, as well as for mortality. As suggested above, few additional studies exist which have investigated individual depression symptoms, or patterns of depressive symptoms, that may occur in patients
with CAD. Utilizing a variety of methods, the present study attempts to investigate whether depressed CAD subjects have depressive symptoms which differ quantitatively and qualitatively from nondepressed CAD subjects.

**Morbidity and Mortality in Cardiac Samples**

Major depression was found to be the best predictor of major cardiac events, including myocardial infarction, bypass surgery, and death, in the 12-month period following diagnosis of (CAD) (Carney et al., 1988b). Depression status was found to predict these events above and beyond both the severity of CAD and cigarette smoking. Among patients treated for heart arrhythmias, those who were also depressed had a five-fold greater risk of death than nondepressed patients (Kennedy, Hofer, Cohen, Shindledecker, & Fisher, 1987). Patients manifesting considerable preoperative anxiety and depression were at increased risk for death during and immediately following surgery than other patients (Kimball, 1969). Tufo and Ostfeld (1968) found that open heart surgery patients who had depression in the preoperative period were at higher risk of operative death, which could not be accounted for on the basis of worsened cardiac status.

Garrity and Klein (1975) followed myocardial patients for 6 months after discharge. Of 48 patients, 41% of "non-adjustors," (defined by increased behavior disturbances and decreased positive behavior), died within 6 months of
discharge, compared to only 8% of "adjustors." Among predictors, behavioral response was a more likely determinant of death than was previous heart trouble. Garrity and Klein stated that chronic psychophysiological arousal, especially in subjects with previously impaired hearts, may lead to a greater risk of reinfarction and/or death. In an earlier study by Lebovits, Shekelle, Ostfeld, and Paul, (1967), CAD patients were followed for 5 years. Non-survivors had higher previously obtained scores on most scales of the Minnesota Multiphasic Personality Inventory (MMPI) than did survivors. Clinically elevated scores on the depression scale occurred in 33% of deceased subjects but in only 14% of the survivor group.

**Physiological Aspects of Depression**

Hall et al. (1980) noted that the cardiovascular system is the most common medical cause of depression and the most common medical cause of psychiatric symptoms overall, followed by endocrine, infectious, and pulmonary disorders. However, a substantial number of patients have reported that their depressive symptoms were present before myocardial infarction or identification of heart disease (Cay, Vetter, Philip, & Dugard, 1972). Clearly, a linear relationship of causation has not yet been established. It is quite possible that the association between CAD and depression is bidirectional and that each condition carries additional risks for the other present. What has been shown however,
is that several underlying physiological changes are responsible for increases in adverse medical outcomes. The following sections discuss research related to the effects of altered sympathetic nervous system activity on cardiovascular functioning and outcomes. Such alterations frequently include changes in heart rate, heart rate variability and hemodynamic balance, which are reviewed individually.

**Increased sympathetic activity.** Elevated sympathetic nervous system activity, which accompanies affective disorders, has been implicated in adversely altering the course of CAD. Clinical depression in otherwise medically well psychiatric patients has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) and increased sympathetic activity (Esler, Turbott, Schwarz, Leonard, Bobik, Skews, & Jackman, 1982; Roy, Pickar, Linnoila, & Potter, 1985). The HPA axis is the endocrine system most extensively studied in affective illness (Papolos & Papolos, 1987).

**Heart rate.** Medical patients with depression have been found to have elevated resting heart rates when compared to controls (Carney et al., 1988b; Dawson et al., 1977; Depue & Kleinman, 1979; Esler et al., 1982; Lahmeyer & Bellier, 1987; Lake et al., 1982; Linkouski et al., 1985). Increased resting heart rates are consistent with increased sympathetic and decreased parasympathetic activity. In one
of these studies, Carney et al., (1988b) administered the Diagnostic Interview Schedule (DIS) to 52 CAD patients and found 17% met DSM-III criteria for major depression. Although there was a higher rate of smoking among depressed patients (89%) compared to nondepressed (53%) patients, there were no other baseline differences. After controlling for smoking status, mean heart rate remained higher in the depressed group than in the nondepressed group. There was also a nonsignificant trend toward lower heart rate variability in the depressed than in the nondepressed group ($p < .10$).

At least four additional studies have shown that elevated heart rates are predictive of mortality in patients at risk for myocardial infarction or sudden death (Dyer, Persky, & Stamler, 1980; Friedman, Klatsky, & Siegellaub, 1975; Kannel, Kannel, Paffenbarger, Cupples, & Cupples, 1987; and Kleiger, Miller, Bigger, & Moss, 1987). Alternatively, beta blocker therapy has been shown to decrease morbidity and mortality following an acute myocardial infarction (Baber, Wainwright, & Howitt, 1980), and this decrease was best predicted by the subsequent reduction in heart rate during therapy (Kjekshus, 1986).

Hemodynamic effects. Other evidence for altered autonomic activity and HPA axis activity in clinically depressed medical patients, has included elevated levels of plasma cortisol, (Linkoski et al. 1985; Rubin et al., 1987),
plasma catecholamines, (Esler et al., 1982; Lake et al., 1982; Roy et al., 1985), and adrenocorticotropic hormone (ACTH) (Linkoski et al., 1985). It is ACTH which releases cortisol into the bloodstream. Increased cortisol levels, in turn, potentiate catecholamine activity and inhibit the activity of enzymes which break down catecholamines (Kopin, McCarty, & Yamaguchi, 1980). Increased levels of catecholamines are known to have possible adverse cardiovascular effects. One such effect is increased myocardial oxygen demand due to increased heart rate, heart contractibility, and afterload. Concurrently, catecholamines may reduce myocardial oxygen supply by increasing coronary vascular activity. This imbalance between oxygen supply and demand increase the possibility of ischemic cardiac events in depressed patients. In addition, increased catecholamine levels stimulate platelet aggregation and may contribute to myocardial ischemia (Haft, 1979). Finally, increased catecholamine levels may trigger ventricular tachycardia and ventricular fibrillation which may lead to sudden cardiac death (Kliks, Burgess, & Abildskov, 1975; Schwartz, Snebold, & Brown, 1976; Schwarz & Stone, 1980; Schwartz & Vanoli, 1981; Verrier, Thompson, & Lown, 1974). Clinical evidence for the presence of increased ventricular tachycardia in depressed CAD patients was reported by Carney, Freedland, Rich, Smith, and Jaffe, (1993). In their sample group of 103 CAD patients, 20% met
either the DSM-III-R criteria for MD or RDC for minor depression. Depressed patients were more than eight times as likely as nondepressed patients to be experiencing one or more episodes of ventricular tachycardia during 24 hours of Holter monitoring, even after controlling for the potential effects of beta blocker use, smoking, and other confounds.

Heart rate variability. Intervals between contractions of the healthy heart are not completely regular but vary from beat to beat by tens to hundreds of milliseconds. These variations appear to occur due to changes in autonomic nervous system functioning, mediated by changes in autoregulatory processes, respiration, physical or mental stress, exercise, and various other influences (Kleiger, Stein, Bosner, Rottman, 1992). Heart rate variability (HRV), is not based on beats per minute, but rather on the analysis of interbeat intervals and frequency oscillations usually determined from a 24-hour ambulatory electrocardiogram. The activity of the autonomic nervous system can be determined from brief periods of electrocardiographic (ECG) monitoring, including parasympathetic or vagal activity slowing the heart rate, and sympathetic stimulation, increasing heart rate. Short-term measurements that analyze the differences between adjacent beats, such as high frequency power at 0.15-0.40 Hz, reflect primarily respiratory variations. Although these indices of short-term HRV are measured over a long
period of time (24-hours), they are virtually independent of
diurnal trends and reflect almost wholly alterations in
autonomic activity that are predominantly vagally
(parasympathetically) mediated (Kleiger et al., 1992).

