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Review

Biological mechanisms in the relationship between depression and heart disease

Angela J. Grippo[a,b], Alan Kim Johnson[a,b,c,*]

[a]*Department of Psychology, The University of Iowa, 11 Seashore Hall E, Iowa City, IA 52242-1407, USA*
[b]*The Cardiovascular Center, The University of Iowa, Iowa City, IA 52242, USA*
[c]*Department of Pharmacology, The University of Iowa, Iowa City, IA 52242, USA*

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Abstract

Psychological depression is shown to be associated with several aspects of coronary artery disease (CAD), including arrhythmias, myocardial infarction, heart failure and sudden death. The physiological mechanisms accounting for this association are unclear. Hypothalamic–pituitary–adrenal dysregulation, diminished heart rate variability, altered blood platelet function and noncompliance with medial treatments have been proposed as mechanisms underlying depression and cardiovascular disease. Recent evidence also suggests that reduced baroreflex sensitivity, impaired immune function, chronic fatigue and the co-morbidity of depression and anxiety may be involved in the relationship between depression and cardiovascular dysregulation. An experimental strategy using animal models for investigating underlying physiological abnormalities in depression is presented. A key to understanding the bidirectional association between depression and heart disease is to determine whether there are common changes in brain systems that are associated with these conditions. Such approaches may hold promise for advancing our understanding of the interaction between this mood disorder and CAD.

Keywords: Animal models; Anxiety; Autonomic nervous system; Baroreflex; Cardiovascular; Central nervous system; Coronary artery disease; Depression; Fatigue; Heart rate variability; Immune system

Contents

Major depression is characterized by significantly depressed mood and the reduced responsiveness to pleasurable stimuli (anhedonia) coupled with behavioral and cognitive changes such as sleep alterations, weight gain or weight loss, and

* Corresponding author. Address: Department of Psychology, The University of Iowa, 11 Seashore Hall E, Iowa City, IA 52242-1407, USA. Tel.: +1-319-335-2423; fax: +1-319-335-0191.
E-mail address: alan-johnson@uiowa.edu (A.K. Johnson).

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difficulty concentrating and making decisions [6]. This psychological disorder is multifaceted, and it significantly affects an individual's mental and physical health. Depression is also a recognized risk factor for coronary artery disease (CAD). This risk is shown to be independent of traditional cardiovascular risk factors such as hypertension, high cholesterol and increased body mass index [19,192]. Previous research has demonstrated that depression may predispose an individual to atherosclerosis, arrhythmias, myocardial infarction, heart failure and sudden death. This association has been identified in current cardiac patients as well as individuals with no history of heart disease.

Recently, increased attention has been devoted to studying the link between mood states and cardiovascular diseases. Aside from several epidemiological and prospective studies [7,18,44,81,89,90,228,254] and comprehensive review articles [46,62,95,178,182], there have also been attempts to disseminate information about this relationship to the general biomedical community and the lay public. For instance, in a 2001 online article titled 'Depression can break your heart,' the National Institute of Mental Health presented a summary of recent data linking depression to CAD and stated its commitment, along with the National Heart Lung and Blood Institute, to supporting research on the basic mechanisms involved in the co-morbidity of mental and physiological disorders [181]. An article discussing the importance of depression and cardiovascular health recently appeared in a newsletter distributed by Wellmark Blue Cross and Blue Shield health insurance company [253]. Likewise, a 2002 article appearing in *My Generation*, a periodical targeted toward individuals over 50 years of age, discussed the importance of cardiovascular diseases in producing depression [67].

In spite of the overwhelming evidence that depression is associated with CAD, the pathophysiological mechanisms underlying the association remain unclear. It is important to recognize possible limitations in our understanding of the etiology of mental disorders and consequently the difficulty in classifying and diagnosing such conditions. Signs and symptoms of psychiatric disorders such as depression are often evaluated in an interview setting, with a primary focus on self-reports from patients regarding behavioral criteria, perhaps impeding objective interpretations of mental conditions. The subjective nature of current diagnostic criteria coupled with the challenges of assessing neurobiological correlates of psychological conditions may hinder a thorough analysis of mental illness (see Ref. [110] for a relevant discussion of this issue). Thus, there are two objectives to the present review. First, this review is a discussion of key neurobiological alterations in depression that may underlie its association with cardiovascular regulation. The relationship between depression and CAD will be addressed, with a specific focus on anatomical, neurochemical, neuroendocrine and physiological analysis of changes that may relate the relevant mental and cardiovascular conditions. The second goal is to provide suggestions for an experimental strategy, involving animal models combined with behavioral and physiological analyses, that can be used to empirically evaluate neurobiological changes in mental and physiological illnesses.

1. Depression and cardiovascular disease

Several studies, including both cross-sectional and prospective analyses, have demonstrated an extensive co-morbidity of depression and cardiovascular disease [7,13,18,19,44,83,89]. Converging evidence (reviewed later) suggests that depression is an important cardiovascular risk factor both in medically healthy individuals and cardiac patients, and conversely, the presence of cardiovascular disease can influence mood states. Similar to cardiovascular diseases, the prevalence of depression is also greater than average in other medical conditions such as cancer, erectile dysfunction and cerebrovascular diseases; however, unlike its relationship with CAD, a bi-directional relationship between depression and these conditions has not been found [202,204,229].

Depression has been cited as a significant risk factor for recurrent cardiac events in patients with established cardiovascular disease. Depending on the study, 20–50% of patients who die from myocardial infarction are thought to be significantly depressed prior to the infarction [95,99,152]. Major depression doubles the risk that patients with newly diagnosed CAD will experience an adverse cardiovascular event within 12 months, and its predictive value is independent of the extent of disease, left ventricular ejection fraction and smoking [44].

Compared to nondepressed individuals, patients with depression are at a much greater risk of death due to cardiac-related events for up to 10 years following the diagnosis of established CAD [18] (Fig. 1). Independent of risk factors such as arrhythmias and history of previous myocardial infarction, major depression is a significant predictor of mortality in patients at both 6 (hazard ratio 5.74, 95% confidence interval 4.61–6.87) and 18 (odds ratio for Diagnostic Interview Schedule 3.64, 95% confidence interval 1.32–10.05; odds ratio for Beck Depression Inventory (BDI) 7.82, 95% confidence interval 2.42–25.26) months following myocardial infarction [89,90]. Its predictive ability on subsequent cardiovascular events is equivalent to that of left ventricular dysfunction [89], history of previous myocardial infarction [90] and smoking [30].

Depression not only increases the risk of adverse cardiovascular events in patients with established heart disease, but it also predicts incidence of CAD in patients with no history of cardiac problems. The enhanced risk of detrimental cardiovascular events due to depression in medically well patients has been shown to be similar to the risk in patients with established cardiovascular disease [192]. Further, approximately one-half of patients who are depressed at the time CAD is initially diagnosed have had

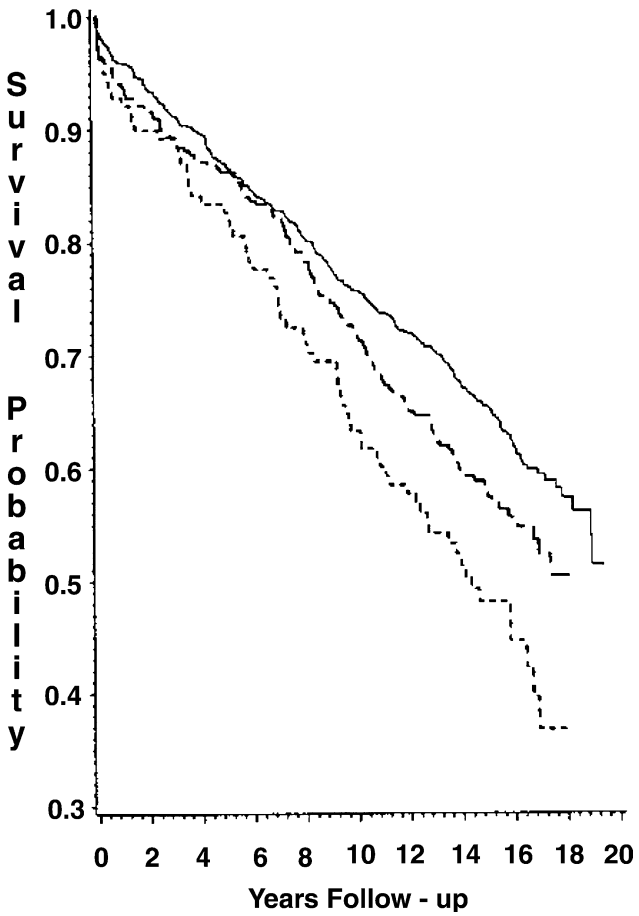

Fig. 1. Probability of survival following myocardial infarction based on self-reported depression scores, shown as unadjusted Kaplan–Meier curves. Top curve, no depression; middle curve, mild depression; bottom curve, moderate/severe depression. From Barefoot et al. [18] with permission, copyright 1996 Excerpta Medica Inc.

one or more prior depressive episodes [40]. In many patients, the first episode of depression is evident before any manifestation of cardiovascular disease [92]. In a prospective analysis, Anda et al. [7] demonstrated that symptoms of depression, including depressed affect and moderate-to-severe hopelessness, predicted an increase in fatal and nonfatal heart disease in medically well patients, independent of baseline medical variables, education, marital status, physical activity and smoking. Other studies have found a similar relationship between symptoms of depression and incidence of cardiovascular disease [19,81]. For instance, Barefoot et al. [19] found that symptoms of depression predicted acute myocardial infarction and total mortality in a community sample of patients, and that the level of risk was related to severity of depressive symptoms.

