NEWS AND VIEWS

The Relationship of Depression to Cardiovascular Disease

Epidemiology, Biology, and Treatment

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This article reviews the burgeoning literature on the relationship of mood disorders and heart disease. Major depression and depressive symptoms, although commonly encountered in medical populations, are frequently underdiagnosed and undertreated in patients with cardiovascular disease (CVD). This is of particular importance because several studies have shown depression and its associated symptoms to be a major risk factor for both the development of CVD and death after an index myocardial infarction. This review of the extant literature is derived from MEDLINE searches (1966-1997) using the search terms "major depression," "psychiatry," "cardiovascular disease," and "pathophysiology." Studies investigating pathophysiological alterations related to CVD in depressed patients are reviewed. The few studies on treatment of depression in patients with CVD are also described. Treatment of depression in patients with CVD improves their dysphoria and other signs and symptoms of depression, improves quality of life, and perhaps even increases longevity. Recommendations for future research are proposed.

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People never die of love or grief alone: though some die of inherent maladies, which the tortures of those passions prematurely force into destructive action.

Charlotte Bronte, Shirley, 1848

Depressive syndromes and major depression are exceedingly common. A recent comprehensive study, the National Comorbidity Study, reported lifetime prevalence rates of major depression and dysthymia of 13% and 5%, respectively.[1] Point prevalence rates of major depression in primary care outpatients range from 2% to 16% and from 9% to 20% for all depressive disorders[2-7] and are even higher in medical inpatients; 8% for major depression and 15% to 36% for all depressive disorders.[8,9]

Minor depressive disorder (depressive symptoms subthreshold in severity to major depression and dysthymia) is also common in the community[10-14] and in primary care clinics.[2,4,15-17] The Epidemiologic Catchment Area Study of more than 18 500 people reported the lifetime prevalence rate of subthreshold depressive symptoms to be 23%, in comparison with 6%, the sum of the prevalence rates of major depression and dysthymia.[14]

Though depression in patients with coronary artery disease (CAD) is rarely diagnosed by primary care physicians and cardiologists,[18-23] recognition and treatment of major depression is crucial, especially for patients after myocardial infarction (MI). Not only do depressed patients experience great difficulties in problem solving and coping with challenges, but depression adversely affects compliance with medical therapy[24] and rehabilitation[25,26] and increases medical comorbidity.[25] Minor depressive disorder is also associated with significant functional impairment and substantial increases in health care utilization.[13,14,27,28]

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In patients with CAD, depression predicts future cardiac events[21,29,30] and hastens mortality.[23,31,32] Since the 1960s, multiple longitudinal and cross-sectional studies have scrutinized the association of cardiovascular disease (CVD), especially CAD, with depressive symptoms, as well as with major depression. This review of the extant literature is derived from MEDLINE searches (1966-1977), using the search terms "major depression," "psychiatry," "heart disease," and "pathophysiology."

Table 1. Prevalence of Major Depression in Patients With Cardiovascular Disease*

Study	No. and Type of Patients	Diagnostic Method	Prevalence, %
Carney et al[29]	52 patients with CAD undergoing elective cardiac catheterization	DIS	18
Schleifer et al[22]	283 patients hospitalized with MI	SADS	18
Frasure-Smith et al[23]	222 patients hospitalized with MI	DIS	16
Gonzalez et al[37]	99 patients hospitalized with CAD	DIS	23

*CAD indicates coronary artery disease; DIS, Diagnostic Interview Schedule, version III[35]; MI, myocardial infarction; and SADS, Schedule for Affective Disorders and Schizophrenia.[36]

EPIDEMIOLOGY

Depression and Cardiovascular Disease

Early studies reported the prevalence of depression to be from 18% to 60% in patients with CAD.[18,19,25,33,34] Later studies report relatively consistent prevalence rates of depression in patients with CVD, ranging from 16% to 23% (mean, 19%; median, 18%), despite the potential methodological weaknesses of some of the studies listed in **Table 1** (such as the use of unmodified psychiatric diagnostic instruments to determine the prevalence of depression, excluding patients because of severity of CVD, and measuring depressive symptoms at different times after hospital admission) and methodological differences among the studies (dissimilar patient populations, different diagnostic instruments, hospitalization status, or unspecified type of heart disease). Furthermore, structured clinical interviews such as the Diagnostic Interview Schedule[35] may not have the same validity in patients with CAD as in the general population.

Although severity of physical illness is one of the most important variables associated with depression in patients with other medical illnesses, studies of patients with CVD do not document a higher prevalence rate of depression in patients with measures of more advanced CVD or with a greater level of disability.[21-23,32]

Depression as a Risk Factor for Ischemic Heart Disease

The notion that having a psychiatric illness such as major depression increases one's risk for developing ischemic heart disease remains controversial and has been often intuitively "explained" by the hypothesis that persons with psychiatric disorders generally have other risk factors for the development of CAD.[38] **Table 2** contains studies with the most rigorous methods that are prospective in design, have used structured clinical interviews or diagnostic instruments, have included other risk factors for CVD in their analysis (such as hypertension, hypercholesterolemia, nicotine and other substance abuse, and physical inactivity), and controlled for demographic factors (such as age, sex, and socioeconomic status).