Ultra low frequency (ULF), which contains most of the
variance in the 24-hour spectrum, is based on the entire 24-
hour recording but also reflects circadian rhythms. Very
low frequency (VLF) however, may be obtained from a 15-
minute sequence of beat to beat intervals (Stein et al.,
1994). Frequencies in both these ranges (ULF and VLF) may
represent the influence of the thermoregulatory and
peripheral vasomotor (Fallen, Ghista, & Kamath, 1988), or
renin-angiotensin (Akselrod, 1981) systems, and reflect both
sympathetic and parasympathetic components of HRV. Finally,
the standard deviation of all the normal beat to beat
intervals in the entire 24-hour ECG recording (SDNN) is
equivalent to the square root of the total variance in a 24-
hour ECG recording, and therefore represents the sum of all
sympathetic and parasympathetic components in the 24-hour
ECG recording. Since no "pure" measure of sympathetic
nervous system functioning is believed to be available, and
because elevated sympathetic activity has been commonly
associated with increased rates of morbidity, all measures
used for this study reflected both sympathetic and
parasympathetic nervous system activity.
Measures of HRV have been found to be stable, even over short periods of time in normal subjects (Kleiger et al., 1991) and in patients with previous myocardial infarction and ventricular arrhythmias (Bigger, Fleiss, Rolnitzky, & Steinman 1992a). Measures of HRV in patients with CAD have been found to be reduced (Airaksinen, Ikaheimo, Linnaluoto, Niemela, & Takkunen, 1987; Hayano et al., 1990; Hayano et al., 1991).

Decreased indices of HRV may reflect increased sympathetic or decreased parasympathetic activity, either of which may predispose the patient to ventricular fibrillation (Dalack & Roose, 1990) or lethal arrhythmias (Kent, Smith, Redwood et al., 1973). Indeed, postinfarction studies clearly demonstrate that decreased HRV is associated with increased mortality and increased arrhythmic death following infarction in humans (Bigger et al., 1993; Kleiger et al., 1987; Lombardi et al., 1989). These findings are compatible with a number of experimental studies showing that decreased parasympathetic and increased sympathetic activity decreased ventricular fibrillation threshold and increased spontaneous ventricular tachycardia in ischemic animal models and in humans (Kleiger et al., 1992).

In a comparative study of hospitalized psychiatric patients and normal controls, HRV was not found to be significantly different between depressed patients and controls, utilizing SDNN (described below) as the measure of
HRV. However, employing a cut-off of 2.5 msec., pNN50 (the percent of successive beat to beat intervals that vary by more than 50 milliseconds) was found to be markedly diminished in depressed patients. (Dalack & Roose, 1990).

Heart rate variability is measured in the time or frequency domain. The time domain indices of HRV are based on interbeat intervals on a comparison of lengths of adjacent cycles. Some of these measures have been shown to identify patients at risk for increased morbidity and mortality. Time domain indices of HRV for the this study, as defined by Kleiger et al., (1992), included: AVGNN (the average interbeat interval of all normal to normal beats). The AVGNN measure is equivalent to heart rate. Several previous studies have documented higher heart rates in depressed patients (Carney et al., 1988b; Dawson et al., 1977; Depue & Kleinman, 1979; Esler et al., 1982; Lake et al., 1982; Lahmeyer & Bellier, 1987; Linkouski et al., 1985). SDNN is the standard deviation of all the normal beat to beat intervals in the entire 24-hour ECG recording. Decreased HRV, as measured by SDNN has been found to be a reliable independent risk factor for mortality (Kleiger et al., 1987). SDANN is the standard deviation of the mean of all 5-minute beat to beat segments averaged over 24-hours. In a population of severe endstage heart failure patients awaiting cardiac transplantation, those with SDANN values of < 55 msec had a twenty-fold increased risk of death when
compared to patients with SDANN values > 55 msec (Binder et al., 1992). Among 100 cardiac catheterization patients, SDANN < 50 msec was associated with an 18-fold one-year mortality rate when compared to patients with SDANN values > 50 msec (Rich et al., 1988). In a group of 77 depressed and nondepressed cardiac catheterization patients, HRV as measured by SDANN, was lower in depressed patients when compared to nondepressed patients, but the difference did not achieve significance (p = .10)(Carney et al., 1988b).

Another class of HRV indices are frequency domain measures, which are used to examine periodic oscillations of heart rate at various frequencies (Stein, Bosner, Kleiger, & Conger, 1994). Frequency analysis utilizes Fourier analysis to partition the total variance of the heart rate into the variance accounted for by underlying groups of frequencies (Stein et al., 1994). The frequency domain measures for the this study as defined by Bigger et al., 1992b) include: ULF(<0.0033 Hz, ultra low frequency)/ VLF (0.0033 to <0.04 Hz, very low frequency). After adjusting for other risk predictors, ULF and VLF remained as significant and strong predictors of mortality (Bigger et al., 1992b).

Potential Confounding Factors in HRV Measurement

Age and depression. Among the elderly, those who are affected by depression appear to be at increased risk for mortality. For example, 15-month mortality rates were determined in a group of over 3000 adults age 55 and over in
the New Haven Epidemiological Catchment Area project. After controlling for age, sex, and physical health, the mortality rate was 4 times higher for individuals with affective disorders than for others in the sample (Bruce & Leaf, 1989). In another study of age and depression (Mirowsky & Ross, 1992) results showed that depression is lowest among the middle aged, higher among younger and older adults, and highest among the old. The overall optimum age, defined as that associated with the lowest predicted incidence of depression, was reported to be 44.7 years. The authors concluded that retirement, widowhood, and economic hardship accounted for steady increases in depression following the optimum age, with physical degeneration and the loss of personal control making additional contributions. It has also been shown that normal aging results in a reduction of autonomic control of the heart (Corrall, 1986; Obrien, O'Hare, & Kleiger et al., 1992), resulting in decreased heart rate variability.

Sex and depression. Large, general population prevalence studies of MD have found that a greater number of women suffer from depression than do men (Bland, Newman, & Orn, 1988; Weissman, Leaf, Holzer, Myers, & Tischler, 1984; Zung, Broadhead, & Roth, 1993). Other studies utilizing smaller groups have reported no sex differences in general population samples (Henderson, Duncun-Jones, Byrne, Scott, & Adcock, 1979; Oliver & Simmons, 1985) or college students
(Hammen & Padesky 1977; Wilhelm & Parker, 1989). Ernst and Angst (1992) argued that there is still a consistent female surplus in major depression which may be due to their findings that females present with a higher first incidence of depression in adolescence, a longer duration of episodes, and a greater recurrence of depression with a more chronic course. Females have a significantly higher incidence of major depression at all age groups (Eaton et al., 1989), with a rise to the peak years of onset in the middle forties, declining thereafter. For males, the probability of an onset is a monotonically decreasing function of age. Eaton et al., added that major depression rarely has onset in the elderly, expect in one site, St. Louis, which had a fairly high rate of onset in older adults of both sexes.

**Sex and CAD.** Almost 6 million people in the United States are living with CAD (DeStefano, Merritt, Anda, Casper, & Eaker, 1993). In a recent review of CAD incidence by sex in the United States, the age-adjusted CAD incidence rate for men was 110 per 10,000 person-years; and 64 per 10,000 person-years for women (MMWR, 1992). Within each age group, men had a higher rate of CAD incidence. Furthermore, men were more likely than women to be first diagnosed with an acute form of CAD. Myocardial infarction was diagnosed in 41.3% of incident CAD events among men and 29.7% among women. Death was the incident CAD event among 18.6% of men, compared with 12.5% of women. Although death rates in the
United States for CAD have been decreasing for both sexes since the mid-1960's, Higgins and Thom (1989), the prevalence for nonfatal CAD increased overall during the 1980's, especially among women (DeStefano et al., 1993).

**Smoking.** An undisputed risk factor for the development of heart disease is cigarette smoking. Smoking is also more common in depressed patients than in non-depressed controls (Carney et al., 1988b; Hughes, Hatsukami, Mitchell, & Dahlgrenet, 1986). Carney et al. (1988b) found that 89% of depressed patients smoked compared to 53% for non-depressed patients. These studies suggest cigarette smoking is coexisting risk factor that must be controlled for in CAD/depression studies using measures of autonomic functioning.

Pickering (1985) argued that smoking has dynamic effects due to nicotine or carboxyhemoglobin on platelet aggregation and because smoking cessation confers a prompt reduction of risk. However, even more immediate may be the effect of smoking on HRV. Mean beat to beat interval HRV was found to decrease after one cigarette (Hayano, 1990b), and the decrease was maintained overnight following abstinence in young heavy smokers. Multiple regression analysis showed an independent inverse relationship between rMSSD, (a short-term, time domain index of HRV which is based on the root mean square of successive beat differences), and cigarette smoking (Kupari, Virolainen,
Koskinen, & Tikkanen, 1993). Chronic cigarette smokers were found to have increased resting heart rates and a decreased HRV as measured by SDNN, with even less variability in the heavy smokers. (Levin, Levin, & Nagoshi, 1992). In a psychiatric population, panic disorder patients who were also smokers had higher resting heart rates and higher standing diastolic blood pressure (Yeragani, Balon, & Pohl, 1990). Whether the adverse effects of cigarette smoking are more acute or insidious, it is likely that the increased incidence of acute myocardial infarction and sudden death in smokers is due, in part, to altered autonomic activity.