The associated vulnerability between depression and cardiovascular dysregulation is not unidirectional. Depression can influence cardiovascular function, but cardiovascular diseases also influence affective states. While the prevalence of major depression in the general population at any one point in time is 2–9% [6], it is currently estimated to be 45% among post-myocardial infarct patients [216]. Cardiovascular disease-induced depression may be the result of psychological factors (for instance, contemplation of one's mortality, dealing with significant lifestyle changes, changes in social relationships) or physiological factors (e.g. humoral factors released during states of cardiovascular pathology). It is likely that a combination of both psychological and physiological mediators links cardiovascular disease and mood changes.

Cardiovascular disease may induce depression. Consequently, the presence of depression increases an individual's likelihood of experiencing an adverse cardiovascular event. Yet it is important to recognize that a few [7,19,81] prospective studies have demonstrated that depression increases the likelihood of a detrimental cardiovascular event in medically well patients. It is also possible that a common pathology may initiate both conditions. Specific neurophysiological and behavioral abnormalities have been observed in depressed patients, which may account for the relationship between this disorder and cardiovascular illness. Some of these abnormalities include sympathoadrenal dysregulation, decreased variability in heart rate, dysfunctional blood platelets and negative health behaviors (such as noncompliance with medical treatment regimens). Some of these mechanisms will be addressed in the present article. Recent evidence will also be presented, suggesting that attenuated baroreflex control of heart rate, immune system dysfunction, excess fatigue, and the co-morbidity of depression and anxiety may play mediating roles in the association between depression and cardiovascular dysregulation. Such candidate mechanisms are reviewed later, with a focus on the nature and directionality of the association between depression and cardiovascular dysfunction.

1.1. Hypothalamic–pituitary–adrenal–sympathetic interactions and the role of stress

The hypothalamic–pituitary–adrenal (HPA) axis is a physiological system involved in stress responses. In response to a stressor, hypothalamic neurons increase the synthesis and release of corticotropin-releasing hormone (CRH) to the hypothalamo-hypophyseal portal system, which promotes the secretion of adrenocorticotropic hormone (ACTH). ACTH and the sympathetic nervous system signal the adrenal glands to secrete cortisol and catecholamines, respectively. Adrenal glucocorticoids normally modulate activity of the HPA system by providing feedback to the pituitary, hippocampus and hypothalamus. Endocrine and autonomic changes associated with depression—including excess cortisol secretion and impaired feedback regulation of plasma cortisol, altered CRH and ACTH concentrations, and the abnormal regulation of catecholamines—are not unlike those

accompanying exposure to stress. Some of these changes may directly or indirectly affect cardiovascular regulation.

Findings from research regarding the dexamethasone suppression test provided early evidence that depression was associated with dysfunction of the HPA system. In 1976, Carroll et al. [49] initially presented the dexamethasone test as a measure of neuroendocrine function that might possibly aid in the diagnosis of 'endogenous' depression (i.e. depression that does not result from a reaction to environmental factors). Dexamethasone is a synthetic glucocorticoid that mimics cortisol by inducing negative feedback to the pituitary, hypothalamus and hippocampus. The normal physiologic response to its administration is decreased cortisol secretion due to negative feedback influencing the HPA pathway. However, cortisol is not suppressed upon the administration of dexamethasone in approximately 50% of adult depressed patients [14], indicating that this glucocorticoid may be hypersecreted in depressed individuals.

More recent evidence also suggests hyperactivity of CRH in depressed individuals. Several investigators have identified elevated concentrations of CRH and CRH-like immunoreactivity in the cerebrospinal fluid of depressed subjects [17,183]. Increased CRH levels are also found in the paraventricular nucleus of the hypothalamus in patients with depression [198]. Furthermore, when this hormone is administered intracerebroventricularly to rats or monkeys, it induces several depression-like effects including decreased food intake and sexual activity, disturbed sleep, altered motor behavior and impaired learning [96,143,222].

Dysfunction in the HPA axis in depressed patients is mirrored by dysfunction in the sympathetic nervous system. Altered catecholamine function is evident in depressed individuals. Norepinephrine and dopamine have both been implicated in the pathophysiology of depression [94]. Treatment with reserpine, an antihypertensive agent which depletes monoamine stores, induces depression in some individuals [70]. The monoamine depletion hypothesis is supported by findings that monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) increase synaptic levels of monoamines in the central nervous system. Interestingly, while central norepinephrine may be decreased in depression, increased plasma norepinephrine levels derived from the peripheral nervous system have also been reported [149]. Research on the role of norepinephrine in the HPA system demonstrates that patients who are dexamethasone test nonsuppressors exhibit higher basal plasma concentrations of norepinephrine than patients who are suppressors [209]. Researchers have also demonstrated an elevation of norepinephrine in vascular and extravascular compartments in depressed individuals, relative to control subjects [246]. In addition to increased basal levels, depressed patients display exaggerated levels of norepinephrine in response to a cold challenge, compared with normal controls [209].

Interactions between the HPA axis and the sympathetic nervous system may be involved in the risk of adverse cardiovascular events in depression. CRH pathways have been demonstrated to have extrahypothalamic connections to central components of the autonomic nervous system. For instance, Brown et al. [36] have shown that CRH acts within the brain to stimulate sympathetic outflow. In addition, norepinephrine and epinephrine acting on cardiac β-adrenergic receptors increases heart rate and contractility. An increased heart rate may also derive from increased sensitivity of norepinephrine receptors [130]. Elevated heart rate has been observed in depressed patients both with and without cardiovascular disease [45,84]. Both hypertensive [97] and normotensive [153] depressed patients exhibit higher heart rates than nondepressed individuals. Similarly, depressed patients with CAD exhibit higher heart rates than nondepressed patients with CAD [41].

Elevated heart rate is associated with sudden death, myocardial ischemia, arrhythmias and cardiac failure, along with other cardiovascular risk factors such as hypertension, increased body mass index and increased blood glucose [41,73,130,187]. It is a risk factor for adverse cardiovascular events in elderly individuals, hypertensive patients and post-myocardial infarct patients, as well as the general population [186]. Dyer and colleagues [73] have shown elevated heart rate to be a significant risk factor for sudden death, independent of age, blood pressure, serum cholesterol, smoking and body weight. Increased heart rate is also a risk factor for atherosclerosis through increased arterial wall stress [98]. Consequently, sinoatrial node ablations to reduce heart rate have been shown to retard atherosclerosis in cynomolgus monkeys [23].

It is possible that depression is associated with altered HPA axis function and elevated sympathetic activity, which in turn may lead to cardiovascular dysregulation. However, a common variable—the presence of exogenous stressors—may influence both mood and cardiovascular regulation. The role of stress is an important component in the etiology of depression as well as the influence of depression on cardiovascular regulation. Stressful life events have been shown to influence the pathogenesis of depressive disorder. The predisposing influence of stress on depression has been reviewed elsewhere [8–10]. Environmental stress can lead to altered neurochemical function, such as changes in the utilization and synthesis of norepinephrine, changes in dopamine activity and enhanced synthesis of serotonin [2,112,119,128]. Several behavioral changes, including those in escape performance, appetitive responses and exploration, have been observed in rats following exposure to stressors [10]. Stressors such as marital conflicts, health problems and work overload have been shown to be associated with both unipolar and bipolar depression [26]. Furthermore, it has been suggested that chronic stressors, which do not favor the development of

adaptation (coping), are likely to be associated with depressive symptoms [9]. Hippocampal damage due to stress has been posited as a central nervous system mechanism leading to depressive symptoms via its influence on HPA activity [244].

Indeed, stress can also influence CAD and its antecedent risk factors [127,140]. Evidence from both animal and human studies shows an interaction of stress with ventricular arrhythmias, sudden cardiac death and hypertension. A variety of stressful environments have been shown to lower the cardiac threshold for ventricular fibrillation in both normal and acutely ischemic hearts of dogs [60,167]. A reduced threshold for ventricular fibrillation is a primary mechanism responsible for sudden cardiac death [247]. Behavioral stress, such as presenting food beyond the reach of a hungry animal, has been shown to affect ventricular arrhythmias in the ischemic hearts of pigs [48]. Interestingly, post-myocardial infarct patients are at a greater risk of mortality if they have a combination of ventricular premature beats (greater than $10\,h^{-1}$) and a high score on the BDI [21], relative to patients with fewer premature ventricular contractions and patients with a low BDI score [90].

Psychosocial variables such as educational level, social class, bereavement, major life events, retirement, nervous tension, anxiety, and anger have all been linked to sudden cardiac death [63]. Acute psychological stressors, including death of a close friend, grief, loss of self-esteem, and threat of personal danger have also been associated with sudden death [77]. In addition, behavioral and environmental factors—including type A behavior pattern, a life crisis and restricted coping options—have been suggested to affect myocardial disorders and electrical instability [76]. Stress likewise influences blood pressure in both humans and animals. Many animal models of stress-induced hypertension have been developed and used to demonstrate that environmental stressors are involved in the pathogenesis of hypertension [213]. In humans, hypertensive and borderline hypertensive patients display increased blood pressure reactivity to several behavioral and mental stressors [22,243]. In addition, significant blood pressure increases have been reported in normotensive subjects when facing mental stress [211]. Stress may promote hypertension through repeated blood pressure elevations, stimulation of the nervous system to produce vasoconstricting hormones, changes in vascular resistance or central nervous system alterations.

