Published in final edited form as:
Rev Bras Psiquiatr. 2010 June ; 32(2): 181–191.

Pathophysiological basis of cardiovascular disease and depression: a chicken-and-egg dilemma

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Abstract

Objective—To describe the pathophysiological basis linking cardiovascular disease (CVD) and depression; to discuss the causal relationship between them, and to review the effects of antidepressant treatment on cardiovascular disease.

Method—A review of the literature based on the PubMed database.

Discussion—Depression and cardiovascular disease are both highly prevalent. Several studies have shown that the two are closely related. They share common pathophysiological etiologies or co-morbidities, such as alterations in the hypothalamic-pituitary axis, cardiac rhythm disturbances, and hemorheologic, inflammatory and serotoninergic changes. Furthermore, antidepressant treatment is associated with worse cardiac outcomes (in case of tricyclics), which are not observed with selective serotonin reuptake inhibitors.

Conclusion—Although there is a strong association between depression and cardiovascular disease, it is still unclear whether depression is actually a causal factor for CVD, or is a mere consequence, or whether both conditions share a common pathophysiological etiology. Nevertheless, both conditions must be treated concomitantly. Drugs other than tricyclics must be used, when needed, to treat the underlying depression and not as mere prophylactic of cardiac outcomes.

Descriptors

Heart; Depression; Cardiovascular disease; Coronary artery disease; Antidepressive agents/ adverse effects

Introduction

Major depressive disorder (MDD), described by Hippocrates as melancholia 2,500 years ago, was one of the first medical disorders of unknown etiology to be fully characterized as a clinical entity. It is primarily manifested in a triad of symptoms: sadness and its correlates (feelings of worthlessness, guilt and suicidality); lack of pleasure or interest in activities; and low levels of energy, or fatigability. Currently, in the general population, the point prevalence of MDD is about 4% to 7%,[1,2] whereas lifetime prevalence estimates range from

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15% to 20%.[2,3] MDD is more prevalent in women (the female:male ratio is typically 2:1, but it can be as high as 5:2) and its median age of onset is 25 years.[4] Depressed patients have decreased life expectancy, and cardiovascular disease (CVD) may be one possible explanation for the increased risk of premature death in those patients.

Among adults ≥ 20 years old, the prevalence of coronary heart disease is 8.6% in men and 6.8% in women. Among adults at age 60 to 79, the prevalence is 24.4% in men and 15.1% in women. According to data from the National Health and Nutrition Surveys (NHANES), the incidence of myocardial infarction (MI) for white men is about 0.9% at ages 35 to 44 years, 3.0% at 45 to 54 years, 6.1% at 55 to 64 years, and 9.2% at 65 to 74 years. For women, the estimates are substantially lower: 0.3, 1.0, 2.4, and 5.1%, respectively. The sex ratio for incidence of coronary events narrows progressively with advancing age, but the incidence is still higher for men than for age-matched women. The incidence at ages 65 to 94 compared to ages 35 to 64 more than doubles in men and triples in women.[5] But compared to men, women's CVD (cardiovascular disease) risk is increased to a greater extent by some traditional risk factors (such as diabetes, hypertension, hypercholesterolemia and obesity), as well as by socioeconomic and psychologicalfactors.[6]

Despite a long anecdotal link between CVD and depression, this relationship has only been investigated in depth over the past 15 years.[7] The mechanisms linking depression to CVD and cardiac mortality are not yet well established. There are three plausible hypotheses that could account for their co-morbidity, and each of them will be discussed in this article. We will discuss here the pathophysiological basis for the association between depression and CVD and will conclude with a discussion of the impact of pharmacological treatment of depression on CVD.

Method

We selected the most relevant studies in the literature using the PubMed database, with the keywords "heart disease", "coronary disease", "depression", "cardiovascular disease" and "mood disorder". The manuscripts included in this article were selected based on their methodological aspects and the strength of their findings. We addressed this important topic comprehensively in three major areas: 1) the causal relationship between depression and CVD, 2) the pathophysiological basis for that relationship, and 3) the impact of pharmacological treatment for depression on CVD.