Nearly all the recent studies in Table 2 document increased cardiovascular morbidity and mortality in patients with depressive symptoms or major depression, thereby implicating depression as an independent risk factor in the pathophysiologic progression of CVD, rather than merely a secondary emotional response to the illness. Such large epidemiologic studies may use self-report instruments, rather than clinical interviews, to evaluate the importance of psychological factors in predicting CVD. Assessments of this type are typically added to large, multiple risk factor studies in which population-based samples are followed up prospectively.[38] The advantage of using "dimensional" measures of depression (rather than a categorical diagnosis of major depression) is the increased statistical power to detect smaller "effects." However, such epidemiologic data are not equivalent to clinical data.

A relatively large clinical study supporting depression as an independent risk factor for CVD observed that patients with major depression experience elevated mortality rates from CVD. Frasure-Smith and colleagues[23,32] found depression to be a significant predictor of mortality ($P<.001$) in 222 patients 6 months after MI. Depression remained a significant predictor of mortality ($P = .01$), even after multivariate statistical methodology was used to factor out the effects of left ventricular dysfunction and previous MI. Multiple logistic regression analyses revealed depression was significantly related to 18-month cardiac mortality, even after controlling for other significant multivariate predictors of mortality (previous MI, Killip class, frequency of premature ventricular contractions [PVCs]) ($P = .003$).

BIOLOGY

Hypothalamic-Pituitary-Adrenocortical and Sympathomedullary Hyperactivity

Recent advances in biological psychiatry have included the discoveries of numerous neurochemical, neuroendocrine, and neuroanatomic alterations in unipolar depression. Proposed as important adjuncts in the diagnosis of depressed subjects, certain of these biologic markers may reflect important pathophysiologic alterations that contribute to the increased vulnerability of depressed patients to CVD. These include sympathoadrenal hyperactivity, diminished heart rate variability (HRV), ventricular instability and myocardial ischemia in reaction to mental stress, and alterations in platelet receptors and/or reactivity (**Figure 1**).[61]

Two primary components central to the "fight or flight" stress re-

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Table 2. Antecedent Depression and Subsequent Risk of Cardiovascular Disease (CVD)*

Source	No. and Type of Patients	Diagnostic Method	Relative Risk (RR) of Major Depression or Depressive Symptoms for CVD or CVD-Related Death
Ostfeld et al[39]	1990 male Western Electric employees	MMPI[40] 16 PF[41]	None
Brozek et al[42]	258 men	MMPI[43]	None
Goldberg et al[44]	82 pairs (male and female) of case/control subjects randomly selected from 2 communities	CES-D Scale[45] (plus 4 other depression scales)	None
Murphy et al[46]	1003 male and female subjects from the community	DPAX algorithm[47]	For CVD-related death, men = 2.5, women = 1.5
Anda et al[48]	2832 men and women (aged 45-77 y)	Depression subscale of GWS[49]	For IHD-related death, 1.5-2.1
Aromaa et al[30]	5355 men and women (aged 40-64 y)	PSE[50]	For MI, men = 2.62, women = 1.90
Ford et al[51]	1198 men	Depression questionnaire	For MI, 1.9
Vogt et al[52]	1187 men and 1386 women (aged ≥18 y) in an HMO	Depression scale[53]	Depressive symptoms not related to incidence of CVD
Simonsick et al[54]	1063 men and 2398 women (aged ≥65 y with hypertension	CES-D Scale[45]	Elevated rates of CVD-related death in women with high scores of depressive symptoms
Everson et al[55]	2428 men (aged 42-60 y)	Hopelessness self-report questionnaire	For CVD-related death, RH = 2.52 (with moderate hopelessness score); RH = 3.90 (with high hopelessness scores)
Barefoot and Schroll[56]	409 men and 321 women (all born in 1914)	MMPI[57]	For MI, 1.7
Pratt et al[58]	1551 men and women	DIS[35]	For MI, odds ratio = 2.07 (history of dysphoria); odds ratio = 4.54 (history of major depressive disorder)
Wassertheil-Smoller et al[59]	4736 men and women >60 y with hypertension	CES-D[60]	Baseline CES-D score ≥16 did not predict future MI; RR of future MI per 5-unit increase in CES-D score: women = 1.2

MMPI indicates Minnesota Multiphasic Personality Inventory; PF, Personality Factor; CES-D, Center for Epidemiological Studies Depression Scale; DPAX, computer diagnosis of depression and anxiety; GWS, General Well-Being Schedule; IHD, ischemic heart disease; PSE, Present State Examination; MI, myocardial infarction; HMO, health maintenance organization; RH, relative hazard; and DIS, Diagnostic Interview Schedule.

sponse observed by Cannon in 1911[62] and the "general adaptation syndrome" described by Selye[63] are the hypothalamic-pituitary-adrenocortical axis and sympathoadrenal system. In response to stress, hypothalamic neurons containing corticotropin-releasing factor (CRF) increase synthesis and release of corticotropin (ACTH), β-endorphin, and other pro-opiomelanocortin products from the anterior pituitary gland. Many studies have documented evidence of hypothalamic-pituitary-adrenocortical axis hyperactivity within medication-free patients with major depression, ie, elevated CRF concentrations in cerebrospinal fluid,[64-69] blunting of the ACTH response to CRF administration, nonsuppression of cortisol secretion following dexamethasone administration, hypercortisolemia, and pituitary and adrenal gland enlargement, as well as direct evidence of increased numbers of hypothalamic CRF neurons in the postmortem tissue of depressed patients as compared with controls.[70,71] Administered corticosteroids have long been known to induce hypercholesterolemia, hypertriglyceridemia, and hypertension. Other atherosclerosis-inducing actions of steroids include injury of vascular endothelial cells,[72] intima,[73-75] and inhibition of normal healing.[76] Indeed, elevated morning plasma cortisol concentrations have been significantly correlated with moderate to severe coronary atherosclerosis in young and middle-aged men.[77]