Because major unipolar depressive episodes may recur (American Psychiatric Association, 1987), with lifetime averages ranging from 5 to 7 episodes, for those with any history of major unipolar depression (Papolos & Papolos, 1987), depressed CAD subjects may have had a greater history of cigarette use, due to their history of depression, when compared to non-depressed CAD subjects. This study attempted to match subjects by current smoking status, and investigate their history of cigarette use.

Summary and Hypotheses

The high occurrence of CAD, accounting for one-third of all deaths in the United States, argues for further research that can more clearly identify physiological and psychological parameters that contribute to the morbidity and mortality associated with CAD. Studies of depression
and depressive symptomology in CAD groups have been reviewed and evidence suggesting that depression may be an important risk factor for CAD continues to gain support. Despite increasing evidence of an association between depression in CAD, studies suggest that physicians still misjudge, underestimate, or tolerate psychological comorbidity in their patients.

As discussed earlier, depression is associated with both elevated sympathetic nervous system activity (Carney et al., 1988b; Dawson et al., 1977; Depue & Kleinman, 1979; Esler et al., 1982; Lahmeyer & Bellier, 1987; Lake et al., 1982; Linkouski et al., 1985), and increased morbidity and mortality (Kennedy, Hofer, Cohen, Shindledecker, & Fisher, 1987). Few studies to date have systematically reviewed depression in CAD patients utilizing refined physiological mediators such as HRV in their investigations. Several refined heart rate variability measures now available, which reflect the functioning of the autonomic and other systems, have been shown to have great value as predictors of mortality in various clinical population. Therefore, research opportunities exist for the study of HRV as a potential mechanism that could help to explain the reported adverse medical effects of depression in patients with CAD.

It was hypothesized that CAD subjects who also meet criteria for major and minor depression would have higher resting heart rates, as measured by AVGNN; lower time domain
indices of HRV as measured by SDNN and SDANN; and lower frequency domain indices of HRV as measured by ULF and VLF, when compared to matched, nondepressed CAD subjects. These indices of HRV were selected because they measure both sympathetic and parasympathetic activity, and have been found to predict increased morbidity and early mortality in CAD patients.
CHAPTER II

METHOD

Subjects

Forty-two of 103 inpatients (subjects) from an ongoing study who underwent cardiac catheterization, were later found to have coronary artery disease (CAD), and had valid 24-hour ECG Holter monitor recordings were used as subjects for the study. At the time of initial data collection, all patients were undergoing elective diagnostic cardiac catheterization with coronary arteriography and left ventriculography for evaluation of CAD during a 12-month period at Barnes and Jewish Hospitals in the Washington University Medical Center, St. Louis, Missouri. Demographic, medical, and psychological interview data were obtained from these subjects following signed, informed consent.

Original criteria for CAD subject participation were selected in order to minimize extraneous effects on heart rate and heart rate variability and to obtain stable, non-surgically altered measurements of the extent of heart disease and heart functioning. Inclusion and exclusion criteria for subjects were: aged 75 years or younger, no history of arrhythmias of any kind, no evidence or history
of a recent (within 4 weeks) myocardial infarction or other severe systemic illness, no history of coronary bypass surgery or coronary angioplasty, no evidence of valvular heart disease other than mitral valve prolapse, no evidence of cardiomyopathy, found to have 50% or greater stenosis (blockage) in one or more major coronary arteries, never experienced cardiac arrest, and were not taking beta blockers. Subjects undergoing emergency catheterization were also excluded. All subjects were previously assessed for major depression based on the Diagnostic Interview Schedule (DIS). Additionally, these data were used for assessing the presence of minor depression, based on Research Diagnostic Criteria (RDC). Subjects were operationally defined as positive for CAD in the presence of 50% or more stenosis in one or more major coronary arteries. Smoking was assessed in pack years. A pack year was defined as one pack of cigarettes smoked per day for a period of one year. The ECG Holter tapes of five subjects who met the above-listed criteria were found to be invalid.

Forty-two subjects met all criteria and had valid ECG Holter tapes. Among these 42 subjects (66.7% male), were 9 meeting criteria for major depression, 12 for minor depression, and 21 nondepressed matched subjects, selected from the remaining 81 patients in the research database pool. All subject pairs were matched 100% by sex and matched by age within 7 years (mean difference in years =
0.74). Although matching by current smoking status for all subjects was attempted, 6 subject matches could not be made, and these subjects were only matched by sex and age. As a net result of this matching, there were 3 more smokers among the depressed subjects than among the nondepressed subjects.

**Psychiatric Instruments**

**The Diagnostic Interview Schedule (DIS).** On the day of catheterization, a modified version of the depression section of the National Institute of Mental Health Diagnostic Interview Schedule Version III-A (DIS) (Robins, Helzer, Croughan, Williams, & Spazer, 1981) (see Appendix) was administered to determine the presence of major depression. In addition, the DIS version employed also provided for a symptom-based DSM-III-R diagnosis of generalized anxiety disorder and panic disorder.

The DIS is a highly structured interview designed for use by lay interviewers in epidemiologic studies of psychiatric disorders. The DIS elicits information about symptoms, their severity, frequency, distribution over time, and whether those symptoms are explainable by physical illness, use of drugs or alcohol, or the presence of another psychiatric disorder (Zimmerman & Coryell, 1988). By design therefore, the DIS had been burdened with respect to its diagnostic reliability (Rogers, 1994), in its reliance on nonprofessional administrators. However, the present study employed Masters-level research students who had training in
psychopathology and diagnostic interviewing, which may have contributed to high interrater reliability.

Zimmerman and Coryell (1988) investigated the concurrent validity between the DIS and the Inventory to Diagnose Depression (IDD), a self-report measure. They found that the concordance rate was inversely related to the length of the delay between the two measures. When administered within two days, the kappa coefficient was .80. However, when there was two weeks or less between the measures, this dropped to .43. The authors suggested that this increasing discrepancy in the detection of depression was, in part, due to relatively brief durations of major depressive episodes in those assessed. The weighted diagnostic agreement rate for major depression between physician and lay interviewers was reported to be 90% (Helzer et al., 1985). Typically, physician-positive cases of major depression were judged by the lay interviewers to be just below the diagnostic threshold, resulting in a significant underdiagnosis of depression.

Although mood disorders are considered a stronger diagnostic category for the revised DIS Version III-A (Rogers, 1994), the modified form utilized for the present study may not possess the same concurrent test reliability as did the original DIS Version III-A with other measures diagnostic instruments such as the IDD.
However, due to the inpatient setting and proximity in time to the scheduling of cardiac diagnostic procedures, an effort had to be made to modify the DIS in order to minimize interviewing time. Reductions were made in the three graded clinical symptom codes to either "present" or "absent", and "worst period" questions were deleted. Subjects were also not asked to provide speculation about the etiology of each of their symptoms, as included on the original DIS Interview. Alterations in individual item sentence structure were made to obtain currently present symptom information. This was a modification from the previous a historical, "ever had" format. Added questions provided for the duration (in weeks) of currently experienced depressive symptoms.

Subjects were administered all DIS depression symptom items regardless of indications of their depression status from structured or unstructured interview information. Diagnosis of either major depression, based on DSM-III-R criteria of the American Psychiatric Association (APA), or minor depression, based on the Research Diagnostic Criteria (RDC) (Spizer, Endicott, & Robins, 1978), were independently derived from the results of the DIS interview by two Ph.D.-level diagnosticians who initially agreed in 97% of the cases. The remaining interviews were subsequently reviewed jointly and consensus was reached in every case. A Cohen's (1960) Kappa, a measure of agreement between two judges on
their classification, corrected for chance. The 97% initial agreement rate corresponds to a Kappa of .94, demonstrating high inter-rater reliability of the depression diagnosis. Psychiatric diagnoses were made without knowledge of the angiographic findings.