Discussion

1. Causal relationship between depression and CVD

A link between the mind and the heart was proposed by William Harvey in 1628. It was only over 300 years later that the aforementioned link was first demonstrated by Frasure-Smith et al., in a study showing that patients who are depressed at the time of an acute myocardial infarction (MI) have markedly elevated mortality as compared with patients who are not depressed.[8]

Since then, more than 200 studies have demonstrated an association between depression and CVD.[9–18] However, the causal relationship between the two conditions remains unclear. There are three hypotheses that can explain that relationship: 1) depression causes CVD; 2) depression is a consequence of CVD; and 3) depression and CVD share common underlying processes.

1) Hypothesis 1: Depression as a cause of CVD—There is compelling evidence that depression is an independent risk factor for both the development of CVD and for worsening prognosis once CVD is established. Depression is linked to metabolic syndrome (MetS) and CVD.[11,16,19–24] as reported by the large INTERHEART multi-centric study. In that study, stress and depression were risk factors for first myocardial infarction (MI) in healthy individuals.[25] The study compared 12,461 acute MI cases with 14,637 matched controls in 54 countries on eight traditional risk factors for coronary heart disease and a composite index of psychosocial factors. The population-attributable risk of the combined psychosocial factors was 33%, with 9% of this attributable to depression. The odds ratio was comparable to those reported for other major risk factors (OR: 1.55; CI 1.42–1.69). After adjustment for geographic and ethnic context, the index remained a strong predictor of MI.

In a prospective cohort study of healthy individuals, current or past (in the previous 12 months) depression increased by 2.7 times the risk of dying from ischemic heart disease.[26] According to other prospective studies with population samples and to case-control studies, depression in patients without coronary heart disease increases the adjusted relative risk for the subsequent development of coronary artery disease 1.5-fold to 2.0-fold.[27–34] A meta-analysis indicated that depression nearly doubles the risk of cardiac events,[11] comparable to the risk conferred by the traditional risk factors, such as dyslipidemia, diabetes and hypertension.[20] Another meta-analysis demonstrated that depression is an independent risk factor for coronary artery disease, with an overall risk ratio of 1.64.[13] Numerous additional meta-analyses examining the role of depression in cardiovascular morbidity and mortality have also demonstrated the correlation between depression and cardiovascular disease.[10,16,35–37]

It is currently evident that depression adversely affects the course of several cardiovascular conditions. Once CVD is established, depression impacts negatively on the prognosis, increasing the risk of both further cardiac events and of mortality. Several randomized studies have shown that depression leads to poorer prognosis in patients with existing CVD. In patients who have had an acute MI, depression is a significant risk factor for recurrent non-fatal MI and cardiac mortality.[19,21,35,36,38–45] In patients with preexisting CVD, depression increases the risk of death by up to 4-fold.[24]

Depression may be the underlying cause of CVD by causing alterations in the heart function and rhythm (with and without the use of antidepressants), by increasing coagulability and platelet aggregation, by predisposing individuals to unhealthy lifestyles, by altering the hypothalamic-pituitary-adrenocortical (HPA) axis, by increasing inflammation, by increasing autonomic tone, and by causing endothelial dysfunction, among other less well-known processes. However, it is not possible to determine whether those conditions are

caused by depression or whether they are part of the underlying co-morbidities. The mechanisms linking depression and CVD will be discussed in due course.

2) Hypothesis 2: Depression as a consequence of CVD—The prevalence of depression after an acute myocardial infarction (MI) is high. About 20% of patients post-MI have depression, and up to 40% of patients have at least one symptom of depression.[46] Another study showed that depression is three times more common in patients after an MI than in the general population.[14] Therefore, it is also possible that depression is a consequence, not a cause, of CVD.