The HPA axis and sympathetic nervous system may mediate the connections between depression and CAD through several mechanisms. Excess hormones, catecholamine alterations, or autonomic dysfunction may be key mediators in the influence of depression on cardiovascular regulation. Additionally, environmental stress may play an important role in influencing both affect and cardiovascular function. Further influences of the HPA axis, autonomic nervous system and stress will be evident throughout the following sections.

1.2. Reduced heart rate variability

Heart rate variability reflects the capacity of the autonomic nervous system to vary the intervals between consecutive heart beats according to hemodynamic fluctuations and other physiologic perturbations. It is defined specifically as spontaneous changes in sinus rate as a result of regular internal body processes [144]. Heart rate variability represents the interaction between sympathetic and parasympathetic influences on the cardiac pacemaker. Both peripheral and central nervous system factors can influence heart rate and its variability. Several neurotransmitters acting both centrally and peripherally, including norepinephrine, dopamine, acetylcholine and serotonin, may be involved in the modulation of heart rate variability. An abnormal variability in heart rate may imply an impairment of the autonomic nervous system [199].

Several investigators have identified reduced overall heart rate variability or beat-to-beat variability in depressed patients both with and without cardiovascular disease, compared to nondepressed controls [47,194,199,200] (but see Yeregani et al. [260] for negative findings). Variability in heart rate may be inversely related to severity of depressive symptoms. Patients with higher depression scores on the Minnesota Multiphasic Personality Inventory-Depression (MMPI-D [108]) showed lower heart rate variability than patients with lower scores on this instrument; however, none of the subjects in this sample were diagnosed with clinical depression [145]. The implications from this study are consistent with others [7,19] suggesting that a clinical diagnosis of major depression is not required when considering the association between depression and altered cardiovascular function; mood states should be considered to lie on a continuum.

Heart rate variability has been observed to increase in depressed patients following pharmacological antidepressant treatment [16] and cognitive-behavioral therapy [42]. However, it is important to note that, while increasing the statistical variability in heart rate may suggest normalization of parasympathetic and/or sympathetic inputs to the heart, further data are necessary to determine whether changes in heart rate variability in treated depressed patients are of clinical significance. For instance, Carney et al. [42], have suggested that heart rate and heart rate variability may improve in treated depressed patients but may never return to baseline levels.

Depression appears to be strongly associated with decreased heart rate variability, which in turn can affect cardiovascular regulation. Decreased heart rate variability is a risk factor for negative cardiovascular events and mortality in cardiac patients. A high degree of variability is common in normal cardiovascular activity [27], whereas decreased variability is found in patients with severe CAD,

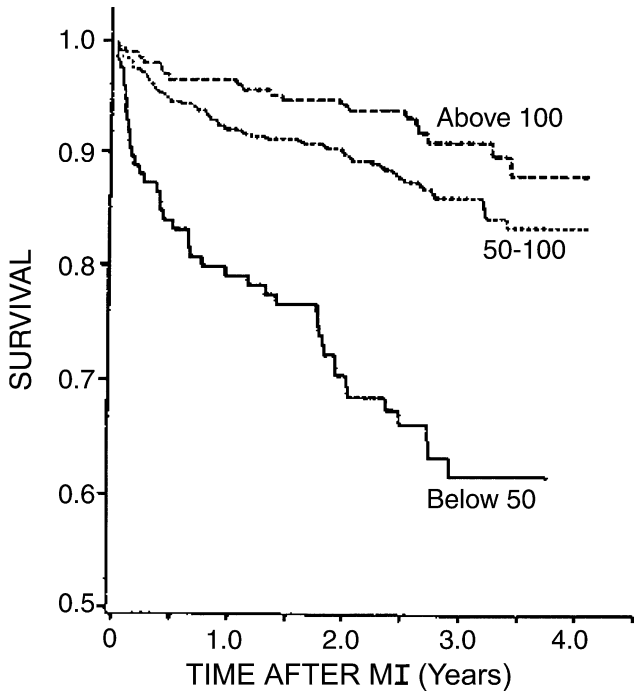

Fig. 2. Cumulative survival after initial myocardial infarction (MI) over total follow-up period as a function of heart rate variability, using Kaplan–Meier curves. From Kleiger et al. [137] with permission, copyright 1987 Excerpta Medica Inc.

heart failure and myocardial infarction [144,212]. In addition, decreased variability has been shown to predict survival following myocardial infarction [137,237] (Fig. 2). Low heart rate variability is related to an increased risk of sudden death in patients with myocardial infarction, congestive heart failure and hypertension [258]. Related research demonstrates that increased sympathetic and decreased parasympathetic tone are predisposing factors for ventricular fibrillation [137,158]. Similarly, it has been shown in dogs that an attenuation of vagal activity may predispose subjects to ventricular arrhythmias, whereas vagal stimulation exerts a protective effect [136].

The decreased heart rate variability seen in depressed individuals may be a result of abnormal catecholamine regulation. Peripheral norepinephrine hyperactivity in depressed patients may lead to increased sympathetic cardiac tone and in turn, reduced heart rate variability. Peripheral or central dopamine may also modulate heart rate variability via its influence on sympathetic activity. Activation of inhibitory dopamine receptors present on noradrenergic nerve terminals in both the central and peripheral nervous systems leads to a decrease in norepinephrine release [50,51]. Conversely, oral administration of a dopamine type 2-like receptor antagonist increases the noradrenergic response to exercise and increases the low/high frequency ratio of heart rate variability [166]. Circulating dopamine may also be associated with sympathetic activity in the normal stress response in humans [225]. These findings taken together suggest that decreased dopamine activity in either the central or peripheral nervous system may lead to norepinephrine alterations, thereby affecting heart rate variability. This hypothesis is consistent with evidence regarding central dopaminergic activity in depression; pharmacological studies suggest that depression is associated with hypoactive dopamine in the central nervous system [126,255]. However, further data are required to determine whether dopamine plays a significant role in reduced heart rate variability in depressed individuals.

Aside from increased sympathetic tone, decreased parasympathetic (cholinergic; vagal) tone to the heart will also reduce heart rate variability. In fact, it has been suggested that decreased heart rate variability in humans is predominantly due to a reduction in vagal tone [144]. The influence of cholinergic innervation to the heart via the vagus nerve in depressed patients has not received much experimental attention. However, cholinergic activity in the central nervous system may be increased in depression [66].

Recent pharmacological data suggest that central serotonergic mechanisms may influence heart rate variability in psychiatric patients. Treatment with fluoxetine, a serotonin reuptake inhibitor, was shown to increase 24 h heart rate variability in depressed subjects [135]. Nefazodone, a serotonin type 2A (5-HT_{2A}) receptor antagonist, was effective in reducing blood pressure and altering sympathetic tone in patients with major depression [3]. Serotonin reuptake inhibitors likewise affect heart rate variability in patients with anxiety and post-traumatic stress disorder [56,242]. However, the treatment of depressed patients with serotonin-altering drugs does not always result in increased heart rate variability; several studies have reported no significant cardiovascular changes (neither positive nor negative) in depressed patients treated with serotonin reuptake inhibitors [182,203,205]. It is possible that central serotonin may mediate sympathetic outflow to affect heart rate variability through its ultimate effects on discharge of peripheral noradrenergic neurons or by its interactions with other central neurotransmitters such as dopamine or norepinephrine.

1.3. Reduced baroreflex sensitivity

The arterial baroreceptors are mechanoreceptors located in the aortic arch and carotid sinus, which serve to regulate blood pressure by affecting cardiac output and vasoconstriction. The baroreceptor reflex (baroreflex) responds to changes in arterial pressure by altering cardiac parameters such as heart rate, contractility and vascular tone. Over the short term (i.e. on the order of tens of seconds to a few minutes), blood pressure is maintained through a balance of sympathetic and parasympathetic mechanisms on the heart and by modulation of sympathetic tone in different vascular beds (e.g. skin, heart, kidneys, brain). A fall in pressure may be restored with increased cardiac rate and contractility and vasoconstriction initiated by activation of the sympathetic nervous system, as well as a withdrawal of

inhibitory influences on heart rate and contractility exerted through vagal mechanisms. The response to a rise in pressure involves a rapid reduction of heart rate, cardiac output and vascular tone [208]. The cardiac baroreflex reflects a combination of sympathetic and vagal activity, and is used experimentally as a tool for studying cardiovascular control mechanisms.

Autonomic reflexes are important in the pathogenesis of cardiovascular disease. An impaired baroreflex is associated with a number of adverse cardiovascular events. In animal models of heart disease, depressed baroreflex sensitivity carries a risk of developing ventricular fibrillation during a brief ischemic episode [28,217]. In addition, coronary occlusion attenuates the baroreflex control of heart rate in anesthetized dogs [241] and in humans [4]. Reduced baroreflex sensitivity has also been shown to differentiate high- from low-risk patients recovering from heart failure and myocardial infarction [177]. Early studies on the baroreflex suggested that dysfunction may be involved in the pathogenesis or maintenance of hypertension [223]. A long-term change of as little as 5 mmHg in blood pressure is associated with an increased risk of stroke and CAD [58]. Low baroreflex sensitivity may contribute to cardiovascular mortality through a reduction in parasympathetic activity as well as an increase in sympathetic activity. In addition, patients with low baroreflex control of heart rate have a reduced capacity to antagonize normal sympathetic perturbations through vagal mechanisms [147].