Many patients with major depression also exhibit dysregulation of the sympathoadrenal system. The adrenal medulla and sympathetic nervous system together comprise the sympathoadrenal system. Although the central nervous system regulation of the sympathoadrenal system is only partially characterized, hypothalamic CRF-containing neurons provide stimulatory input to several autonomic centers involved in regulating sympathetic activity.[78-80] Nerve impulses from regulatory centers in the central nervous system control catecholamine release from the sympathoadrenal system. Physiological and pathological conditions causing sympathoadrenal activation include physical activity, coronary ischemia, heart failure, and mental stress. Epinephrine in plasma is derived from the adrenal medulla whereas plasma norepinephrine (NE) concentrations reflect its secretion largely from sympathetic nerve terminals, with the remaining NE provided from the adrenal medulla and extra-adrenal chromaffin cells. Peripheral plasma NE concentrations are determined not only by rate of release from sympathetic nervous system nerve terminals, but also by reuptake into presynaptic terminals, local metabolic degradation, and redistribution into multiple physiological compartments.

Hypersecretion of NE in unipolar depression has been documented by elevated plasma NE and NE metabolite concentrations[81-84] and elevated urinary concentrations of NE and its metabolites. Not only do depressed patients exhibit higher basal plasma concentrations of NE but those with melancholia

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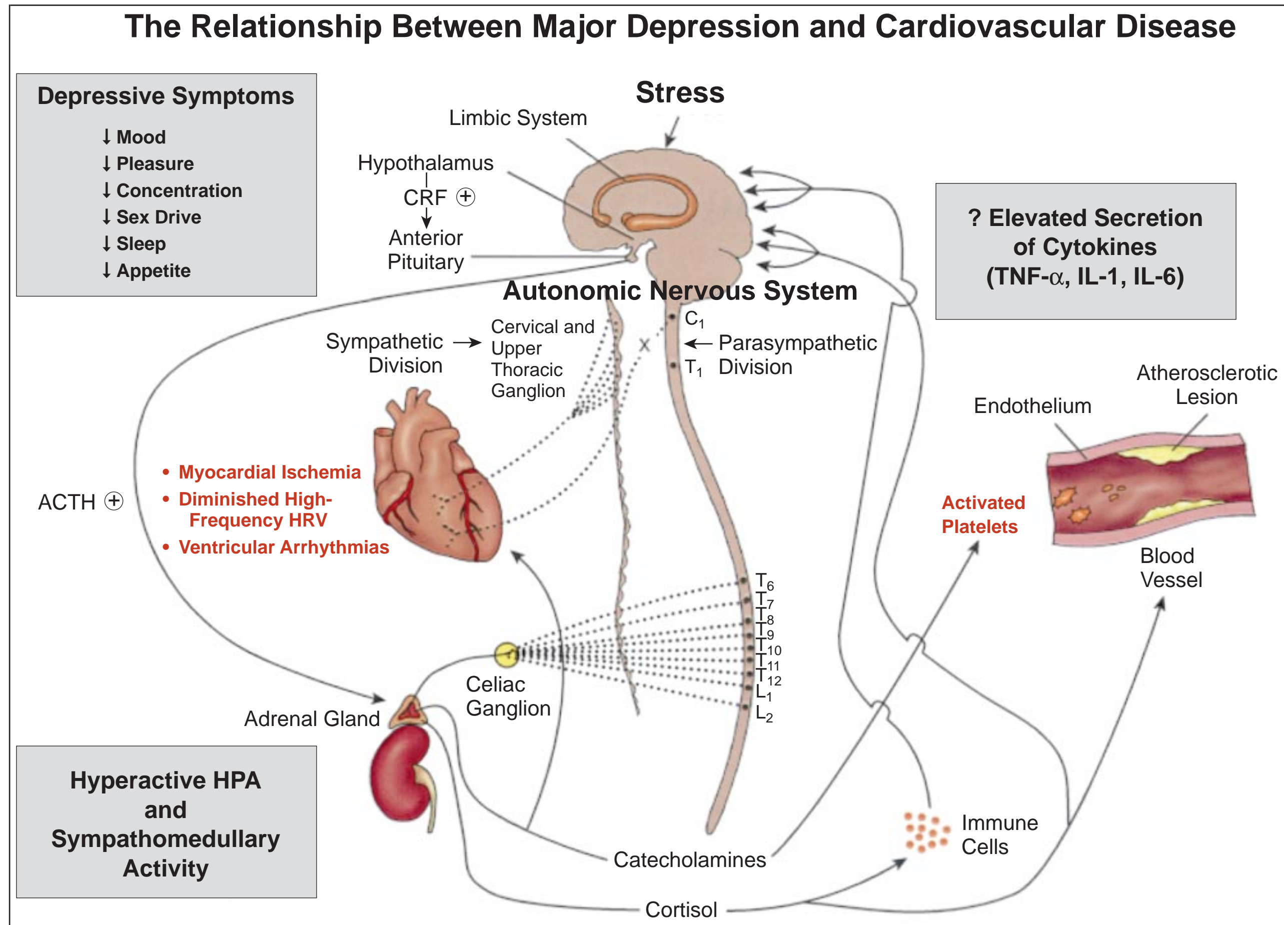