Depression causes a greater increase in the incidence of CVD in women. Conversely, women with CVD seem to experience higher levels of depression when compared to men.[6] In a compilation of 27 studies that reported rates or risks of depression in coronary disease samples,[47] it was observed that all of those studies had reported clinically or statistically significant rates or risks of at least one measure of depression. Concomitantly, among depressed patients, the same compilation showed that, among 47 studies evaluating the risk of coronary disease in depressed patients, 20 reported rates or risks of coronary disease events in depressed samples. All but one study reported at least one significantly increased rate or risk of coronary disease in the depressed group compared to the non-depressed group. Several cross-sectional studies have shown that the prevalence of depression (DSM-IV criteria) in coronary artery disease patients ranges from 15 to 20%,[8,48–51] which is two to four times higher than the prevalence in the general community.

Patients with CVD may become depressed as a reaction to the burden of a co-morbid condition.[12] In that case, the alterations that could explain why depression would lead to CVD (changes in heart function and rhythm, hypercoagulability and increased platelet aggregation, lack of adherence to medication and healthy lifestyles, changes in the HPA axis, and increased inflammation) might be just markers of CVD and not its determinants.

However, studies that used risk adjustment for cardiac and non-cardiac disease burden in their analyses showed that these variables do not appear to eliminate the relationship, supporting the hypothesis that depression is an independent predictor of outcome.[52] Furthermore, depression precedes cardiovascular disease in multiple studies.

3) Hypothesis 3: Depression and CVD share common underlying processes—Depression and CVD may be the consequences of a disseminated vascular disease, causing lesions to the brain and to the heart, due to vascular and subsequent metabolic changes. In addition, the relationships between plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA) and brain-derived neurotrophic factor (BDNF) could be the underlying processes common to both diseases.

It is statistically impossible to prove the direction of causality between depression and CVD.[53] Mosovich et al. have proposed a new model, where depression and CVD share a common underlying cause, and both diseases are possible outcomes of prior stress-related insult to the body.[53] In that model, local and systemic events, mediated by immune

intercellular messengers, would lead to neurotoxicity and disrupted production of serotonin, which in turn would cause depression and increase platelet aggregation.

2. Review of the pathophysiological mechanisms that could link depression and CVD

While the causal relationship between depression and CVD is not clearly understood, a number of associations have been proposed to demonstrate the plausibility and coherence of such a relationship. These include both direct biological and behavioral mechanisms linking depression and CVD.

1) Changes in cardiac rhythms and cardiac autonomic tone—As a result of decreased parasympathetic control and increased sympathetic stimulation due to overstimulation of the HPA axis in depressed patients, those patients present more frequent episodes of ventricular tachycardia,[54] decreased heart rate variability,[54–56] reduced baroreflex sensitivity,[57] increased QT variability,[58] and increased QT dispersion.[59]

Tricyclics have been shown to be associated with increased cardiac risk,[60] by increasing heart rate, weight and insulin resistance, and by inducing orthostatic hypotension, slow intraventricular cardiac conduction and proarrhythmic cardiac activity.[61,62] However, depression by itself, without the use of antidepressants, is associated with increased cardiac sympathetic tone / decreased parasympathetic activity[63,64] and decreased heart rate variability, which have been shown to be associated with increased risk of cardiac mortality.[65] In a Japanese study involving elderly depressed patients, these changes in sympathetic and parasympathetic tone were most evident in men, which could explain the gender differences in the association of depression with morbidity and mortality.[66]

The direct association between rhythm disturbances and depression is not so clear. Most probably, rhythm disturbances that are observed in depressed patients, in the absence of antidepressant use, may be part of another process, such as hypercortisolism, or of disease of the heart itself. Another possible explanation is that the parasympathetic nervous system is directly linked to the etiology of depression,[67] as depressed individuals show less context-appropriate vagal withdrawal.[64]