In a recent paper, Watkins and Grossman [248] reported altered baroreflex sensitivity in cardiac patients with depression (Fig. 3). Using power spectral analysis to assess the magnitude of R–R interval changes associated with systolic blood pressure alterations, the authors found that symptoms of depression were associated with a reduction in baroreflex control of heart rate compared with nondepressed patients. This is one of the first studies to examine baroreflex sensitivity in depressed individuals using a comprehensive method that characterizes both reflex bradycardia and tachycardia. A second study has also reported reduced baroreflex sensitivity, measured by a noninvasive method, in patients with self-reported depression [194]. These findings draw attention to the need for studying baroreceptor function in depression and the corresponding influence on cardiovascular regulation.

The arterial baroreflex is a reflection of sympathetic and parasympathetic nervous system function as well as central nervous system mechanisms involved in cardiovascular control. Like heart rate variability, measurement of the baroreflex in patients with depression and/or co-morbid cardiovascular disease may provide valuable insight into both autonomic nervous system and brain mechanisms. Evidence from Pitzalis et al. [194], showing a reduction in baroreflex function in post-myocardial infarct unmedicated depressed patients but not in depressed patients treated with β-adrenergic receptor antagonists, suggests that cardiac sympathetic tone is important in baroreflex sensitivity (or

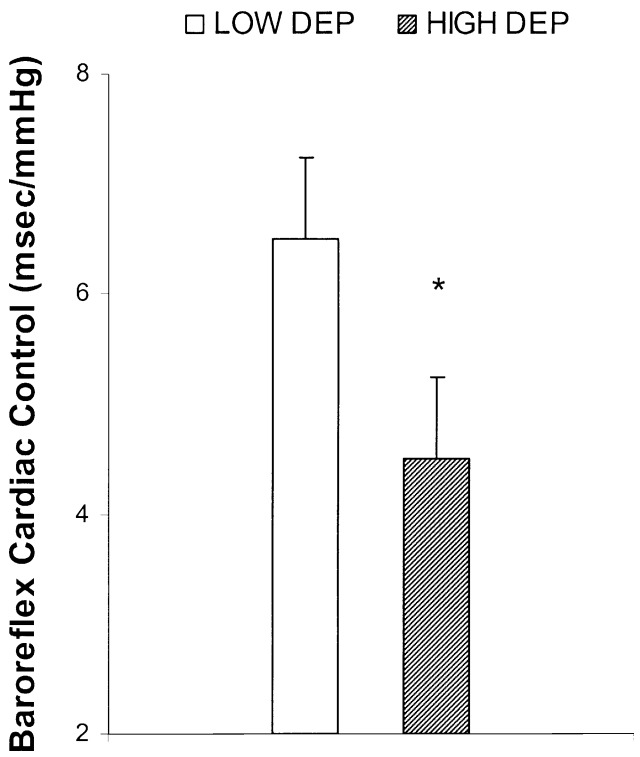

Fig. 3. Baroreflex sensitivity in patients with low depressive symptomatology (LOW DEP) or high depressive symptomatology (HIGH DEP) according to the Beck Depressive Inventory. Data are presented as means ± SE. From Watkins and Grossman [248] with permission, copyright 1999, Mosby.

lack thereof) in depression. Similarly, research from our laboratory indicates that sympathetic tone to the heart is elevated in a rodent model of depression [103]. However, a recent study examining baroreflex function in the olfactory bulbectomized rat, an animal model of depression, suggests that this condition may be associated with a more generalized attenuation of sympathoexcitatory reflexes rather than a specific deficit in the arterial baroreflex [176]. Interestingly, the combination of both reduced baroreflex sensitivity and reduced heart rate variability were of additional prognostic value in a sample of post-myocardial infarction patients, compared to that of either marker alone [148].

Central nervous system mechanisms may influence autonomic (sympathetic and parasympathetic) changes associated with depression and cardiovascular regulation. Changes in blood flow and glucose metabolism have been reported in cortical, limbic and brainstem structures of depressed individuals and in subjects with experimentally induced negative mood [1,68,69,151]. In humans, the dorsolateral prefrontal cortex projects to the anterior cingulate and parahippocampal gyrus, which have connections with the orbitofrontal cortex, hippocampus, amygdala, hypothalamus and thalamus [74]. Alterations of activity in these structures may in turn affect autonomic cardiac tone. For instance, electrical stimulation of the hypothalamus has been shown to increase sympathetic nerve activity, and

stimulation of amygdala, hippocampus and anterior cingulate can induce arrhythmias [235]. Furthermore, pharmacological evidence indicates that receptors in the central nucleus of the amygdala play a role in the control of renal sympathetic nerve activity [141].

1.4. Immune system dysfunction

Recent evidence indicates that several immune alterations are associated with depression. Developments in psycho-neuro-immunology suggest that major depression can modify immune function and conversely, immune system abnormalities may play a role in the etiology of depression. The function of the immune system in depressed individuals is complex, involving both hyperactivity of certain immune components and hypoactivity of others. The influence of the immune system in the link between depression and cardiovascular disease may involve both peripheral and central nervous system mechanisms. The present section will review evidence of bi-directional interactions of immune dysfunction and altered mood states, reciprocal communication between the immune and cardiovascular systems, as well as mechanisms of immune dysfunction as a common pathology in both depression and cardiovascular disease.

Major depression is associated with excessive secretion of interleukin-1β, tumor necrosis factor-α (TNF-α) and interferon, which are proinflammatory cytokines involved in the nonspecific immune response [160,219,224]. When TNF-α is administered to humans, it results in depressive symptoms such as fatigue, malaise, lethargy and anorexia [230]. The administration of α-interferon results in a number of behavioral changes that mimic a major depressive episode, including irritability, anorexia, fatigue and psychomotor retardation [184]. Similarly, interleukin-1β has been shown to induce psychomotor and appetite disturbances, sleep alterations and lethargy [61].

Depressed individuals show an increased number of leukocytes (white blood cells) relative to control subjects [120,146,165]. Neutrophils and monocytes, specific types of leukocytes that engulf and destroy foreign cells, are also increased in depressed patients compared with controls [154,165]. Seidel et al. [218] have found that depressed patients who recover well during hospitalization show a decrease in monocyte counts, whereas those with a slower recovery display greater levels. Moreover, an increase in the phagocytic activity of monocytes has been found in depressed patients; this alteration is reversed following successful antidepressant treatment [169].

In contrast to activation of components involved in the nonspecific immune response, depressed individuals show a blunted cell-mediated immune response, indicating immunosuppression [113,160]. Natural killer cell activity, an indication of cell-mediated immune function, is below average in depressed patients [20,121]. A family history of depression was reported to be related to natural killer cell activity in one study [20]. Aside from natural killer cells, other cell-mediated immune components are altered in depression, including T helper cells [122] and T suppressor-cytotoxic cells [164]. B cells, which are involved in humoral-mediated immunity, are also modified in depression [160,215].

Immunosuppression has likewise been demonstrated in depressed individuals with the examination of mitogen challenge-induced lymphocyte responses. In response to various mitogens, the lymphocytic activity of patients with major depression is blunted relative to controls and patients with minor depression [146,161,162]. Based on data that patients with major depression, but not ambulatory depressed patients, show decreased lymphocyte responses to mitogens, Stein and colleagues [231] proposed that altered immunity may be related to the severity of the depressive symptomatology. However, Bauer et al. [20] reported no difference in the lymphocyte mitogenic responses between patients with major depression and healthy controls.

The nature of the interaction between immune dysfunction and depressive disorder is not well defined. It is unclear whether immune abnormalities play an etiological role in depression or conversely, whether depression leads to immune dysfunction. Indeed, reciprocal communication among the endocrine, immune and central nervous systems has been established [12,29,116]. For instance, negative affective states, which are associated with bilateral activation of the occipitotemporal cortex and cerebellum and increased activity of the left parahippocampal gyrus, amygdala and hippocampus [151] are also associated with decreased lymphocyte responsiveness to the mitogen phytohemagglutinin [93]. According to Smith's [224] macrophage theory of depression, excessive secretion of monokines such as interleukin-1, TNF and interferon-α is hypothesized to be a cause of depression. Macrophages are known to secrete ACTH [180] thereby influencing HPA activity. In addition, interleukin-1, produced by macrophages, has a direct action on the hypothalamus and pituitary, leading to the subsequent release of CRH and ACTH [71].

There are also data to suggest that excess cortisol (which is often found in depressed patients) can impair cell-mediated immunity [113,161]. In addition, exposure to stress led to impaired immune function in an animal model of depression [59]. Impaired cell-mediated immunity may be a result of increased sympathetic activity or increased catecholamine turnover [113,161]. Consequently, catecholamines inhibit immune reactivity by binding directly to the lymphocyte surface or by releasing mediators that increase the function of suppressor lymphocytes [32]. These findings suggest that characteristics of depression may produce changes in immune function. However, the search for causality between immune function and mood disorders may be too simplistic; alterations in immune states may not be reproducible correlates of the psychological state of

depression, but rather might be associated with other variables that characterize the patients such as age, gender, severity of the illness, and duration of the depressive episode [155].