Beck Depression Inventory (BDI). Subjects completed the Beck Depression Inventory (BDI) (Beck, 1967), a 21-item questionnaire designed to measure the number and present severity of depressive symptoms. The BDI is a frequently employed, self-report measure of depression in both research and clinical practice. It has been shown to be reliable in previous studies and can be administered repeatedly without compromising its validity in order to assess the course of depression over time (Murphy, Simons, Wetzel, & Lustman, 1984). Carney et al., (1987a) found that the sensitivity for detecting depression, using a BDI score of 10 or higher and DSM-III diagnosis as the standard for comparison, was 80%, with a specificity of 93%. For the present study, however, the BDI was utilized as a measure of the severity of depression and not to classify subjects as depressed or nondepressed. A total of 32 subjects completed the BDI from the study sample of 42 subjects. Several inventories were not originally obtained do to refusal. However, the response rate for depressed and nondepressed CAD subjects was relatively equal. Any potential situational influences on BDI scores obtained from subjects who were about to
undergo (within 24 hours) a cardiac catheterization for suspected CAD were considered equal for both depressed and nondepressed subjects. Additionally, because all patients were unaware of the extent of their coronary disease at the time of the interview, and because responses to the BDI were based on subject's symptom experience from the previous two week period before hospitalization, it is likely that situational effects on BDI scores, if any, were low and did not systematically differ for depressed and nondepressed subjects.

Diagnostic Cardiovascular Measurement

Ambulatory electrocardiogram. All subjects received a standard 24-hour Holter electrocardiographic (ECG) recording during the day after catheterization. Subjects were monitored during hospitalization instead of at home in order to control for the potential confound between depression and physical activity level. Consequently, physical exertion was minimized in both the depressed and non-depressed groups. The 24-hour Holter recordings were analyzed to obtain the heart rate variability values for the present study.

Cardiac catheterization and angiography. Heart catheterization, hemodynamic studies, and left ventricular and selective coronary angiography were performed according to standard techniques. Coronary arteriograms and left ventriculograms were interpreted independently by
experienced angiographers who were unaware of the results of the psychiatric interview or Holter monitor. Coronary artery disease was defined as 50% or greater reduction in the luminal diameter of one or more major coronary arteries or branches. All other pertinent medical information was obtained from medical records with the use of a data log.

**Left ventricular ejection fraction.** Left ventricular ejection fraction (LVEF), a index of the contractile force of the heart, is measured by the percent of blood volume that is ejected from the heart with each beat. Calculation of LVEF for the present study was made using the standard area-length method. It was determined by one of three non-intrusive procedures: radionuclide ventriculography, cardiac catheterization with left ventriculography, or 2-dimensional echocardiography. All three methods provided a sufficiently accurate index of LVEF.

**Procedure**

Holter ECG monitor cassette recordings from the 42 matched-pair subjects were scanned utilizing a Marquette 8000 scanner. Normal beats, ectopic beats, and artifact, were identified. Intervals outside the normal ranges because of artifact (failure to detect a valid heart beat complex) were excluded from analysis. Supplemental software for the Marquette scanner was used to calculate the heart rate variability indices of SDNN (the standard deviation of all the normal beat to beat intervals), and SDANN (the
standard deviation of the mean of all 5-minute segments averaged over 24-hours). A file containing the ECG data from each subject's tape was generated and saved on a standard 3.5 inch computer disc. Each beat file was then installed and analyzed by a Sun SparcStation ECG computer. The Sun computer allowed for more careful editing of the beat to beat intervals generated by the Marquette Scanner, and also provided algorithms for determining frequency domain measures. Values for SDNN and SDANN, as well as, AVGNN (the average interbeat interval of all normal to normal beats), ULF (ultra low frequency), and VLF (very low frequency) were obtained. Results from these analyses were transferred from the scanner generated reports to a data summary form by the principle investigator. All data were then entered on computer and combined with the existing demographic and biographic database for matched-pair and group comparisons.
CHAPTER III

RESULTS

Demographic characteristics of coronary artery disease (CAD) patients by depressed and nondepressed matched pair groups are presented in Table 1. All data are expressed as percent, or mean ± standard deviation. To determine if depressed and nondepressed subjects varied on a group basis with respect to potentially important covariates for heart rate variability (HRV) or depression, two-tailed t-tests were employed for the comparison of interval data; age, and packyear history. Fisher’s exact tests were used to make the remaining comparisons; current smoking status, history of myocardial infarction (MI), and family history of (CAD). There were no significant differences between groups on any of the demographic variable comparisons. All comparisons were made utilizing the SAS statistical program and were determined significant at the .05 alpha level.

Table 2 presents clinical variables assessed for the depressed and nondepressed matched-pair groups. A two-tailed Fisher’s exact test, which was employed for group comparison of presence of diabetes mellitus, found no significant difference between depressed and nondepressed subject groups.
Table 1

**Demographic Characteristics of CAD Subjects by Matched-Pair Group**

<table>
<thead>
<tr>
<th></th>
<th>Depressed (N = 21)</th>
<th>Non-Depressed (N = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.7±10</td>
<td>58.8±9</td>
<td>0.70</td>
</tr>
<tr>
<td>Currently Smoking</td>
<td>45.0%(n=9)</td>
<td>28.6%(n=6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Packyears</td>
<td>47.3±26(n=9)</td>
<td>56.3±31(n=6)</td>
<td>0.55</td>
</tr>
<tr>
<td>History of MI¹</td>
<td>50.0%(n=18)</td>
<td>41.18%(n=17)</td>
<td>0.74</td>
</tr>
<tr>
<td>Family Hx of CAD¹</td>
<td>55.0%(n=20)</td>
<td>55.0%(n=20)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

¹ represents a subsample of study subjects

Table 2

**Clinical Variables of CAD Subjects by Matched-Pair Group**

<table>
<thead>
<tr>
<th></th>
<th>Depressed (N = 21)</th>
<th>Non-Depressed (N = 21)</th>
<th>z score</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>40.0%</td>
<td>28.6%</td>
<td>---</td>
<td>0.52</td>
</tr>
<tr>
<td>No. of vessels &gt;50% stenosis</td>
<td>2.2±1.0</td>
<td>1.8±1.0</td>
<td>1.24</td>
<td>0.21</td>
</tr>
<tr>
<td>No. of vessels &gt;75% stenosis</td>
<td>1.8±1.0</td>
<td>1.1±0.8¹</td>
<td>-2.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>60.1±17¹</td>
<td>63.6±14¹</td>
<td>-0.62</td>
<td>0.53</td>
</tr>
</tbody>
</table>

¹ n=20 in these subgroups
For the degree of coronary artery disease measure, a Wilcoxon test found no significant difference between depressed and nondepressed subject groups with respect to the number of vessels with greater than 50% stenosis. However, a significant difference was found between groups with respect to the number of vessels with greater than 75% stenosis, by Wilcoxon analysis $z = -2.29; p = 0.022$. An additional Wilcoxon comparison found no significant differences between depressed and nondepressed subject groups on left ventricular ejection fraction (Table 2).

The heart rate and HRV indices utilized for this investigation include the time domain measures of AVGNN, (the average interbeat interval of all normal to normal beats), SDNN (the standard deviation of all the normal beat to beat intervals), and SDANN (the standard deviation of the mean of all 5-minute beat to beat segments averaged over 24-hours). Results of these measures are presented in Table 3 as means ± standard deviations in milliseconds, and $p$ values. Because the distributions of all frequency domain measures are known to be skewed, data were transformed to their natural logs to obtain a more normal distribution before analysis was performed. Matched-pair $t$-tests were conducted to determine whether depressed and nondepressed subjects differed significantly on time domain measures of HRV generated from the Marquette scanner. Significant differences were found between matched pairs for the time
domain measures of SDNN, \( p = 0.009 \) and SDANN, \( p = 0.001 \). Consistent with the Marquette Scanner results, significant differences for these time domain measures were also found following analysis of the same matched-pairs obtained from Sun computer: SDNN, \( p = 0.010 \); SDANN, \( p = 0.012 \). A significant difference was found between matched pairs for AVGNN, \( p = 0.05 \). Frequency domain measures of HRV obtained from Sun spectral analysis approached, but did not achieve significance, for ultra low frequency (ULF), \( p = 0.060 \), and for very low frequency (VLF), \( p = 0.087 \).

An ANCOVA was performed to determine whether depression affects HRV after controlling for the extent of CAD. After controlling for the number of vessels with greater than 75% stenosis, depression was found to retain a significant effect on HRV as measured by SDANN, \( p = 0.0149 \), and SDNN, \( p = 0.018 \). Covariate adjusted least squares SDNN means for depressed and nondepressed groups were 90.5 and 115.5, respectively. Covariate adjusted least squares SDANN means for depressed and nondepressed groups were 73.6 and 95.0, respectively.