Figure 1. *Hypothetical schema of pathophysiologic alterations associated with depression that likely contribute to increased vulnerability to cardiovascular disease (CVD). Autonomic nervous system innervation of the heart via parasympathetic vagus (X) and sympathetic (postganglionic efferents from cervical and upper thoracic paravertebral ganglia) nerves is shown. CRF indicates corticotropin-releasing factor; ACTH, corticotropin; TNF-α, tumor necrosis factor α; IL-1, interleukin 1; IL-6, interleukin-6; HRV, heart rate variability; and HPA, hypothalamic-pituitary-adrenocortical axis.*

exhibit even greater elevations in plasma NE concentrations when subjected to orthostatic challenge than do normal control subjects and depressed patients without melancholia.[85] Furthermore, depressed patients who are dexamethasone test nonsuppressors exhibit significantly higher basal and cold-stimulated plasma concentrations of NE than depressed patients who are dexamethasone test suppressors.[85] Following treatment with tricyclic antidepresssants (TCAs), urinary excretion of NE and its metabolites diminish with plasma NE concentrations,[86-91] though Veith and colleagues[84] reported that long-term treatment with desipramine increased plasma concentrations of norepinephrine. Thus, sympathoadrenal hyperactivity seems to represent a state, rather than a trait, marker of depression, possibly reflecting increased CRF release within the central nervous system.

Sympathoadrenal hyperactivity contributes to the development of CVD through effects of catecholamines upon the heart, blood vessels, and platelets. Sympathoadrenal activation modifies the function of circulating platelets through direct effects on the platelet, catecholamine-induced changes of hemodynamic factors (increased shear stress), circulating lipids, and inhibition of vascular eicosanoid synthesis.[92] Arachidonic acid metabolites, such as prostaglandins and leukotrienes, contribute to diverse circulatory and hemostatic functions including inhibition of platelet aggregation and vascular contractility and permeability.[93] Elevations of plasma NE levels are found most frequently in young hypertensive patients[94] and subjects with high-cardiac-output borderline hypertension who later proceed to established high-resistance hypertension.[95]

Even normotensive depressed patients have been found to exhibit greater heart rates at rest, after orthostasis, and after exercise in comparison with normal controls. These depressed patients also exhibited increased plasma concentrations of NE and serotonin at rest.[96] Thus, the sympathoadrenal hyperactivity observed in many patients with major depression may contribute to the development of CVD via effects of catecholamines on cardiac function and platelets.

Diminished Heart Rate Variability

Alterations in autonomic nervous system activity, as demonstrated by reduced HRV, represent another potential mechanism contributing to the diminished survival of depressed patients with CVD. It is believed that the beat-to-beat fluctuations in hemodynamic parameters

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reflect the dynamic response of the cardiovascular control systems to a myriad of naturally occurring physiological perturbations, such as fluctuations in heart rate associated with respiration. Therefore, fluctuations in heart rate may provide a sensitive measure of the functioning of the rapidly reacting sympathetic, parasympathetic, and renin-angiotensin systems. Cardiovascular homeostasis is maintained by the parasympathetic and sympathetic nervous systems via afferent pressoreceptors and chemoreceptors and efferents that alter heart rate, atrioventricular conduction, and contractility and impinge on the peripheral vasculature, altering arterial and venous vasomotor tone.[97]

Heart rate variability is the standard deviation of successive intervals between 2 successive R waves (the first positive defelection of a QRS complex) on an electrocardiogram in sinus rhythm and reflects the interplay and balance between sympathetic and parasympathetic input on the cardiac pacemaker. Peripheral control of HRV is mainly via the parasympathetic cholinergic vagus nerve.[98] Central generation and control of heart rate is regulated by the hypothalamus, the limbic system, and the brainstem. Numerous central nervous system neurotransmitters are involved in modulating HRV, including acetylcholine, NE, serotonin, and dopamine.[99,100]

A high degree of HRV is observed in normal hearts with good cardiac function, whereas HRV can be significantly decreased in patients with severe CAD or heart failure.[101] Moreover, the relative risk of sudden death after acute MI is significantly higher in patients with decreased HRV.[102-107] Heart rate variability is one of many postinfarction prognostic factors (others include age, left ventricular ejection fraction, and frequency of arrythymias). Its positive predictive power is relatively modest when considered in isolation. Although positive predictive accuracy is not high when HRV is considered in combination with other prognostic factors,[108,109] clinically useful levels of negative predictive accuracy can be achieved.[108-110] Of the many arrhythmogenic factors, autonomic tone is the most difficult to measure,[110] and thus interest in HRV continues. Power spectral analysis measurements of HRV are often used because certain frequency bands of the heart period power spectrum have been associated with autonomic nervous system control of the sinus node.[111-113] The low-frequency power of the heart period power spectrum reflects modulation of sympathetic and vagal tone by baroreflex activity,[114] while high-frequency power reflects modulation of vagal tone, primarily by respiratory frequency and depth (the respiratory sinus arrhythmia).[115,116] The physiological mechanisms contributing to ultra low and very low-frequency power of the heart period spectrum (which account for >90% of the total power in a 24-hour period) remain obscure. In a study of 715 patients after MI, certain frequency bands (total, ultra low and very low-frequencies) of the heart period power spectrum were strongly associated with mortality during 4 years of follow up, even after adjustment for other major risk factors. Indeed, very low-frequency power was most strongly associated with death secondary to arrhythmia.[117]