Immune changes are not only associated with depressive illnesses, but are also directly and indirectly linked to the cardiovascular system. Components of the immune system influence the activity of blood platelets, which may consequently lead to adverse cardiovascular events. Patients with unstable angina have been shown to over-express granulocyte and monocyte receptors [168]; stimulation of these receptors activates platelets. Additionally, many immune cells—including neutrophils, monocytes, and macrophages—synthesize platelet activating factor, which is a stimulator of platelet aggregation and has been implicated in the development of atherosclerosis [80]. Furthermore, myocardial ischemia in rats is associated with elevated TNF and corresponding increases in platelet activating factor [191]. Immune dysfunction may provide insight into the mechanisms of blood platelet abnormalities [75,95,179,234] observed in depression.

Immune alterations have been shown to affect several aspects of cardiovascular regulation in patients with and without cardiovascular disease. Although leukocytes play a beneficial role in the tissue-repair process, their hyperactivity can be detrimental to cardiovascular function. Increased total white blood cell count is related to poor prognosis following myocardial infarction [105]. It is also associated with cardiovascular morbidity and mortality in cardiac patients, as well as incidence of adverse cardiovascular events in patients without a history of heart disease [157,259]. Total white blood cell count is a predictor of heart disease, independent of other risk factors such as cholesterol level, blood pressure and gender [79,100]. However, it should be noted that white blood cell count co-varies with smoking [107], which is an important consideration when examining the interaction between white blood cells and cardiovascular regulation.

Leukocytes can also impair tissue perfusion. Following an adverse cardiovascular event, it is essential that tissues are adequately reperfused with blood. Leukocytes become lodged in capillaries and obstruct the lumen thereby promoting the formation of atherosclerotic plaques [123]. Specific leukocytes such as monocytes (which become macrophages in local tissues) may also influence the development of atherosclerosis [33]. Macrophages are abundant at sites of plaque rupture, and they release substances that promote thrombosis [159]. In addition, leukocytes may increase vascular resistance during reperfusion through the production of vasoactive substances or by the release of elements that are toxic to the endothelium [123,221]. A bolus administration of leukocytes in a rat skeletal muscle preparation has been shown to increase vascular resistance [34]. Conversely, leukocyte depletion has prevented myocardial edema in dogs following tissue reperfusion [78]. Specific receptors on leukocytes, which promote thrombotic processes and vasoconstriction upon activation, are upregulated in patients with stable angina [168].

Proinflammatory cytokines have been implicated in modulating myocardial dysfunction. Cytokines are elevated following coronary bypass surgery, contributing to post-operative myocardial ischemia [111]. Elevated TNF-α levels have been identified in transplant patients following cellular rejection, suggesting that the presence of this cytokine may function as a marker of organ rejection [15]. Increased levels of TNF-α have also been found in patients with myocardial infarction and heart failure [156], and in rodents with experimental heart failure [86].

Cytokines may also affect cardiovascular regulation via their interactions with the central nervous system. Specific cytokines such as interleukin-1β, interleukin-6, interferon-γ and TNF-α contribute to central nervous system functions, including neurodevelopment [125,174]. These polypeptides can affect developing neurons, perhaps by acting directly on receptors or by stimulating the release of neurotrophic factors [171]. Peripheral cytokines influence the release and metabolism of several neurotransmitters, including dopamine [125], norepinephrine [129] and serotonin [55]. These neurotransmitters are involved in sympathetic nerve outflow to the cardiovascular system [117] as well as the pathogenesis of depression [185].

Immune components appear to interact bi-directionally with mood states as well as with the cardiovascular system. It is possible that immune dysfunction may serve as a common pathophysiological mechanism for both altered mood and cardiovascular dysregulation. To the extent that immune dysfunction affects sympathetic nervous system activity and HPA axis, it may modulate both depression and CAD. In addition, the specific interaction of immune regulation with catecholamines may affect cardiovascular function in depressed individuals. Further, immune components interact directly with the central nervous system to influence both depression and cardiovascular regulation. Immune changes, particularly in proinflammatory cytokines, have often been observed in cardiovascular diseases such as myocardial infarction and congestive heart failure [86,156]. Experimental myocardial infarction in rats was shown to be associated with the presence of plasma immunoglobulins in the prefrontal cortex, anterior cingulate, entorhinal cortex, hippocampus and substantia nigra [239]. Ter Horst and colleagues [238,239] hypothesize that immune activation associated with myocardial infarction leads to deregulation of activity in the prefrontal cortex, which in turn produces limbic dysfunction and consequently results in both mood changes and further adverse cardiovascular events (such as arrhythmias).

1.5. Fatigue and physical inactivity

Depressed patients often suffer from chronic fatigue [197]. Chronic fatigue syndrome [115] comprises

a constellation of symptoms, including mental and physical fatigue, sore throat, headache, swelling of lymph nodes, sore muscles and depression [233]. Centers for Disease Control and Prevention criteria for chronic fatigue syndrome include severe chronic fatigue for at least 6 months and four of the following symptoms: (a) substantial impairment in short-term memory or concentration; (b) sore throat; (c) tender lymph nodes; (d) muscle pain; (e) multi-joint pain without swelling or redness; (f) headaches of a new type, pattern or severity; (g) unrefreshing sleep; and (h) post-exertional malaise lasting more than 24 h [52]. Some of the behavioral similarities of depression and chronic fatigue syndrome indicate that these two conditions may share aspects of the same physiologic abnormalities. The widely prescribed antidepressant, fluoxetine, for example, is a successful treatment for some chronic fatigue patients [138]. Chronic fatigue syndrome may occur in individuals with a premorbid vulnerability to depression. However, researchers have also explored the possibility that psychological disturbances may be a consequence of, rather than an antecedent risk factor for, chronic fatigue [114].

Excess fatigue, particularly in elderly individuals, may play an important role in linking altered mood and cardiovascular dysregulation. In a study of depressive symptoms and physical disability in elderly individuals, Bruce et al. [38] suggest that somatic symptoms of depression, for instance fatigue, may be responsible for affecting daily functioning. Furthermore, it has been suggested that the correlation of depressive symptoms with impaired physical function is important in the risk of CAD in older women (however, in this sample depressive symptoms were not associated with an increased risk of adverse cardiac events in older men) [173]. While the major characteristics of exhaustion (lack of energy, increased irritability and demoralization) are prevalent among depressed individuals based on Manual of Mental Disorder, 4th Edition DMS-IV [6], and patients with depression may therefore by definition, be exhausted, it is important to recognize that the converse is not necessarily true. In a preliminary study comparing the DMS-IV classification of major depression with exhaustion in 52 American patients with CAD, over half of the exhausted patients did not meet criteria for depression, whereas nearly all patients meeting criteria for depression also met criteria for exhaustion [142].

Patients with chronic fatigue show immune alterations similar to those of depressed patients, including elevated levels of cytokines (interleukin-1 and TNF-α), reduced natural killer cytotoxicity and impaired cell-mediated immunity [139,190]. Some immune abnormalities in chronic fatigue patients are normalized following fluoxetine treatment [138]. Further, interleukin-1, a proinflammatory cytokine proposed to be increased in depression [224], has been shown to cause prolonged slow-wave sleep in both rats [240] and rabbits [147]. Collectively, these findings indicate that the condition of fatigue is associated with immune dysfunction.

Excess fatigue has also been shown to be a precursor to myocardial infarction and sudden cardiac death [11,201]. A state of 'vital exhaustion' has been described, reflecting loss of vitality and libido, listlessness, tiredness and increased irritability [11,245]. Exhaustion is considered to be a short-term risk factor for recurrent myocardial infarction, and is predictive of future myocardial infarction independent of blood pressure, smoking, cholesterol, age, and the use of antihypertensive medications [11]. While it is possible for subclinical or clinical levels of cardiac decompensation to cause excessive tiredness, data reviewed elsewhere [118,142] indicate that exhaustion is unlikely to be solely a consequence of underlying cardiovascular disease. It is important to recognize, however, that excess fatigue may not be a cause of cardiovascular disease, but rather may interact with other risk factors [232]. For instance, a low level of activity, which is a risk factor for adverse cardiac events, may result from fatigue.

The possibility that fatigue and physical inactivity influence the relationship between depression and CAD is supported by the finding that physical exercise is often included as a component of treatment programs for both depression [188,193] and heart disease [35,170]. Strength training has been shown to improve mood and self-esteem in cardiac rehabilitation patients [24]. In a sample of patients with heart failure, those assigned to 1 year of supervised exercise training showed a 63% reduction in mortality, relative to a control group that continued their normal activities. In addition, exercise training significantly elevates heart rate variability [144] and baroreflex sensitivity [57], having implications for both cardiovascular disease and depression.

1.6. Co-morbidity of depression and anxiety

Depression frequently co-occurs with symptoms of other psychological disorders. In particular, there is a common overlap of depression and anxiety in psychiatric patients. The prevalence of secondary depression in anxiety disorders ranges from 33 [64] to 65% [207], depending on the study. Conversely, the prevalence of secondary anxiety in depressed patients is approximately 57% [175]. The common features of these conditions have been reviewed elsewhere [53,175]. Clark and Watson [54] suggest that the psychological trait of negative affect, which is shared by anxiety and depressive disorders, is primarily responsible for the observed co-morbidity of these conditions. Negative affect is characterized by aspects such as negative mood and cognitions, feelings of nervousness and tension, and low self-esteem [250].