A Pearson correlation was performed for comparison of Marquette and Sun values of SDNN and SDANN. The Marquette values for SDNN were found to be highly correlated with SDNN values obtained from Sun analysis \( r = .999; p = 0.0001 \). The Marquette values for SDANN were also highly correlated with SDANN values obtained from the Sun; \( r = .998; p = 0.0001 \).
Table 3
Matched-Pair Comparisons of Time and Frequency Domain Indices of HRV by Depressed and Nondepressed Subjects

<table>
<thead>
<tr>
<th></th>
<th>Depressed (N = 21)</th>
<th>Nondepressed (N = 21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marquette Scanner Values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>72.8±30.5</td>
<td>88.7±33.3</td>
<td>0.009</td>
</tr>
<tr>
<td>SDANN</td>
<td>95.4±16.5</td>
<td>116.6±26.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Sun Computer Values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>89.4±33.5</td>
<td>117.2±26.8</td>
<td>0.010</td>
</tr>
<tr>
<td>SDANN</td>
<td>73.5±30.6</td>
<td>96.2±17.0</td>
<td>0.012</td>
</tr>
<tr>
<td>AVGNN</td>
<td>893±122</td>
<td>977±157</td>
<td>0.050</td>
</tr>
<tr>
<td>ln VLF</td>
<td>6.8±1.0</td>
<td>7.4±0.9</td>
<td>0.087</td>
</tr>
<tr>
<td>ln ULF</td>
<td>8.8±0.9</td>
<td>9.3±0.6</td>
<td>0.060</td>
</tr>
</tbody>
</table>

A Pearson correlation also demonstrated that Sun values of SDNN and SDANN were highly correlated $r = .924; p = 0.0001$. A correlational analysis was also performed to determine if HRV was associated with left ventricular ejection fraction (LVEF). The LVEF measure did not predict the time domain measures of SDNN, $r = 0.08; p = 0.60$, or SDANN, $r = 0.05; p = 0.76$, by Pearson correlation analysis.

Psychometric scores from the Beck Depression Inventory (BDI) were significantly higher, by t-test analysis, for the depressed subject group compared to the nondepressed subject.
group, \( p = 0.0001 \). Subjects judged to be depressed were assessed for duration of depression. Duration was measured as number of continuous weeks prior to the interview in which subjects met at least one of the following symptom criteria for depression: dysphoric mood or loss of interest. To determine if duration of depression in weeks (\( n = 21 \)), or the severity of depression as measured by the BDI (\( n = 17 \)), were related to HRV in the depressed subjects, Pearson correlation analyses were performed. Non-significant correlations were found for the duration, and severity of depression, and HRV. Values for duration of depression were \( r = -0.22; \ p = 0.34 \) for the SDNN measure of HRV, and \( r = -0.09; \ p = 0.69 \) for the SDANN measure. Values for severity of depression were \( r = 0.29; \ p = 0.26 \) for the SDNN measure, and \( r = 0.25; \ p = 0.32 \) for the SDANN measure.

One subject was identified as having met research criteria for panic disorder and one met criteria for generalized anxiety disorder. Four (12%) of the 21 depressed subjects had been identified and treated for their depression by their primary care physician.

A series of post-hoc analyses were conducted to explore possible relationships between individual and total item responses to the Diagnostic Interview Schedule (DIS) and the Beck Depression Inventory (BDI) and heart rate variability, and measured by the standard deviation of all normal-to-
normal beats (SDNN). First, t-tests were conducted to determine if differences in HRV, as measured by SDNN, exist between subjects who endorsed individual Diagnostic Interview Schedule (DIS) items which relate to a DSM-III-R (APA, 1987) symptom criteria for major depression, and those subjects who did not endorse the same item. T-tests were not conducted for DIS items related to suicidal ideation and for observed agitation/retardation, as none of the 42 subjects were found to be positive for these symptom items. The DIS items included for comparison were: dysphoric mood (DM), loss of interest (LOE), early morning awakening (EMA), onset sleep insomnia (OSI), intermittent sleep insomnia (ISI), fatigue or loss of energy (LOE), feelings of worthlessness or guilt (WOG), difficulty concentrating (DC), and loss of appetite (LOA). Table 4 presents t test results in means ± standard deviation, of HRV (SDNN) in CAD subjects by individual DIS Item endorsement (N = 42). With the exception of dysphoric mood, no significant differences were found in HRV (SDNN) by subject endorsement of individual DIS items.

Point-biserial correlations of individual DIS symptoms with SDNN were also conducted. Endorsement of dysphoric mood, was found to significantly predict reduced HRV (SDNN), \( r = -0.42; \ p = 0.006; \ n = 21 \). No other DIS symptom item was found to significantly predict HRV (SDNN). Table 5 presents point- biserial coefficients and p values for individual DIS symptoms items with SDNN.
Table 4

Comparison of SDNN Heart Rate Variability in CAD

Subjects by Individual DIS Item Endorsement

<table>
<thead>
<tr>
<th>DIS Item</th>
<th>Endorsed Item</th>
<th>Did Not Endorse Item</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>86.3±33.1 (n=17)</td>
<td>113.8±27.9 (n=25)</td>
<td>2.901</td>
<td>0.006</td>
</tr>
<tr>
<td>LOI</td>
<td>95.5±37.8 (n=17)</td>
<td>107.4±28.6 (n=25)</td>
<td>1.166</td>
<td>0.25</td>
</tr>
<tr>
<td>EMA</td>
<td>98.6±34.9 (n=19)</td>
<td>106.0±31.2 (n=23)</td>
<td>0.727</td>
<td>0.47</td>
</tr>
<tr>
<td>OSI</td>
<td>102.6±28.4 (n=15)</td>
<td>104.1±35.4 (n=25)</td>
<td>0.137</td>
<td>0.89</td>
</tr>
<tr>
<td>ISI</td>
<td>109.4±32.7 (n=17)</td>
<td>98.0±32.6 (n=25)</td>
<td>-1.118</td>
<td>0.27</td>
</tr>
<tr>
<td>LOE</td>
<td>101.5±35.3 (n=34)</td>
<td>107.2±18.9 (n=8)</td>
<td>0.438</td>
<td>0.66</td>
</tr>
<tr>
<td>WOG</td>
<td>101.6±38.2 (n=10)</td>
<td>102.9±31.5 (n=32)</td>
<td>0.114</td>
<td>0.90</td>
</tr>
<tr>
<td>DC</td>
<td>99.2±32.1 (n=17)</td>
<td>104.9±33.6 (n=25)</td>
<td>0.552</td>
<td>0.58</td>
</tr>
<tr>
<td>LOA</td>
<td>89.6±13.5 (n=5)</td>
<td>104.4±34.2 (n=37)</td>
<td>0.349</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Note. DM = Dysphoric Mood; LOI = Loss of Interest; EMA = Early Morning Awakening; OSI = Onset Sleep Insomnia; ISI = Intermittent Sleep Insomnia; LOE = Loss of Energy; WOG = Worthlessness or Guilt; DC = Decreased Concentration; LOA = Loss of Appetite.

Another potentially important factor related to each symptom item is the duration prior to admission for catheterization that the symptom was reported to be present. A Pearson correlation was conducted to determine if any
Table 5  
**Point-Biserial Comparison of SDNN Heart Rate Variability with Individual DIS Symptom Items**

<table>
<thead>
<tr>
<th>DIS Item</th>
<th>Pearson r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphoric Mood (DM)</td>
<td>-0.41691</td>
<td>0.006</td>
</tr>
<tr>
<td>Loss of Interest (LOI)</td>
<td>-0.18140</td>
<td>0.250</td>
</tr>
<tr>
<td>Early Morning Awakening (EMA)</td>
<td>-0.11423</td>
<td>0.471</td>
</tr>
<tr>
<td>Onset Sleep Insomnia (OSI)</td>
<td>-0.02229</td>
<td>0.891</td>
</tr>
<tr>
<td>Intermit. Sleep Insomnia (ISI)</td>
<td>0.17411</td>
<td>0.270</td>
</tr>
<tr>
<td>Loss of Energy (LOE)</td>
<td>-0.06911</td>
<td>0.664</td>
</tr>
<tr>
<td>Worthlessness Or Guilt (WOG)</td>
<td>-0.01803</td>
<td>0.910</td>
</tr>
<tr>
<td>Decreased Concentration (DC)</td>
<td>-0.08690</td>
<td>0.584</td>
</tr>
<tr>
<td>Loss of Appetite (LOA)</td>
<td>-0.00273</td>
<td>0.986</td>
</tr>
</tbody>
</table>

relationships exist between the duration of individual DIS symptom items and HRV, as measured by SDNN. Results of these correlations are presented in Table 6. One DIS symptom duration item, feelings of worthlessness or guilt, was found to significantly predicted SDNN, $r = 0.72833; p = 0.017; n = 10$. Interpretation of a subsequently constructed scatter plot, suggests that one outlying subject score was sufficiently removed from the cluster of scores to produce a significant relationship between SDNN and the
Table 6