2) Hemorheologic alterations—Depression and stress are related to sympathetically-mediated changes in blood viscosity and hemoconcentration, such as hematocrit and total plasma protein, which are associated with CVD.[68–74] These alterations, in addition to being mediated by catecholamines (which increase sinus rate, myocardial oxygen consumption and capillary hydrostatic pressure, leading to reduction of plasma volume),[75] are also linked to increases in blood pressure.[76–78]

In a secondary analysis of a randomized trial, we have found that Mexican-American individuals with mild to moderate depression presented hemorheologic measures of stress-related hemoconcentration, and that those measures decreased significantly after 8 weeks of treatment with either fluoxetine or desipramine.[74] In that case, hemoconcentration was at least partially explained by sympathetic nervous system activation.

By increasing hemoconcentration, depression may increase blood viscosity, which leads to a decrease in pressure at vulnerable branching sites of coronary arteries and increased exposure time to atherogenic substances.[76]

3) Increased platelet aggregation—Common to depression and to vascular thrombosis, the serotoninergic signaling pathway is important in the etiology and pathogenesis of both disorders.[79] Brain monoamines play a central role in the genesis of affective disorders, and serotonin potentiates platelet aggregation. More than 99% of the serotonin in the body is found in the dense granules of platelets.[80] The uptake, storage and metabolism of serotonin are similar in platelets and neurons and the same gene encodes for the serotonin transporter in both cell types.[79]

Patients with depression have platelet abnormalities, due to alterations in the serotonin metabolism.[81] In these patients, platelets are more likely to degranulate thrombogenic substances, increasing the risk of CVD. High platelet serotonin levels have been associated with thrombosis, whereas lower levels are associated with increased bleeding.[82] Studies have found contradictory results regarding platelet serotonin levels in depressed patients. Most of the studies showed that platelet serotonin levels are not altered in depressed patients, and few studies observed that only depressed females, not males, have low platelet serotonin levels,[83] which would predispose to bleeding, not to thrombogenesis. Alterations in the platelet serotonin 5-HT2A (5-hydroxytryptamine 2A) receptors may also contribute to increasing thrombogenesis in depressed patients. However, there are discrepancies in the literature. Some studies show that the number of receptors is increased in those patients,[84,85] and others suggest that there is no change regarding the density of receptors.[86] Moreover, the sensitivity of the receptor may be elevated in depressed patients. Some studies showed that depression is associated with a hyperactive 5-HT2A receptor signal transduction system and increased responsiveness of platelets to serotonin.[87–89] However, those findings have not been replicated by others.[90]

By using [^{3}H]-imipramine, studies have been suggested that depressed patients have decreased serotonin transporter (SERT) function in their platelets, which would increase serotonin concentration and increase vasoconstriction and thrombosis.[91] However, studies using [^{3}H]-paroxetine have not replicated those findings.[92,93]

In addition, increased platelet aggregation may be seen in patients with depression, due to decreased platelet and endothelial nitric oxide synthase (eNOS) activity and plasma levels of NO.[94] These decreases in NO may be attributed to the downregulation exerted by C-related protein (CRP), which is increased in depressed patients.[95]

Disturbances in blood clotting proteins regulating platelet aggregation may also be responsible for thrombogenesis. The glycoprotein (GP) IIb/IIIa complex is a receptor for fibrinogen, fibronectin, vitronectin, Von Willebrand factor, and thrombospondin. GP Ib/IX receptors lead to a conformational change and activation of GP IIb/IIa receptors, and the expression of both receptors promotes platelet aggregation. Studies have shown that the expression of GP IIb/IIIa, as well as of GP Ib/IX receptors, is increased in depressed patients.[96–98]

Other explanations for increased platelet aggregation in depressed patients could be increased levels of platelet P-selectin and monoamine oxidase activity.[83] Both substances have been associated with increased platelet aggregation.