The co-morbidity of anxiety and depressive disorders may play an important role in the relationship between depression and cardiovascular disease. While a comprehensive discussion of anxiety disorders is beyond the scope

of this review, certain key features of anxiety can be considered. The current diagnostic system recognizes several types of anxiety disorders, which include symptoms such as fear, apprehension and discomfort toward various stimuli in the absence of any clear threat [6]. All anxiety disorders are posited to share the common component of negative affect [37], but they are distinguished by the object or situation that produces the anxiety. For instance, specific phobias involve anxiety about particular situations or objects (such as social encounters, heights, or spiders), whereas obsessive–compulsive disorder is characterized by excessive preoccupation with a specific condition (e.g. cleanliness) or a specific behavior (e.g. hoarding).

Aspects of anxiety disorders are shown to be associated with detrimental cardiovascular events. Frasure-Smith and colleagues [91] found that anxiety was a significant predictor of recurrent cardiac events (including acute coronary syndrome and arrhythmic events) in a sample of post-myocardial infarct patients. In this study, the influence of anxiety on subsequent cardiac events was independent of current depression, history of major depression and disease severity, and its prognostic value was equal to that of risks associated with previous myocardial infarction and the use of angiotensin converting enzyme infarction. Further, a few large, community-based studies have linked anxiety disorders to sudden cardiac death [106,131,132]; a positive correlation has been noted between the level of anxiety and the occurrence of sudden death [131,132]. It has been suggested that ventricular arrhythmias may be the mechanism responsible for cardiac death among individuals with anxiety disorders [210].

Patients with anxiety show similarities in cardiovascular and autonomic regulation to patients with depression. For example, anxious subjects show reduced heart rate variability independent of mean heart rate and body mass index [133], as well as reduced baroreflex control of heart rate [249]. Symptoms of anxiety are also associated with antecedent cardiovascular risk factors, including hypertension and negative health behaviors. Anxiety may be a stressor that produces sustained sympathetic arousal, leading to chronically elevated blood pressure. It is well established that certain stressors can lead to and precipitate hypertension [140,213]. Further, researchers as early as Cannon [39] and James [124] have discussed sympathetic arousal during anxious states (e.g. fear, fight/flight responses). Anxiety is also closely related to several behaviors which may contribute to the risk of cardiovascular disease, including poor diet, smoking, alcohol intake, and drug use [150,206].

Depression and anxiety are psychologically linked by the component of negative affect; that is, the disposition to experience general distress [175]. Considering the overlap of behavioral manifestations of depression and anxiety, these conditions may share similar central nervous system abnormalities. Not surprisingly, serotonin reuptake inhibitors are used clinically to treat both depressive and anxiety disorders. Moreover, lesions in the lateral prefrontal cortex have been shown to be associated with depressive and anxiety disorders as well as increased frequency of symptoms of depression and anxiety in hospital patients [189]. It is important to note, however, that anatomical and functional changes occur also in nonoverlapping areas of the brain in depression and anxiety [109,134].

Several important points concerning the potential pathophysiological influence of anxiety on altered mood and cardiovascular function are worth noting. First, given the high degree of overlap between depression and anxiety, it is unclear whether co-morbid anxiety influences the relationship between depression and heart disease or whether depression plays a primary role in the association between anxiety and heart disease. Investigators have questioned whether anxiety disorders are actually manifestations of an atypical depression [72]. Also, the weight of anxiety as prognostic of adverse cardiovascular outcomes appears to be less than the weight of depression [65]. Second, several inconsistent findings have been reported with regard to anxiety and cardiovascular regulation. Anxiety was not found to be associated with heart rate variability or baroreflex changes following myocardial infarction in a sample of patients for whom depression was positively associated with these changes [194]. Further, Young and colleagues [261] observed reduced cardiovascular reactivity to isometric handgrip and mental arithmetic in a group of patients showing high anxiety, whereas those with low anxiety actually demonstrated increased reactivity.

Another point worth noting is that anxiety and depressive disorders each show extensive co-morbidity with other types of psychopathology, such as personality disorders and substance use disorders, that may influence cardiovascular control [175]. Thus the interactions of anxiety and depression may be complicated by their strong associations with these other psychological conditions. A final consideration is the observation that anxiety is not associated with myocardial infarction [106,131,132], which is an important cardiovascular endpoint in patients with depression. Given these considerations, it remains to be determined whether anxiety plays a significant role in the relationship between depressive disorders and CAD.

2. A strategy for the mechanistic analysis of the association between depression and heart disease

A clear association exists between depression and cardiovascular dysregulation. The challenge lies in mechanistically accounting for this relationship. Depression may perhaps be conceptualized to influence cardiovascular function via neuroimmunomodulatory autonomic dysregulation. Fig. 4 presents an integrative pathophysiologic model of the important pathways that may influence the association between depression and cardiovascular

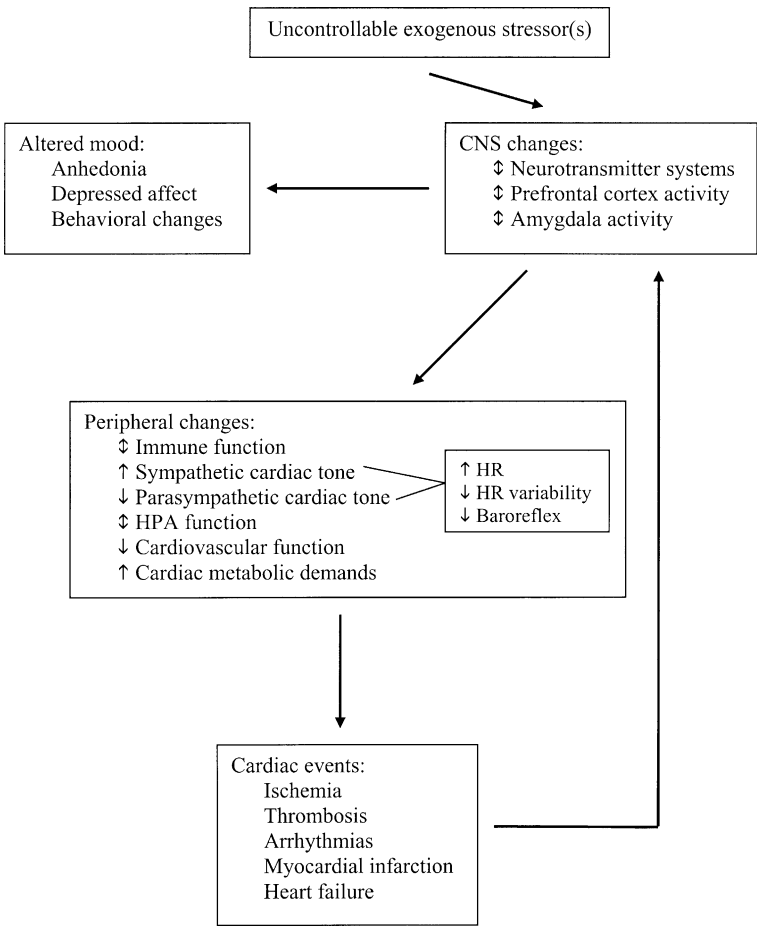

Fig. 4. A pathophysiologic model of neuroimmunomodulatory autonomic dysregulation, illustrating a working hypothesis of the interactions between mood changes and altered cardiovascular function. The central nervous system is proposed to play a major role in the etiology of both depression and cardiovascular dysregulation. Peripheral nervous system changes are likely mediated by brain mechanisms that can lead to specific cardiac events. Feedback from the cardiovascular system to the brain perpetuates the cycle of dysregulation, and may also lead to depressive symptoms. The influence of exogenous stressors, either alone or coupled with a genetic or experiential predisposition, may play a role in the initiation of depression and in the pathogenesis of heart disease. Abbreviations: CNS, central nervous system; HPA, hypothalamic–pituitary–adrenal; HR, heart rate.

regulation. Autonomic function is altered in depression, evidenced by reduced heart rate variability, impaired baroreflex sensitivity and changes in heart rate. These changes may influence the pathogenesis of diseases that affect the cardiovascular system. As previously discussed, HPA axis and sympathetic nervous system are indeed important in depression and cardiovascular disease.

Several lines of evidence also point to a modification of immune function in depression. Pathology of the immune system is associated with several variables that influence both mood changes and heart disease. Immune dysfunction influences both central and peripheral components of the autonomic nervous system. The proposed model in Fig. 4 may provide a working hypothesis that can be used to guide experimental investigations of mechanisms underlying depressive disorders and CAD. The following sections will suggest an experimental strategy as well as some examples of the utility of these suggestions based on studies conducted in both our laboratory and others.

2.1. The use of animal disease models for developing a mechanistic understanding of the association between depression and heart disease

The limited knowledge of neurobiologic mechanisms of psychopathology, as well as the lack of experimental research in the study of mental illness, makes it difficult to form comprehensive theories to describe the mechanisms of interaction between altered mood and cardiovascular disease. It is important to perform objective experimental analyses of the specific neurobiological aspects that characterize mood disorders and cardiovascular regulation. To this end, interdisciplinary research and communication can promote the advancement of scientific knowledge that has both clinical relevance and practical utility.