Pearson Coefficients of Individual DIS Symptom Durations with SDNN Heart Rate Variability

<table>
<thead>
<tr>
<th>DIS Item</th>
<th>Pearson r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphoric Mood (DM)</td>
<td>-0.17052</td>
<td>0.513</td>
</tr>
<tr>
<td>Loss of Interest (LOI)</td>
<td>0.12404</td>
<td>0.647</td>
</tr>
<tr>
<td>Early Morning Awakening (EMA)</td>
<td>-0.23431</td>
<td>0.349</td>
</tr>
<tr>
<td>Onset Sleep Insomnia (OSI)</td>
<td>0.49266</td>
<td>0.062</td>
</tr>
<tr>
<td>Intermit. Sleep Insomnia (ISI)</td>
<td>-0.22163</td>
<td>0.393</td>
</tr>
<tr>
<td>Loss of Energy (LOE)</td>
<td>-0.30470</td>
<td>0.085</td>
</tr>
<tr>
<td>Worthlessness or Guilt (WOG)</td>
<td>0.72833</td>
<td>0.017</td>
</tr>
<tr>
<td>Decreased Concentration (DC)</td>
<td>-0.24719</td>
<td>0.356</td>
</tr>
<tr>
<td>Loss of Appetite (LOA)</td>
<td>-0.37514</td>
<td>0.359</td>
</tr>
</tbody>
</table>

worthlessness/guilt item. One additional DIS symptom duration item, sleep onset insomnia, approached, but did not achieve significance; \( r = 0.49266; \ p = 0.062; \ n = 15 \).

A Pearson correlation was conducted to determine if any relationships exist between individual Beck Depression Inventory (BDI) symptom items and HRV, as measured by SDNN. Only one BDI symptom item, loss of appetite, significantly predicted SDNN, \( p = -0.36199; \ p = 0.045; \ n = 31 \). An
additional BDI item relating to decreased interest in sex, approached but did not achieve significance: $r = 0.33653$; $p = 0.064$; $n = 31$. All coefficients for this comparison are presented in Table 7.

A Pearson correlation was conducted to determine if any relationships exist between SDNN, total Beck Depression Inventory (BDI) score ($n = 32$), and the number of Diagnostic Interview Schedule (DIS) symptom items ($N = 42$) endorsed, for all depressed and nondepressed subjects. These results are presented in Table 8. A significant and positive correlation was found between the total BDI score and the total number of DIS items endorsed; $r = 0.604$; $p = 0.0003$; $n = 32$. The total Beck Depression Inventory score (BDI) was not found to significantly predict SDNN; $r = -0.101$; $p = 0.58$; $n = 32$. The total number of Diagnostic Interview Schedule (DIS) items endorsed showed a non-significant trend toward predicting HRV (SDNN) $r = -0.259$; $p = 0.097$; $N = 42$. 
Table 7

Pearson Coefficients of Individual BDI Scores with SDNN HRV

<table>
<thead>
<tr>
<th>BDI Item</th>
<th>N</th>
<th>Pearson r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>-0.16177</td>
<td>0.3764</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>0.05162</td>
<td>0.7790</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>0.08305</td>
<td>0.6514</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>0.03562</td>
<td>0.8466</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>-0.07388</td>
<td>0.6878</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>-0.02531</td>
<td>0.8906</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>-0.08583</td>
<td>0.6434</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>-0.10110</td>
<td>0.5819</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>-0.17450</td>
<td>0.3395</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>-0.02211</td>
<td>0.9044</td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>0.18825</td>
<td>0.3105</td>
</tr>
<tr>
<td>12</td>
<td>31</td>
<td>-0.13463</td>
<td>0.4702</td>
</tr>
<tr>
<td>13</td>
<td>32</td>
<td>0.08305</td>
<td>0.6514</td>
</tr>
<tr>
<td>14</td>
<td>32</td>
<td>0.03562</td>
<td>0.8466</td>
</tr>
<tr>
<td>15</td>
<td>31</td>
<td>-0.10435</td>
<td>0.5764</td>
</tr>
<tr>
<td>16</td>
<td>32</td>
<td>-0.02531</td>
<td>0.8906</td>
</tr>
<tr>
<td>17</td>
<td>30</td>
<td>-0.19033</td>
<td>0.3137</td>
</tr>
<tr>
<td>18</td>
<td>31</td>
<td>-0.36199</td>
<td>0.0454</td>
</tr>
<tr>
<td>19</td>
<td>27</td>
<td>-0.04114</td>
<td>0.8386</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>0.05173</td>
<td>0.7860</td>
</tr>
<tr>
<td>21</td>
<td>31</td>
<td>-0.33653</td>
<td>0.0642</td>
</tr>
</tbody>
</table>
Table 8

Correlation Coefficients Between SDNN, Total BDI Score, and Number of DIS Symptoms

<table>
<thead>
<tr>
<th></th>
<th>SDNN</th>
<th>BDI Total</th>
<th>DIS Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI Total</td>
<td></td>
<td></td>
<td>r = 0.0003</td>
</tr>
<tr>
<td>DIS Total</td>
<td></td>
<td>r = 0.6037BDI</td>
<td></td>
</tr>
</tbody>
</table>

r = -0.1001, E = 0.5827, n = 32
r = -0.2590, E = 0.0976, n = 42
CHAPTER IV

DISCUSSION

The purpose of this study was to determine whether measurements of heart rate variability (HRV), which reflects autonomic nervous system activity and predicts morbidity and mortality in cardiac populations, differs between depressed and nondepressed subjects with coronary artery disease (CAD). Depressed subjects had significantly lower HRV than nondepressed subjects as measured by the standard deviation of all normal to normal beats (SDNN) and the standard deviation of all normal to normal beats averaged over five minutes (SDANN). The significantly lower HRV found in depressed subjects supports the primary hypothesis. This finding is consistent with studies that have documented dysregulation of sympathetic nervous system activity in depressed patients with CAD (Carney et al., 1988b; Dawson et al., 1977; Lahmeyer et al., 1987; Lake et al., 1982). Dysregulation of sympathetic activity has been associated with increased manifestations of ischemic heart disease, lethal arrhythmias, and increased atherosclerosis, (Carney et al., 1988b), and thus may lead to higher rates of morbidity and mortality.

These results support the findings of Dalack and Roose (1990), who reported HRV to be markedly diminished in
depressed patients compared to normal controls, using pNN50 (the percent of successive beat to beat intervals that vary by more than 50 milliseconds) as the index of HRV, and Carney et al., (1988b), in which a non-significant trend (p = 0.10) toward decreased SDANN was found in their depressed subject group. It is tenable that the increased power afforded by the matched-pair design in the present study, which controls for several relevant covariants (age, sex, and smoking status), made it possible to detect differences in HRV between depressed and nondepressed subjects.

The obtained HRV differences contrast with the results obtained by Yeragani et al., (1991), who reported no significant differences in any HRV measurements utilized between depressed patients and normal controls. However, there are several important differences between Yeragani et al. (1991) and the present study. For instance, the mean age for subjects in the former study was 33 years, 25 years younger than the mean of 58 obtained for subjects in the present study. As HRV decreases as a function of age, differences may be less pronounced, and therefore more difficult to detect in younger, depressed samples. There were also differences in design. The Yeragani study instructed subjects to assume standing and supine positions during a total of approximately 6 minutes of HRV recording. The present study utilized 24-hour Holter ECG monitoring of hospital inpatients whose physical exertion was minimized.
The authors discussed shortcomings of their study which included the absence of a computerized program for the detection of beat to beat intervals, and no drug screening of patients before their participation (Yeragani et al., 1991). Given these design factors, and lack of controls, HRV differences between depressed and nondepressed subjects may have been difficult to detect.