Reduced high-frequency HRV has been observed in depressed patients in comparison with nondepressed groups,[101,118] though discrepant reports exist.[119,120] In patients with angiographically confirmed CAD, diminished HRV during 24-hour Holter monitoring was significantly more common in depressed patients than in matched nondepressed patients.[121] Diminished high-frequency HRV is thought to reflect decreased parasympathetic tone, possibly predisposing to ventricular arrhythmias and perhaps to the excessive cardiovascular mortality found in patients with CVD and comorbid major depressive disorder.[122] One study (without a placebo control group) revealed normalization of reduced HRV of depressed patients after effective treatment.[123] The prognostic importance of antidepressant-induced improvement in diminished HRV in depressed patients remains an intriguing area of research. Subsequent investigation will seek to determine the processes underlying ultralow and very low-frequency bands of the heart power spectrum; whether these bands are altered in depressed patients (with or without CVD) remains obscure.

Myocardial Ischemia and Ventricular Instability in Reaction to Mental Stress

It has long been thought that the combination of a vulnerable myocardium after MI, acute ischemia, and negative emotional arousal can trigger fatal ventricular arrhythmias.[124] The interplay of these factors in patients with CAD is being increasingly scrutinized. Jiang and colleagues[125] followed up 126 patients with CAD during a 5-year period. Mental stress–induced myocardial ischemia at baseline in patients with CAD was associated with significantly higher rates of subsequent fatal and nonfatal cardiac events, independent of age, baseline left ventricular ejection fraction, and previous MI. This study proposed that the relationship between psychological stress and adverse cardiac events is mediated by myocardial ischemia. Although myocardial ischemia is likely the most significant factor in predisposition to ventricular instability, other factors contribute. Central nervous system control mechanisms can significantly decrease the threshold for ventricular fibrillation.[126] Ventricular fibrillation is believed to be the mechanism underlying sudden cardiac death, the most common cause of fatality among patients with CAD.[127] Psychological stress predisposes to abnormal ventricular activity by lowering the ventricular vulnerable period threshold even to the point of fibrillation. The vagus nerve, however, exerts antiarrhythmic activity by direct action on the ventricular myocardium and interference with sympathetic activity.[128] Increased parasympathetic activity has a protective effect on myocardium electrically destabilized by increased adrenergic tone.[127]

Psychological and physical events can elicit a stress response; ie, the reaction of an organism to deleterious forces that disturb physiologic homeostasis.[129,130] Psychological stress in humans with CAD

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increases ventricular ectopic activity and increases the risk of ventricular fibrillation.[131,132] There are several similarities between the stress response and major depression. Both can be characterized by increased blood pressure and heart rate, as well as increased arousal and increased mobilization of energy stores.[133] Particularly relevant to both the stress response and depression are 2 critical brain structures, the locus coeruleus and the central nucleus of the amygdala, which are in turn both innervated by CRF-containing nerve terminals.[134,135] The stress response and major depression do differ, however, in some respects. In depression, some aspects of the normal stress response seem to escalate to a pathologic state[136] that fails to respond appropriately to usual counterregulatory responses, resulting in a sustained version of a usually transient phenomenon (such as hyperactivity of the hypothalamic-pituitary-adrenocortical axis or sympathoadrenal system). However, although many studies have linked stressful life events to onset of major depression,[137,138] some depressions are clearly endogeneous; ie, they have no obvious environmental precipitant.

Frasure-Smith and colleagues[32] proposed that depression worsens prognosis after MI via another mechanism, PVCs. The risk of sudden cardiac death associated with significant depressive symptoms was greatest among patients with 10 or more PVCs per hour (60% of these patients died within 18 months), suggesting arrhythmia as the link between depression and sudden cardiac death.[32] Depressed patients with CAD are not more likely to have arrhythmias than patients with CAD and no depression, but the risk associated with depression is largely confined to patients with PVCs. Patients who were not depressed experienced little increase in risk associated with PVCs, even in the presence of low left ventricular ejection fraction.[32] Thus, the prognostic impact of PVCs may be more related to depression than to PVCs per se. In the Cardiac Arrhythmia Supression Trial,[139] suppression of PVC frequency in post-MI patients did not reduce and actually increased mortality, even though previous studies revealed that PVCs are associated with increased mortality after MI. Treatment of depression may be the necessary component to improve survival in patients with PVCs.

Alterations in Platelet Receptors and/or Reactivity

The adverse effects of depression on cardiovascular disease may be also mediated via platelet mechanisms. Markovitz and Matthews[140] first proposed that enhanced platelet responses to psychological stress might trigger adverse coronary artery ischemic events. This association between platelet activation and vascular disease is indirectly supported by studies linking cerebrovascular disease and depression. The Established Populations for Epidemiologic Studies of the Elderly prospectively studied 10 294 persons aged 65 years and older for 6 years and determined that rates of stroke (adjusted for age, physical disability, and other medical disorders) were 2.3 to 2.7 times higher in persons designated with "high" vs "low" levels of depressive symptoms.[54] In another prospective study, 103 consecutive stroke patients[141] were assessed for major depression or dysthymia approximately 2 weeks after stroke. Patients with major depression or dysthymia were 3.4 times more likely to have died during the 10-year follow-up period than were nondepressed patients ($P = .007$), even after controlling for confounding variables (age, medical comorbidity, type of stroke, and lesion location) ($P = .03$).