It is important for experimenters to focus on core behavioral and neurobiological features of the conditions in question which can be operationally defined, quantified, observed, and systematically studied. For instance, the key

feature of anhedonia is central to depression, and can be influenced by psychological, neurochemical and physiological factors. This component should not be overlooked when examining depression as a risk factor for cardiovascular disease. CAD also has central components that can be examined closely, including ischemia, arrhythmias and myocardial infarction. Especially important is the development and use of animal models of both mood disorders and cardiovascular disease to permit a mechanistic analysis of the factors that influence depression and cardiovascular risk.

2.2. The use of animal models of depression to study cardiovascular dysregulation

Research with human subjects is useful for answering certain experimental questions; however, animal methods are valuable tools for studying, among other phenomena, the interactions between psychological and physiological conditions. Several animal models of depression have been developed and reasonably well validated. These include the learned helplessness model created by Seligman [220], the chronic mild stress model described by Willner and colleagues [257], and the behavioral despair model developed by Porsolt [195]. While some animal models were especially designed to have high predictive validity for the purpose of screening antidepressant drugs, others are high in both face and construct validity as well as predictive validity [220,257]. These models may allow for the direct study of the pathogenesis, biological mechanisms, and treatments for depression.

Another potential application of animal models of depression is to examine aspects of cardiovascular function that may be related to depressive signs. For instance, an initial study in our laboratory focused on arterial baroreflex and general sympathetic function in the olfactory bulbectomized rat model of depression [176]. We hypothesized that autonomic function would be impaired in this rat model of depression. Rats that had bilateral lesions of the olfactory bulbs were tested for baroreflex and sympathoexcitatory responses to various pharmacological and behavioral stimuli, including sodium nitroprusside and phenylephrine, air jet stress and cigarette smoke exposure. Our findings indicated that olfactory bulbectomized rats displayed a generalized attenuation in sympathoexcitatory responses to the pharmacological and behavioral stimuli, however they did not display any change specific to the arterial baroreflex. These findings implicate autonomic dysregulation in an animal model of depression.

As the olfactory bulbectomy model of depression is considered to be high in predictive validity and therefore used primarily in drug screening paradigms, we then turned our attention to the chronic mild stress rodent model of depression. This model is focused on the behavioral sign of anhedonia (a central feature of depression characterized by an impaired responsiveness to pleasurable stimuli) and is posited to have high predictive, face and construct validity [252,256,257]. In this paradigm, we exposed rats to 4 weeks of chronic mild stress, consisting of a combination of stressors—such as exposure to strobe light or white noise, paired housing and acute water deprivation—presented in an unpredictable manner. Rats that displayed anhedonia (operationally defined as a reduction in sucrose intake relative to an experimentally established baseline) also displayed similar cardiovascular alterations to human depressed patients, including increased resting heart rate and decreased heart rate variability (Fig. 5A and B) and exaggerated heart rate and pressor responses to an acute environmental stressor (Fig. 6A and B) [103]. We hypothesized that the cardiovascular changes in chronic mild stress were due to alterations in autonomic cardiac tone. Our hypothesis was confirmed with pharmacological autonomic blockade analyses indicating an elevation of sympathetic tone in rats exposed to chronic mild stress.

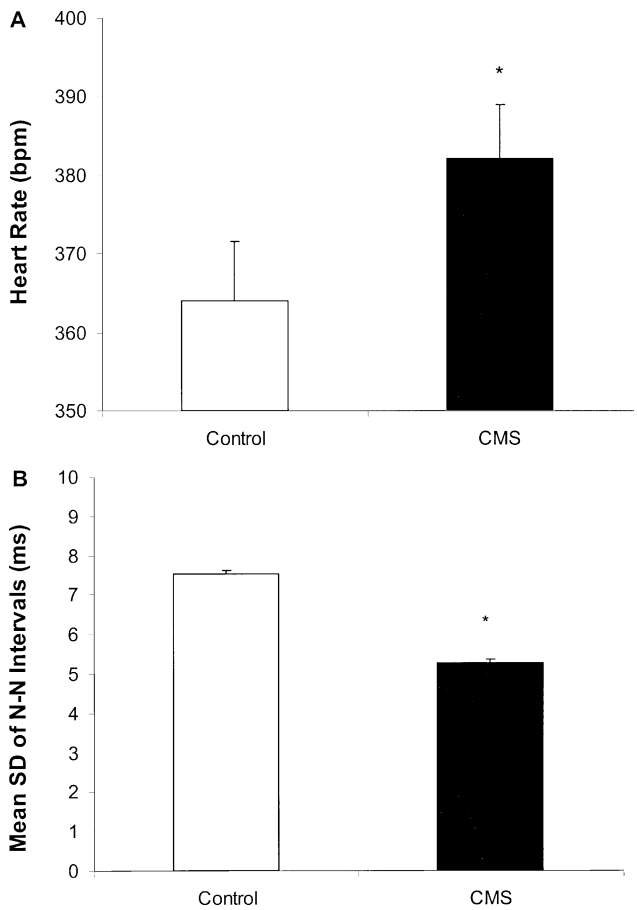

Fig. 5. Mean (±SEM) heart rate (Panel A) and heart rate variability (mean of the standard deviation of normal-to-normal intervals during a 5 min period of rest (SDNN Index); Panel B) in rats exposed to 4 weeks of chronic mild stress (CMS; $n = 12$) and a control group (control; $n = 10$). Rats in the CMS group displayed significantly elevated resting heart rate and reduced heart rate variability, relative to the control group. $^*P < 0.05$ vs. control. Data from Grippo et al. [103].

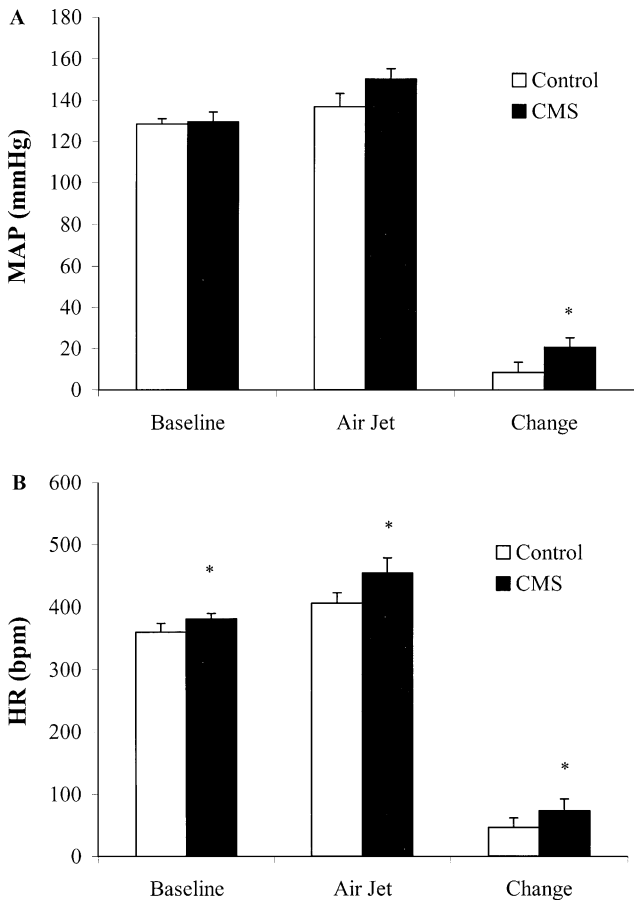

Fig. 6. Mean (± SEM) absolute mean arterial pressure (MAP; Panel A) and heart rate (HR; Panel B), and corresponding changes from baseline, in response to air jet stress in rats exposed to 4 weeks of chronic mild stress (CMS; $n = 12$) and a control group (control; $n = 10$). Pressor and HR responses to air jet stress were significantly elevated in the CMS group, compared to the control group. $^*P < 0.05$ vs. respective control value. From Grippo et al. [103] with permission, copyright 2002 American Physiological Society.

Following our initial study with chronic mild stress, we have become interested in the association of behavioral and cardiovascular changes in this animal model. We exposed another group of rats to 4 weeks of chronic mild stress while measuring sucrose intake (anhedonia) and spontaneous locomotor activity throughout this period. Rats exposed to chronic mild stress displayed both anhedonia and reduced activity level in a running wheel. We then discontinued the stressors and continued to monitor sucrose intake and locomotor activity for another 4 weeks (stress-free period). At the end of this period we examined baseline cardiovascular parameters and heart rate responses to pharmacological sympathetic blockade. While the behavioral responses to chronic mild stress recovered by the end of the 4 week stress-free period, the cardiovascular changes seen in this animal model of depression appear to be chronic in nature. Similar to the cardiovascular responses we observed in the first chronic mild stress paradigm [103], chronic mild stress rats displayed elevated heart rate, reduced heart rate variability and elevated sympathetic cardiac tone at the end of the 4 week stress-free period [101]. Given the persistence of cardiovascular changes following exposure to chronic mild stress, it would be of great interest to determine whether pharmacological antidepressant treatments can effectively alter both the behavioral and cardiovascular consequences in this animal model.