In addition to the serotoninergic system, the adrenergic system also regulates platelet function and may be related to increased thrombogenesis in depressed patients. Some studies have shown that these patients have a higher density of platelet alpha-2A receptors, as well as increased sensitivity.[99] In response to adrenaline, increased platelet aggregation may be observed.[100]

Vascular endothelial dysfunction is also associated with increased platelet aggregation and thrombogenesis. Some studies showed a correlation between depression and endothelial dysfunction,[101,102] which in turn can lead to CVD. However, it is unclear whether the dysfunction is caused by the depression itself, the antidepressant therapy or a combination of the two.

4) Behavioral factors—Poor compliance with advice to adhere to a healthy lifestyle (e.g. through adequate diet and physical activity),[103,104] and to take medication that lowers the risk of CVD (such as statins, anti-hypertensive medication and acetylsalicylic acid)[105,106] may also explain why depressed patients had an increased prevalence of CVD. It is also known that depressed patients are more likely to be smokers,[107] which undoubtedly increases the risk of CVD. The Heart and Soul Study, which prospectively evaluated 1017 outpatients with stable coronary heart disease, suggested that the association between depressive symptoms and adverse cardiovascular events is largely explained by behavioral factors, particularly physical inactivity.[18] However, non-compliance and adoption of unhealthy lifestyles may also be mere markers of depression.[108]

5) Alterations in the HPA axis—The association between depression and hypercortisolism has been extensively described. Depression is associated with higher cortisol levels, non-suppression of endogenous cortisol secretion after dexamethasone administration, and alterations in cortisol circadian rhythms.[109–111] These changes in the HPA axis determine important cardiovascular alterations, which can lead to CVD.[112,113]

Cortisol has hypertensive and atherogenic effects, and adversely affects components of the MetS (metabolic syndrome), such as such as diabetes, truncal obesity, hypercholesterolemia, hypertriglyceridemia, increased blood pressure, and elevated heart rate.[114,115] Elevated serial morning plasma cortisol has been associated with moderate to severe coronary atherosclerosis and stenosis.[116,117] In the InChianti Study, a prospective population-based study of older Italians, depression scores (per SD increase: OR = 1.20, 95% CI = 1.02–1.41) and urinary cortisol levels (per SD increase: OR = 1.23, 95% CI = 1.01–1.51) were significantly associated with the presence of metabolic syndrome. The odds of metabolic syndrome in persons with both depressed mood and urinary cortisol excretion in the highest tertile was 1.84 (95% CI = 1.02–3.34) compared to persons with neither condition.[118] Although depressed and non-depressed patients had similar urinary cortisol levels, the association between depression and higher urinary cortisol levels increased the likelihood for metabolic syndrome, which is an important risk factor for CVD.

Cortisol also accelerates insult to vascular endothelial cells, and increases sympathoadrenal activity, which results in vasoconstriction, platelet activation, elevated heart rate and rhythm disturbances. All those changes are highly deleterious to the cardiovascular system, predisposing to atherosclerosis, thrombogenesis and coronary disease.

6) Inflammation—Increased levels of tumor necrosis factor and other proinflammatory cytokines, such as such as C-reactive protein (CRP), fibrinogen, interleukin (IL)-1 and IL-6, are often observed in depressed patients,[119–121] as well as in patients with MetS and CVD. Those substances mediate immune cells' chemoattraction, release of growth factors, muscle cell proliferation and atherosclerosis. At a more advanced phase, they mediate the rupture of the atheromatous plaque. Those substances, released in the depressed state, may contribute to the development of CVD. Depressed patients also present shifts in the relative distribution of T and B lymphocytes,[122] which can contribute to the alterations in the inflammation biomarkers. In the WISE study, women with depression had a 70% higher CRP ($p = 0.0008$) and a 25% higher IL-6 ($p = 0.04$). Depression was a significant predictor of CVD (hazard ratio 2.58, $p = 0.0009$). Both depression and inflammatory biomarkers remained independent predictors of CVD. However, inflammation explained only a small portion of the association between depression and CVD.[123]