Platelets play a central role in hemostasis, thrombosis, development of atherosclerosis, and acute coronary syndromes[142] through their interactions both with subendothelial components of damaged vessel walls and plasma coagulation factors, primarily thrombin. Human platelets contain adrenergic, serotonergic, and dopaminergic receptors. Through stimulation of the α_2-adrenoceptors on platelet membranes, increases in levels of circulating catecholamines (>4 nmol/L) potentiate the effects of other agonists and, at higher concentrations, initiate platelet responses, including secretion, aggregation, and activation of the arachidonate pathway. Following injury to vessel endothelium, platelets and circulating leukocytes attach to the newly exposed subendothelial layer. Platelet adhesion to collagen (and other components of the subendothelial matrix) exposed within a denuded area of the vascular endothelium and thrombin stimulates platelet activation. Activation converts platelet membrane GPIIb/IIIa complexes into functional receptors for fibrinogen. Activation is also accompanied by extrusion or secretion of platelet storage granule contents into the extracellular environment. Platelets activated at the interface with a vessel wall injury accelerate the local formation of thrombin and release a variety of products from their storage granules, including chemotactic and mitogenic factors inducing leukocyte migration from the blood stream and vascular cell proliferation. These secreted platelet products, such as platelet factor 4, β-thromboglobulin, and serotonin, stimulate and recruit other platelets and cause irreversible platelet-platelet aggregation, leading to formation of a fused-platelet thrombus. Platelets also contribute to vascular damage by stimulating lipoprotein uptake by macrophages and mediating vasoconstriction through the production and/or release of substances such as thromboxane A_2, platelet-activating factor, and serotonin.[96] Clinical trials have confirmed the importance of the platelet in vascular damage; antiaggregating medications are useful in secondary prevention[143-145] and delay progression of atherosclerotic lesions.[146] Many of these processes are depicted in **Figure 2**.

We wondered whether heightened susceptibility to platelet activation might be a mechanism by which depression in physically healthy young persons acts as a significant risk factor for heart and cerebrovascular disease and/or mortality after MI. Utilizing fluorescence-activated flow cytometric analysis, we discovered that, in comparison with 8 normal controls, 12 depressed patients exhibited enhanced baseline platelet activation and responsiveness.[147]

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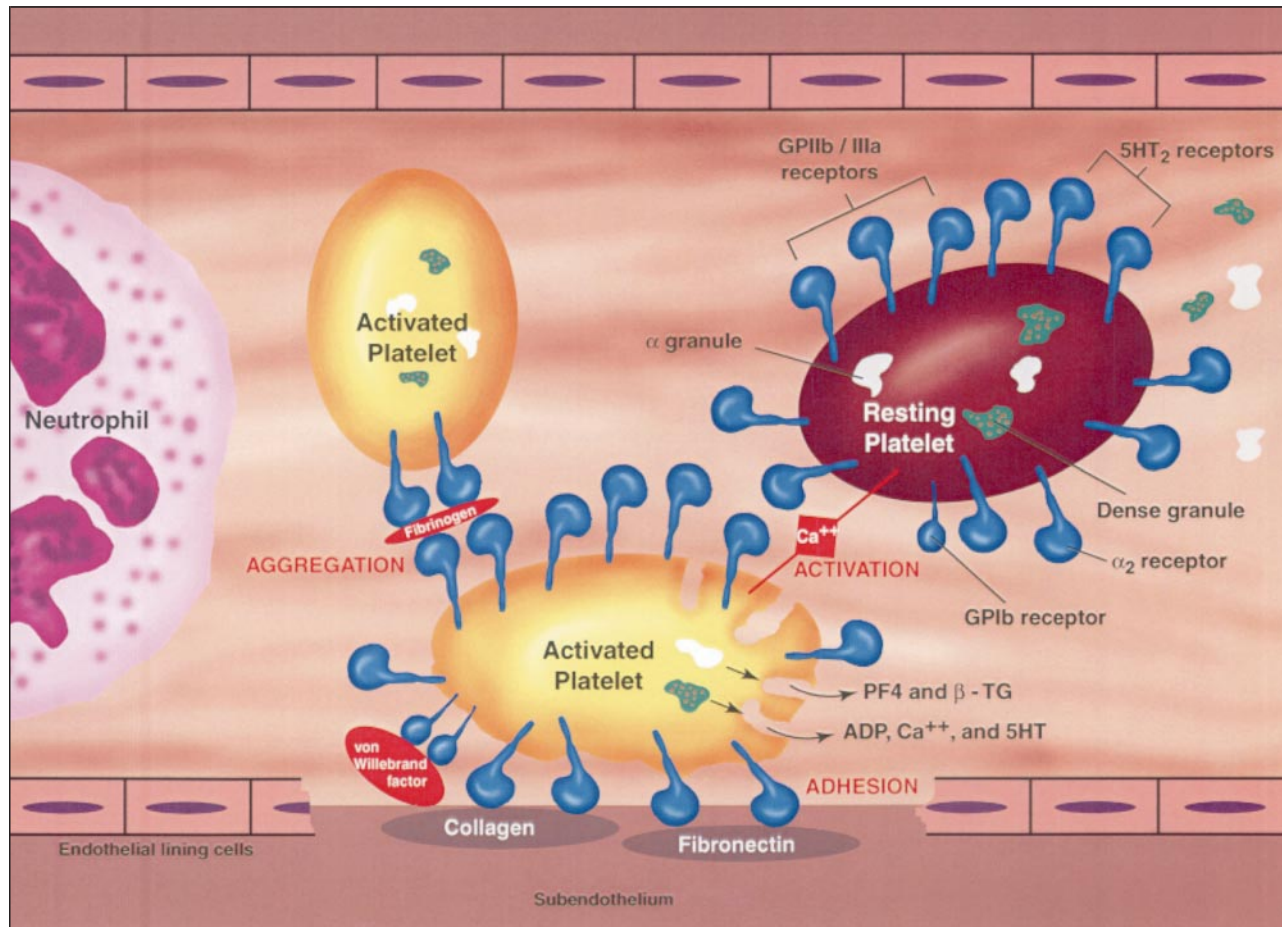