Although depressed and nondepressed subjects differed with respect to the number of vessels assessed to be greater than 75% occluded, a subsequent ANCOVA, controlling for the degree of coronary stenosis, found depression to retain a significant effect on HRV. Subject groups did not differ on left ventricular ejection fraction, history of myocardial infarction, or any other relevant medical variable assessed.

With respect to the two systems for detecting HRV utilized, values for SDNN from the Marquette Scanner and Sun Computer were found to be highly correlated. Similar results were found for the SDANN measure. Comparison of SDNN values with SDANN values, both obtained from the Sun analysis, were found to be highly correlated, $r = 0.924$. This is generally consistent with Kleiger et al. (1992), who found a correlation of 0.85 between SDNN and SDANN in normal patients. It is expected that these measures would have a strong positive correlation because SDANN is an averaging of SDNN over 5 minutes intervals, and they both reflect longer term variations in heart rate.
Frequency domain measures of HRV obtained from the Sun analysis, ultra low frequency (ULF) and very low frequency (VLF), approached but did not achieve significance. A limitation of this study was that the ECG Holter monitors used were not equipped with internal timing tracks which mark the recording tape at regular intervals. Refined measurements of HRV such as ULF and VLF, which rely on the spectral analysis of frequency data obtained over shorter periods of time, may require ECG monitors with timing tracks which are less sensitive to variations in motor speed. The lack of a timing track may introduce an additional noise component which may have reduced the sensitivity of the frequency measures. Comparatively, time domain measures, such as SDNN and SDANN, are relatively insensitive to small variations in tape speed.

A difference was found between depressed and nondepressed matched-pair groups with respect to the average interbeat interval of all normal to normal beats (AVGNN). The significant difference obtained on AVGNN, which is equivalent to heart rate, supports several previous studies which have documented higher heart rates in depressed patients (Carney et al., 1988b; Dawson et al., 1977; Depue & Kleinman, 1979; Esler et al., 1982; Lahmeyer & Bellier, 1987; Lake et al., 1982; Linkouski et al., 1985).

A non-significant correlation was found for the duration of DIS-assessed depression and the SDNN ($r = -0.22$;
p = 0.33; n = 21) and SDANN (r = -0.09; p = 0.69; n = 21), measures of HRV, respectively. Non-significant results were also found for the severity of depression, as measured by the Beck Depression Inventory (BDI), and SDNN (r = 0.29; p = 0.25; n = 17) and SDANN (r = -0.20; p = 0.42; n = 21) measures of HRV, respectively.

Another limitation of this study was that there were only a small number of subjects available for these comparisons. Therefore, nonsignificant findings should not be interpreted as evidence for the absence of a relationship between severity or duration of depression and HRV. As would be expected, depressed subjects scored significantly higher on BDI compared to nondepressed subjects.

Based on results of the Diagnostic Interview Schedule, only one depressed subject was identified as having met DSM-III-R criteria for panic disorder and one for generalized anxiety disorder. This incidence of psychiatric comorbidity was not likely to affect differences between matched-pair subjects with respect to the HRV measures assessed. Only four (19%) of depressed subjects had been identified and treated for their depression by their primary care physician. This finding is consistent with previous studies in which depression in patients with CAD has rarely been identified either by primary care physicians or by cardiologists (Carney et al., 1987b; Kurosawa et al., 1983; Mayou, 1979; Wynn, 1967).
An exploratory analyses was conducted of individual and total DIS and BDI items for all depressed and nondepressed subjects who completing these measures. Although a strong positive correlation was found between the total BDI score (n = 32), and the total number of DIS symptoms (N = 42), neither of these two overall measures predicted HRV (SDNN).

Although higher BDI scores did not predict decreases in HRV in the present study, the BDI has been shown to have moderately high sensitivity and high specificity for detecting DSM-III-R symptom-based major depressions when using a score of 10 or higher (Carney et al., 1987a), and could improve the primary health care provider’s ability to identify at-risk patients. The BDI is also a quickly administered instrument which can be given repeatedly without compromising its validity in order to assess the course of depression over time (Murphy et al., 1984).

Because depressed patients have been found to have altered sympathetic nervous system functioning, as evidenced by higher resting heart rates, increased episodes of ventricular tachycardia, (Carney et al., 1993), and in the present study, reduced HRV, it is tenable that identifying and treating CAD patients for their depression could reduce further morbidity and mortality. Both cognitive therapy and anti-depressant drug treatment can be effective in treating outpatients with primary unipolar depression of moderate or greater severity (Murphy, 1984), and relapse rates for
subsequent affective disorders are reduced when patients are treated after recovery with medication and continued psychotherapy (Keller, 1983). Within cardiac populations, Avery and Winokur (1976), found significantly higher nonsuicide death rates, particularly from myocardial infarction, among inadequately treated depressed patients than among depressed patients who received adequate pharmacologic treatment or electroconvulsive therapy.

Regarding screening, the Beck Depression Inventory is a fairly accurate clinical tool which can be used to screen patients for depression, and administered by primary care physicians and paraprofessionals. The identification of depressive affect would be necessary before any available treatments can be delivered. Greater emphasis on the recognition and treatment of affective illnesses, through formal medical training or incumbent physician in-service programs is indicated. Alleviation of aversive affective states is warranted, independent of any potential reductions in cardiac mortality and morbidity.

Recently, Balough et al. (1993) demonstrated that pharmacologic treatment leading to improvement in patients with major depression was associated with increases in HRV (SDNN). The ability of HRV to index treatment efficacy was strongest in patients who responded to treatment with nontricyclic antidepressants. Patients who did not respond to antidepressant treatment showed no consistent changes in
HRV. The authors suggested that changes in HRV associated with pharmacologic treatment may be mediated through the effects of that treatment on major depressive symptoms. They also suggested that the autonomic dysfunction reflected by reduced HRV may be correctable in depressed patients.

A point-biserial comparison of individual DIS items and HRV found that only the presence of dysphoric mood predicted reduced HRV, as measured by SDNN. Dysphoric mood, however, was not a significant predictor of HRV when examining the duration of each symptom item. One DIS item, related to feelings of worthlessness and guilt, was found to predict HRV when duration of depressive symptoms was considered. This individual item relationship was the only one found that supports the hypothesis that increases in depressive symptomology lead to decreases in HRV.

Several factors may be important to the above-mentioned findings. First, all subjects were administered all DIS depression items regardless of their depression status, and therefore, all were included in the point-biserial comparisons. As dysphoric mood is one of two necessary DSM-III-R criteria for major depression, and a required RDC criteria for minor depression, it was endorsed by 68% of the total depressed group. Because there had been found to be significant differences in HRV between depressed and nondepressed groups and individually matched pairs, it was likely that the presence of dysphoric mood would predict
decreases in HRV in such an overall comparison. For this same reason, however, it is not clearly understood why the presence of other DIS items did not also predict HRV. A possible explanation may be that other DIS depression symptom items are reported less frequently than dysphoric mood, therefore resulting in low study incidence of reported items and a reduced likelihood of demonstrating the symptom’s ability to predict HRV. Also, other DIS depression items may be more commonly related to symptoms of both depression and those of CAD. For instance, Freedland et al., (1992), found fatigue to be common both among depressed and nondepressed cardiac patients. Finally, given the number of individual DIS and BDI depression items available, the total number of subjects available for these comparisons was probably too low to determine their ability to predict reliable changes in HRV. Therefore, a substantially larger subject population would likely be necessary to perform a cluster analysis of depressive symptoms.

The finding that the presence, but not duration, of dysphoric mood was a predictor of HRV, but not for duration, may highlight two separate actions for adverse effects of depression in CAD. These represent the possible acute and chronic effects of depression in coronary-prone patients. Although research on the mechanisms which may mediate depression’s effect on CAD has only begun, it is becoming
clearer that depression’s influence on the course of CAD is not as strong as once believed. For instance, the effects of depression have been found in most studies to be independent of the severity of CAD, the size of myocardial infarction, and the extent of left ventricular function (Carney et al., 1988a; Frasure-Smith, Lesperance, & Talajic, 1993; Kimball, 1969; Stern, Pascale, & Ackerman, 1977). The results of the present study contribute to an area of research which is investigating depression’s relationship with mechanisms that are primarily associated with acute cardiac events. However, the effects of chronically decreased HRV on CAD, regardless of depression status, has not been investigated.