However, it is also possible that those immune mediators are the common cause of depression and CVD, via systemic effects or via local endothelial damage and ischemia.[124] A recent prospective study has shown that increased inflammation did not appear to be a likely mechanism for explaining the link between depression and incidence of coronary heart disease.[125]

7) Disseminated vascular disease—Another hypothesis is that both depression and CVD may be the consequences of disseminated vascular disease. This disease would affect not only the heart, leading to CVD, but also the brain, causing depression.[126,127] Depression may be a direct outcome of subcortical brain lesions caused by cerebral atherosclerosis, in patients with underlying disseminated vascular disease. These lesions may disrupt the striatopallido-thalamo-cortical pathways,[128,129] which are involved in the pathogenesis of depression.[129] Therefore, depression, as a metabolic encephalopathy (i.e., a disturbance in cellular metabolism in the brain evoked by conditions of hypoxia, hypoglycemia, oxidative stress and/or inflammation), would be a marker of severe and disseminated vascular disease, of which the most serious outcome would be an MI. In addition, depression may be caused also by blood-borne mediators, such as soluble intercellular adhesion molecule 1 (a cell adhesion biomarker for inflammatory processes), released when disseminated vascular disease is present and targeted against brain structures.[130]

8) Fibrinolytic system and the brain—Recently, dysfunction of the tissue plasminogen activator (tPA)-plasmin pathway has also been suggested as a link between major depression and CVD.[131] tPA is a thrombolytic enzyme, with neuroplastic and apoptotic functions in the brain.[132] Its expression is upregulated in stress,[133] and low levels of tPA have been found in depressed patients.[134] The cleavage of proBDNF to BDNF is regulated by tPA, and low levels of tPA would increase proBDNF and decrease BDNF, which in turn would impair the

regulation of neuronal plasticity and survival, playing an important role in the pathogenesis of depression.

Plasminogen activator inhibitor-1 (PAI-1) is a regulator of tPA, and is also involved in the pathogenesis of CVD. As tPA, it is also regulated by stress,[135] and higher levels of PAI-1 are found in depressed patients.[136,137] Since tPA is regulated by PAI-1, higher levels of the latter would increase proBDNF and decrease BDNF and, therefore predispose to depression. In that case, alterations in tPA and PAI-1 levels would be a common cause of CVD and depression.

9) Menopause—Depression is more prevalent in women. After menopause, their risk for coronary disease increases and becomes closer to that of men. It is therefore worth considering the possibility that depression might be an epiphenomenon, essentially a surrogate marker for female sex and postmenopausal age, which could by themselves explain the observed association between depression and increased risk for coronary disease. In this scenario it would not be depression *per se*, but estrogen-deficiency, the most important risk factor for coronary disease in postmenopausal women. However, this line of reasoning is flawed, as studies have shown that depressed men are also at higher risk for coronary disease than non-depressed men, which favors the hypothesis that depression is important in the pathogenesis of coronary disease in both men[32] and women.

10) Other explanations—Other explanations for the increased risk of CVD in depressed patients are reduced baroreflex cardiac control;[57] endothelial dysfunction;[102,138,139] and a low red blood cell membrane level of long-chain polyunsaturated fatty acids,[140,141] which is observed in depressed patients[142] and is associated with an increased risk of atherosclerosis and sudden death.[143]

In addition, risk factor clustering is frequently observed in depressed patients,[144] as many of them have increased insulin resistance,[145] hypertension,[146,147] visceral fat accumulation,[148] diabetes[149] and low levels of homocysteine.[150] Obesity may predispose to depression in women,[151,152] but not in men.[151]

The short allele of a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been shown to predict depression.[153–155] A study has shown that carriers of that allele have an increased prevalence of depression, and have higher levels of 24-hour urinary norepinephrine excretion.[156] These increased levels of norepinephrine would enhance sympathetic nervous activation, which would then increase cardiac risk.