Figure 2. *Platelet adhesion to collagen exposed within the denuded area of vascular endothelium has stimulated platelet activation. Activation is accompanied by extrusion of platelet storage granule contents, which recruits other platelets, causes irreversible platelet-platelet aggregation, and forms a fused platelet thrombus. Ca++ indicates intracellular free calcium concentrations; PF4, platelet factor 4; β-TG, β-thromboglobulin; ADP, adenosine diphosphate; and 5HT, serotonin. Adapted from R&D Systems, Minneapolis, Minn. Used with permission.*

In another recent pilot study, 21 patients suffering from comorbid CVD and major depression exhibited increased platelet activation as measured by markedly elevated plasma concentrations of platelet secretion products platelet factor 4 and β-thromboglobulin when compared with 17 healthy control subjects and 8 nondepressed patients with CVD.[148] Although the mechanism(s) responsible remain unknown, we believe that heightened susceptibility to platelet activation and secretion underlies, at least in part, the increased vulnerability of depressed patients to CVD and/or mortality after MI.

Serotonin secreted by platelets induces both platelet aggregation and coronary vasoconstriction, both mediated by $5HT_2$ receptors. Vasoconstriction especially occurs when normal endothelial cell counterregulatory mechanisms of vascular relaxation are defective, as often occurs in patients with CAD.[148-150] Indeed, essential hypertension, elevated plasma cholesterol levels, older age, and smoking, well-known predisposing factors for development of CVD, all contribute to serotonin-mediated platelet activation. Moreover alterations of platelet serotonin-mediated activation have also been described in affective disorders, most notably major depression. Considerable evidence has accrued in the last 2 decades supportive of the hypothesis that alterations in central nervous system and platelet serotonergic function occur in depressed patients.[151]

Serotonin-mediated platelet activation can contribute to the development of atherosclerosis, thrombosis, and vasoconstriction. Even though serotonin itself is a weak platelet agonist, it markedly amplifies platelet reactions to a variety of other agonists such as adenosine diphosphate, thromboxane A_2, catecholamines, or thrombin. By an action on $5HT_2$ receptors, serotonin enhances the extent of platelet aggregation and the release of intragranular products and arachidonic acid metabolites in response to otherwise ineffective agonist concentrations.[150] Such serotonergic platelet amplification occurs at low concentrations attained when serotonin is released from seeping platelets subjected to shear stresses[152] and from platelet activation by contact with an arterial wall lesion.[153,154]

Several investigators have reported increases in platelet $5HT_2$ binding density in depressed patients.[155-159] Moreover, the changes seem to be state-dependent, in that $5HT_2$ binding-site density decreased to control values only in those patients who showed clinical improvement. Depressed patients have been found to exhibit significant reductions in the number of platelet and

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brain serotonin transporter sites as detected by [^{3}H]imipramine hydrochloride binding,[160-163] as well as the more selective ligand [^{3}H]paroxetine hydrochloride.[151,164] The increased $5HT_2$ receptor–binding density and decreased serotonin transporter sites suggest that depressed patients may be particularly susceptible to serotonin-mediated platelet activation and coronary artery vasoconstriction. Decreased numbers of platelet serotonin transporters would potentially hinder uptake and storage of periplatelet serotonin, exposing the increased numbers of $5HT_2$ receptors to serotonin.[165]

Platelets of depressed patients exhibit significantly increased elevations of intracellular free calcium concentrations after serotonin stimulation in comparison with controls.[166-168] Even functionally trivial increases in intraplatelet calcium "prime" the platelet secretion and aggregation response to stimulation by even a "weak" agonist (such as serotonin)[169] or in response to increased rate of blood flow. Thus, platelets with elevated intracellular free calcium concentrations, as observed in depressed patients, would likely exhibit increased activation in comparison with normal comparison subjects under basal conditions or in response to shear-induced aggregation (eg, following an orthostatic challenge). Future investigations will seek to confirm and interconnect the pathophysiological mechanisms of sympathoadrenal hyperactivity, exaggerated platelet reactivity, and alterations in the platelet serotonin system in depressed patients to their propensity for the development of CVD.

TREATMENT

Although some stress management or behavioral counseling programs with CVD patients have been associated with reduced risk of recurrent cardiovascular events[170] and increased rates of long-term (5-year) survival,[171-173] more recent studies report no benefit to patients[174,175] or an even worse outcome for women in comparison with usual care.[176]