A recent study in our laboratory focused on a potential mechanism for heart disease in depression by examining the susceptibility to ventricular arrhythmias in the chronic mild stress model [104]. We hypothesized that rats exposed to chronic mild stress would display an increased susceptibility to life threatening arrhythmias. In this study, rats exposed to 4 weeks of chronic mild stress displayed anhedonia (similar to previous studies), as well as a shorter latency to onset of ventricular premature beats, salvos and ventricular tachycardia in response to a chemical stressor (relative to a control group). These findings suggest that rats exposed to chronic mild stress are vulnerable to arrhythmic events, which may influence further detrimental cardiac events (such as myocardial infarction or death). The types of studies described here may help to elucidate the pathophysiological mechanisms that underlie lowered mood and CAD.

2.3. The use of animal models of CAD to study components of psychopathology

Animal models of cardiovascular disease, such as those for study of hypertension [213] and heart failure [87], are also well established. These models can be used to determine specific neurochemical, neuroendocrine and behavioral changes associated with cardiovascular disease, and may provide insight into the mechanisms of cardiovascular disease-induced depression. For instance, studies from our laboratory have examined anhedonia in animals with experimental congestive heart failure. We used operant responding for rewarding electrical brain stimulation to test for a decline in reward value of a positive reinforcer (a reduction in response rate for electrical brain stimulation relative to an experimentally established baseline was used as the operational definition of anhedonia). Rats with heart failure, produced by coronary artery ligation, displayed anhedonia compared to baseline responses and sham ligated rats, evidenced by a significant reduction in responding for intracranial stimulation at 7 days following coronary artery ligation [102] (Fig. 7). We hypothesized that elevated plasma levels of the proinflammatory cytokine, TNF-α, played a role in heart failure-induced anhedonia. Indeed, plasma TNF-α levels were increased in the heart failure group relative to the sham ligated rats (Fig. 8). When we blocked TNF-α with an antagonist, etanercept (a soluble TNF receptor), the attenuated responding for rewarding electrical stimulation reverted to baseline (pre-heart failure) levels in the heart failure group.

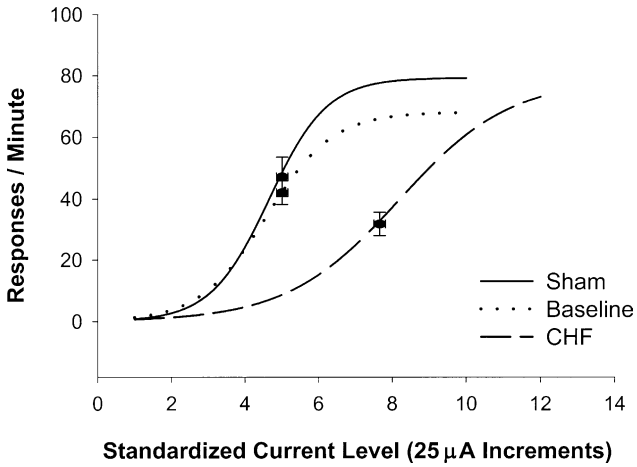

Fig. 7. Mean current–response curves for congestive heart failure (CHF; $n = 15$) and sham heart failure (Sham; $n = 13$) groups, relative to baseline, on day 7 following coronary artery ligation showing a parallel rightward shift in the current–response function of the CHF group. In contrast, the current–response function for the sham heart failure group was similar to the baseline function. Data are displayed with a sigmoid curve fit to mean values; black dots indicate midpoint of each curve ± SEM (vertical and horizontal). A combined baseline curve for both CHF and sham heart failure groups is depicted. From Grippo et al. [102] with permission, copyright 2003 American Physiological Society.

The occurrence of anhedonia described earlier mirror the behavioral changes seen in human cardiac patients and suggests that cardiovascular disease may lead to neurochemical alterations that can induce the symptoms and signs of depression accompanying heart failure. The precise mechanisms by which peripheral cytokines act to influence central nervous system function are not known, but may involve actions at the circumventricular organs, the stimulation of prostaglandins at the vascular–brain interface or actions on visceral afferent nerves. These mechanisms require further investigation. Methodological approaches such as those described here can provide important insight regarding depressive symptoms that follow a detrimental cardiac event, as well as the importance of biological mediators in heart disease-induced mood changes. Furthermore, given the extent of bidirectional communication between the brain and cardiovascular system, the mechanistic study of animal models of heart disease may help us gain a better understanding of the influence of the central nervous system on cardiovascular function and depression.

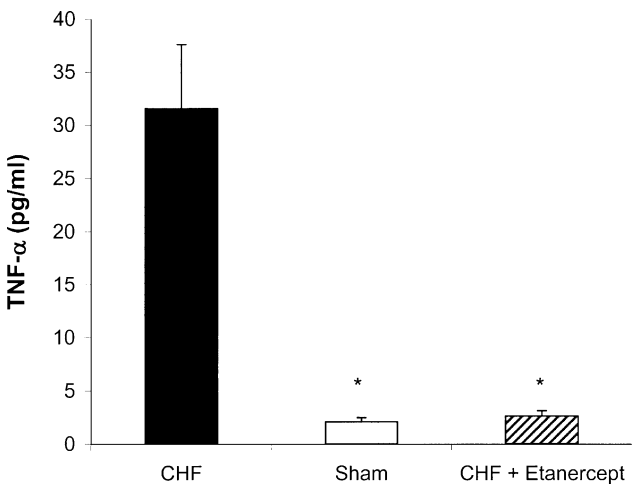

Fig. 8. Mean (± SEM) plasma tumor necrosis factor-α (TNF-α) levels in rats with congestive heart failure (CHF; $n = 4$), sham heart failure rats (Sham; $n = 4$), and CHF rats treated with etanercept ($n = 6$). Tumor necrosis factor-α levels were elevated in the CHF group relative to the sham heart failure group and the CHF rodents treated with etanercept. *$P < 0.05$ vs. CHF. From Grippo et al. [102] with permission, copyright 2003 American Physiological Society.

2.4. A focus on common central nervous system mechanisms

An additional important goal for future scientific research is to devote significant attention to central nervous system changes in both depression and cardiovascular disease. The bidirectional association between depression and heart disease may involve common central nervous system mechanisms involving key neurochemical alterations. The examination of serotonergic influences in depression and cardiovascular regulation may provide fruitful research. Abnormalities in serotonin function have been hypothesized to occur in depression [25,31,172]. Also, Sole and colleagues [226] have demonstrated serotonergic alterations in specific central nuclei during acute myocardial ischemia in the rat. Treatment with the serotonin reuptake inhibitor, fluoxetine, was shown to reduce the risk of myocardial infarction in smokers with cardiovascular disease [214]. It is possible that serotonin dysfunction plays an etiological role in both depression and cardiac dysfunction. Alternatively, depression may influence cardiovascular regulation via serotonergic mechanisms or vice versa.

It is warranted to assess serotonin and other neurotransmitter function in areas of the brain associated with affective disorders (e.g. medial prefrontal cortex and hippocampus [252]) and cardiovascular regulation (e.g. nucleus tractus solitarius, rostral ventrolateral medulla and paraventricular hypothalamic nucleus [236]). Furthermore, some recent reports suggest that serotonin may be related to immune function. For example, reduced plasma tryptophan has been shown to influence inflammatory responses in patients with depression and sleep disorders [227], as well as in alcoholics [163].

Examination of forebrain mechanisms (such as those involving the hypothalamus and lamina terminalis) in depression and cardiovascular disease may also provide valuable insight into this important link. Several recent studies suggest that changes in forebrain structures take place in myocardial infarction and congestive heart failure, likely involving interactions of the renin–angiotensin–aldosterone system and the paraventricular hypothalamic nucleus [85,251,262]. Interestingly, central mineralocorticoid receptor blockade was shown to improve volume regulation and reduce sympathetic drive in

an animal model of heart failure [88]. Felder et al. [82] have reviewed the role of the renin–angiotensin–aldosterone system and forebrain mechanisms in heart failure. It would be of interest to determine whether these particular forebrain mechanisms are also involved in altered mood states.

3. Final comments

Cardiovascular disease claims 12 million lives per year worldwide [5]. It is the leading cause of death for both males and females, accounting for approximately 50% of all deaths in developed and developing countries. Over 59 million Americans currently have one or more forms of cardiovascular disease and 900,000 will die from the disease this year [5]. According to recent estimates, approximately 75,000 deaths per year in the United States among patients discharged after an initial myocardial infarct are attributable to co-morbid depression [43]. Increased knowledge about the relationship between depression and cardiovascular regulation opens the possibility for attenuating the influence of depression on cardiovascular diseases as well as reducing mortality rates among depressed cardiac patients.

To reduce cardiovascular-related morbidity and mortality in depressed individuals, it may be insufficient to treat depression in cardiac patients with conventional therapies. Depressive episodes can have residual physiological effects that do not normalize, even in successfully treated cases [196]. More importantly, widely used pharmacological antidepressant treatments, such as MAOIs and TCAs, are potentially cardiotoxic [205]. It is, therefore, necessary to design comprehensive research programs to gain a greater understanding of the central and peripheral nervous system mechanisms that underlie affective disorders and the pathogenesis of CAD. When the specific mechanisms responsible for the effects of depression on cardiovascular endpoints are determined, this line of research will have maximal influence on clinical practice. The study of pathophysiological mediators underlying depression and cardiovascular dysfunction will lead to enhanced knowledge of causal and/or common mechanisms and the development of more comprehensive treatment programs for patients with mood disorders and CAD.

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