Although there is extensive literature demonstrating disturbances in circadian rhythms and neuroendocrine features of major and endogenous forms of depression (Syvalahti, Eskola, Ruuskanen, & Teijo, 1985), the same does not exist for reactive, minor and other subtypes of depression. Interestingly, in the present study, loss of appetite, a recognized symptom of endogenous depression, was the only BDI item to significantly and positively predict HRV (SDNN). Anda et al. (1993) found that both depressed affect and hopelessness were associated with an increased risk for CAD incidence and mortality, regardless of smoking status. No other studies were found which have investigated the relationship of individual depression symptom items and
increased medical risks associated with CAD. Future research will need to determine whether cardiac risks are attributable to specific features of depression, and whether increased risk is only associated with major depression, or subtypes of depression as well, such as grief reactions, or perhaps even transient demoralization, which occasionally accompanies a physical illness.

Health-related psychological concepts are increasingly being refined. In an effort to understand better the health-damaging aspects of psychological factors, distinctions have been made between subjective stress and life events, functions of social support and social network or integration, hostile attitudes, neuroticism, and attributional style (Adler et al., 1994). Health psychology is now seeing the development of more sophisticated models that consider genetic predispositions, environmental challenge, and individual differences in behavior in understanding disease risk.

These factors clearly apply to studies of increased morbidity and mortality in CAD patients when depression is present. However to date, these comparisons have included patient-subjects with little or no concurrent physical illness. Similarly, they are also typically free, by design, of current comorbid psychiatric illnesses. Therefore, substantially large epidemiological models will need to constructed to determine the cumulative and/or
comorbid effects of psychosocial, physical, and psychiatric influences on mechanisms which are known mediate adverse effects in patients with CAD.

Depression may also be found to be a more important risk factor for women than for men. The prevalence of depression is known to be at least twice as high among women as men with CAD (Carney, Freedland, & Jaffe, 1990; Carney et al., 1987a), and depressed or bereaved women may be particularly vulnerable to sudden cardiac death (Cottingham, Mattews, Talbot, & Kuller, 1980; Kuller, Perper, & Cooper, 1975; Talbott, Kuller, Detre, & Perper, 1977). This differential prevalence of depression may help explain why the morbidity rate following myocardial infarction is higher in women than in men (Carney et al., 1994).

Since there is now at least some preliminary data which suggests that successful pharmacologic treatment of patients with major depression may be associated with increases in HRV (Balough et al., 1993), it will need to be determined whether any obtained increases in HRV are associated with a reduction in adverse cardiac events. Although effective treatment of depression can improve medical and psychosocial outcomes in cardiac patients, there is not yet much direct evidence to support this prediction. Controlled treatment outcome studies are needed to determine if other forms of treatment for depression, such as psychotherapy, can also increase HRV.
Finally, with respect to measurements of HRV, there have been several studies in which lowered HRV has predicted mortality. Most of these studies have used gross millisecond cut-offs to define low and high HRV groups, such as SDANN values of < 55 msec and > 55 msec, Binder et al., (1992), < 50 msec and > 50 msec, Rich et al., (1988), and < 50 msec and > 100 msec, Kleiger et al., (1987). If the association between depression and decreases in HRV are found to be reliable, it will be necessary to more precisely determine when lowered levels of HRV become clinically meaningful.

The results of this study suggest that depression is associated with decreases in heart rate variability in patients with coronary artery disease. This finding provides further evidence that altered autonomic nervous system activity may mediate, perhaps by predisposing the patient to lethal arrhythmias or ventricular fibrillation, the increased rate of cardiac events which has been observed in depressed CAD patients. The results are preliminary and will require replication. However, the potential importance of decreased HRV as a marker for increased risk of adverse outcomes in CAD when depression is present is worthy of further investigation.
Modified Diagnostic Interview Schedule for Major Depression

CODES: 0=NO 1=YES N=N/A  R=REFUSED  U=UNABLE TO ASSESS

<table>
<thead>
<tr>
<th>Rating</th>
<th>Duration in Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Rating</th>
<th>Duration in Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS THERE BEEN A CHANGE IN YOUR APPETITE LATELY?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF YES, HOW MANY POUNDS HAVE YOU LOST?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF YES, WERE YOU DIETING TO LOSE WEIGHT?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF YES, DID YOU LOSE WEIGHT FROM TAKING WATER PILLS (DIURETICS)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAVE YOU GAINED ANY WEIGHT LATELY?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF YES, HOW MANY POUNDS HAVE YOU GAINED?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF YES, HAVE YOU BEEN TRYING TO GAIN WEIGHT (OR HAS YOUR DOCTOR HAD YOU ON A SPECIAL DIET TO HELP YOU GAIN WEIGHT?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVER THE LAST TWO WEEKS, ABOUT HOW MANY HOURS ON AVERAGE HAVE YOU BEEN SLEEPING PER (24-HOUR) DAY?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS THAT LESS THAN USUAL, MORE THAN USUAL, OR ABOUT THE SAME AS YOU USUALLY SLEEP?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0=ABOUT THE SAME  2=MORE THAN USUAL (ATTRIBUTED TO MEDICATION)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1=LESS THAN USUAL 3=MORE THAN USUAL (NOT ATTRIBUTED TO MEDS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAVE YOU BEEN HAVING TROUBLE FALLING ASLEEP?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAVE YOU BEEN WAKING UP TOO EARLY IN THE MORNING AND BEING UNABLE TO GO BACK TO SLEEP?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAVE YOU BEEN WAKING UP OFTEN DURING THE NIGHT?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAVE YOU BEEN SLEEPING TOO MUCH?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IF ANY SLEEP PROBLEMS: DOES YOUR INSOMNIA (OR OTHER SLEEP PROBLEM) INTERFERE WITH YOUR DAILY ACTIVITIES?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HAVE YOU FELT TIRED, FATIGUED, OR LOW ON ENERGY LATELY?  

HAVE YOU LOST INTEREST IN, OR STOPPED GETTING MUCH PLEASURE OUT OF THINGS THAT YOU USUALLY CARE ABOUT OR ENJOY?  

DO YOU HAVE LESS INTEREST IN SEX LATELY THAN USUAL?  

HAVE YOU BEEN FEELING GUILTY LATELY?  

HAVE YOU BEEN FEELING WORTHLESS OR INADEQUATE, OR FEELING THAT YOU DON'T LIKE YOURSELF VERY MUCH LATELY?  

HAVE YOU HAD TROUBLE CONCENTRATING OR MAKING DECISIONS LATELY?  

DO YOUR THOUGHTS COME MUCH SLOWER THAN USUAL OR SEEM MIXED UP?  

DO YOU FIND YOURSELF DWELLING ON UNPLEASANT EVENTS MORE OFTEN?  

HAVE YOU BEEN FEELING SAD OR DEPRESSED OR BLUE LATELY? (IF NO SKIP A-C)  

A. IS THAT DIFFERENT FROM HOW YOU USUALLY FEEL?  

B. DO YOU FEEL WORSE IN THE MORNING?  

C. DOES ANYTHING YOU DO HELP YOU FEEL BETTER?  

HAVE YOU BEEN FEELING HOPELESS LATELY?  

LATELY, HAVE YOU BEEN THINKING A LOT ABOUT DEATH - EITHER YOUR OWN DEATH, OR SOMEONE ELSE'S, OR ABOUT DEATH IN GENERAL? (IF PATIENT IS BEREAVED, SPECIFY RELATIONSHIP TO THE DECEASED AND APPROXIMATE DATE OF DEATH).  

HAVE YOU BEEN FEELING LIKE YOU WANT TO DIE?  

HAVE YOU HAD ANY RECENT THOUGHTS ABOUT HARMING YOURSELF OR COMMITTING SUICIDE?
HAVE YOU BEEN IRRITABLE LATELY?

HAVE YOU BEEN CRYING LATELY?

HAVE YOU FELT WITHDRAWN OR HAVE YOU LOST INTEREST IN SPENDING TIME WITH OTHER PEOPLE?

HAVE YOU RECENTLY EXPERIENCED A LOT OF STRESS (E.G., FROM PROBLEMS WITH FAMILY, JOB, FINANCES, ETC?)

OBSERVE: DOES PATIENT APPEAR TO BE HYPOMANIC?

OBSERVE: DOES PATIENT MOVE MORE SLOWLY THAN AGE/CONDITION WARRANTS?

OBSERVE: DOES PATIENT SOUND AGITATED OR APPEAR TO BE AGITATED?

OBSERVE: DOES PATIENT APPEAR SAD, DEPRESSED OR TEARFUL?
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