Because of fewer potential adverse effects on the cardiovascular system and the lack of lethality in overdose, somatic treatment with selective serotonin reuptake inhibitors (SSRIs) or other atypical antidepressants (such as buproprion or nefazodone) may offer significant advantages in depressed patients with CVD. The cardiac toxic effects of the TCAs and related antidepressants limit their clinical use in patients with CVD. The reader is directed toward excellent reviews on the safety and efficacy of TCAs in patients with CVD.[177,178] Monoamine oxidase inhibitors and trazodone are generally free of effects on cardiac conduction, but, like the TCAs, may cause postural hypotension.[179] Because the SSRIs are newer than TCAs, little systematic research on their efficacy in elderly or CAD patients has been performed, including large-scale, randomized, treatment trials of post-MI patients with comorbid major depression.[180,181] A recent randomized, double-blind multicenter study compared the efficacy of nortriptyline and paroxetine in depressed patients with ischemic heart disease.[182] Both antidepressants were effective in the treatment of depression but, not surprisingly, there were more dropouts because of adverse effects and more cardiac-related effects with the TCA. The ongoing SADHART study, a randomized, multicenter, double-blind trial of sertraline vs placebo in the treatment of post-MI patients with comorbid major depression, seeks to determine the efficacy of this antidepressant in the depressed post-MI patient. Although these agents may be as effective as TCAs in depressed patients with CVD, their safety is not well established in this patient population.

Psychotherapeutic and/or psychopharmacologic treatment of the 15% to 23% of post-MI patients who fulfill the criteria for major depression, as well as those with significant dysphoria but subsyndromal depression, may have a significant effect (positive or negative) on both medical morbidity and mortality. Although the belief that the outcomes of CVD patients may be improved if their comorbid depressive symptoms are treated is tantalizing, the patient's perspective and preferences must be respected. Feelings of sadness are an expected response to painful life experiences, including being informed that one has a diagnosis of heart disease or has experienced an MI. These feelings may be coupled with reactions of shock, disbelief, anxiety, and other responses. Many patients would not agree that their persisting "sadness" or "loss of interest" constitutes a depressive syndrome. However, when these symptoms are of such a magnitude and duration that they fulfill *DSM-IV* criteria for major depression, a clinician's threshold for psychotherapeutic or psychopharmacologic intervention is reached, given the increased morbidity and mortality of depressed CVD patients. Because of advances in medical management of CVD patients, therapeutic trials determining improvement in survival must be quite large[176]; for example, the 22-month CAST trial was composed of 1489 subjects.[139] Such experience cautions against the raising of hopes toward demonstrating improving cardiac outcome via antidepressant treatment of depression in patients with CVD. Yet, awaiting the completion of a large-scale mortality trial similar to the CAST may not be appropriate given the interpersonal, social, and medical burden of depression and early indications of SSRI efficacy in depressed CVD patients. After short-term treatment with paroxetine or fluvoxamine, depressed patients exhibited no changes in HRV.[119] The only currently known cardiac effect of SSRIs is severe sinus node slowing, to date reported in only a few cases.[183,184] There have been some reports of alterations of hemostasis[185-187] and platelet aggregation[188] following treatment with fluoxetine. Because serotonin has been implicated both in platelet aggregation and coronary artery vasoconstriction, it is of paramount importance to determine whether the SSRIs, widely used to treat major depression, produce effects on platelet function. Because of inhibition of cytochrome P450 isoenzymes, SSRIs must be used with caution, particularly in those patients receiving medications metabolized by the P450 2D6 isoenzyme (such as lipophilic β-blockers and type 1C antiarrhythmics [encainide, flecainide, mexiletene, and propafenone]) and the P450 3A4 isoenzyme (such as calcium channel blockers and warfarin).[189]

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FUTURE DIRECTIONS FOR RESEARCH

The principal unanswered questions in this field remain primarily prognostic, etiologic, and treatment-related: By what mechanisms does dysphoria and other depressive symptoms affect the cardiovascular and thrombotic systems—and will treatment of depression prevent or reduce CVD? Investigative strategies would include additional prospective studies of post-MI patients with comorbid depression. Because sociodemographic and medical variables do not reliably identify post-MI patients who are depressed while hospitalized nor predict those who will become depressed soon after hospital discharge,[190] identification of certain so-called biologic markers associated with depression (such as hypothalamic-pituitary-adrenocortical axis or sympathoadrenal system hyperactivity) might accurately identify those CVD patients with prodromal or subsyndromal depressive symptoms vulnerable to complications or even early death after MI. Certainly such investigations will determine whether such biologic alterations in depressed patients with CVD normalize after effective psychiatric treatment, and whether such change is associated with diminished morbidity and mortality of post-MI patients.

Other prospective studies might scrutinize biologic markers in depressed patients (without CVD); longitudinal follow-up of these patients (and fluctuations of such markers) over time could determine their utility as markers for the development of CVD. These biologic markers include platelet reactivity and markers of systemic inflammation,[191,192] as well as certain components of HRV, myocardial ischemia, or ventricular instability, particularly in those persons who respond to mental stress with depressive symptoms.[190]

Future studies should focus on women to assess gender-specific psychosocial and physiologic measures.[193,194] Despite the fact that women are more vulnerable to depression and that CVD is the leading cause of death among adult women in the United States, relatively little research has focused on the etiology and pathogenic mechanisms of major depression among women with CVD.[190,195] Which treatment modalities (psychotherapeutic vs psychopharmacologic or a combination) will be most effective in patients with recurrent or more severe depression remains to be determined. Commonly used SSRIs might be more effective and more easily tolerated than TCAs in patients with CVD, particularly in elderly patients. Treatment studies may also assess the relationship between depression and subsequent compliance with medication and risk factor modification for CVD.[32]

Illumination of the interplay between central nervous system, platelet, and cardiovascular processes, particularly in those patients with CVD and major depression, will undoubtedly lead to the development of new treatment modalities that will not only improve these patients' quality of life but potentially decrease their morbidity and improve long-term survival rates.

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