3. Impact of pharmacological treatment of depression on CVD

In a few uncontrolled studies, serotonin reuptake inhibitors (SSRIs) have been shown to have the opposite outcomes of those of tricyclics, by reducing cardiac risk.[157,158] However, randomized placebo-controlled trials failed to show cardiac benefits in patients using antidepressants.

The SADHART (Sertraline Antidepressant Heart Attack Trial) study was the first trial to investigate the safety and efficacy of sertraline treatment of MDD in patients with CVD. Patients with MDD and either acute MI or unstable angina were randomized to receive sertraline 50 to 200 mg or placebo for 24 weeks. Sertraline was safe and effective in treating severe depression, and did not change cardiac function. When evaluated regarding efficacy in preventing post-MI cardiovascular events, the sertraline group was not superior to placebo in preventing cardiovascular outcomes (death, myocardial infarction, congestive heart failure, stroke, and recurrent angina).[159]

In the Myocardial Infarction Depression Intervention Trial (MIND-IT), 91 depressed patients post-MI were randomized to a 24-week, double-blind, placebo-controlled trial with the SSRI mirtazapine. Antidepressant treatment did not alter long-term depression or improve cardiovascular outcomes (cardiac death or hospital admission for documented non-fatal myocardial infarction, myocardial ischemia, coronary revascularization, heart failure or ventricular tachycardia) in depressed post-MI patients in 18 months of follow-up.[160]

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial compared the efficacy of citalopram (an SSRI) with interpersonal therapy in patients with coronary artery disease. Citalopram was superior to placebo regarding efficacy of depression treatment, and interpersonal therapy had no advantage over clinical management (a shorter, 20-minute supportive intervention).[161] The authors of that study suggested that an SSRI plus clinical management should be considered as a first-step treatment for patients with coronary artery disease and major depression. That study showed no 12-week increased risk of cardiovascular events for citalopram, similar to placebo.

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study[162] was designed to evaluate the effects of psychosocial intervention in depressed cardiac patients. This type of intervention did not change the incidence of cardiac events, but did improve depression scores. Moreover, patients who did not respond to cognitive behavioral treatment nor had severe depression received sertraline or other antidepressant drug on a non-randomized basis. In an uncontrolled secondary observational analysis, the authors showed that the treated patients had a 42% lower incidence of death or recurrent MI.[158]

SSRIs seem to have a better profile as regards to adverse effects, and safety, than tricyclics. However, one should be aware of the effects of SSRIs on platelet aggregation. Patients on SSRIs may have increased bleeding due to those effects,[163] and these drugs should be used with caution, especially when anticoagulants are also being used.

By 2011, the study known as UPBEAT (Understanding Prognostic Benefits of Exercise and Antidepressant Treatment), which is randomizing 200 patients with elevated depressive symptoms to exercise, treatment with sertraline (an SSRI), or placebo for 4 months, will provide further insight on the roles of SSRIs in heart rate variability, vascular function, inflammation and platelet aggregation. Until then, the effect of SSRIs on cardiac outcomes is unknown – probably null, given the published results of large randomized trials.[159–161]

Conclusion

There is irrefutable evidence that depression and CVD share common pathways. Both of these conditions are stress-reactive disorders of unknown etiology. Interestingly enough, anxiety traits are also associated with CVD.[164] It is at present statistically impossible to prove which one of these disorders is the cause, and which is the consequence, or whether both share the underlying mechanisms. A better understanding of the heterogeneity of MDD may help clarify its link with CVD. Recently, Kendler et al. have delineated two genetic pathways to depression examining 4,785 twin pairs from the Swedish Twin Registry: 1) a group of high familial loading for MDD, which consists predominantly of patients with early age of onset, and 2) a group of high familial loading for vascular disease, which consists predominantly of patients with late age of onset.[165] Thus, it would be possible that all three previous hypotheses may not be exclusive. Most likely, the causal relationship varies among patients: in some, depression is the underlying disease, in others, it is the consequence of a heart condition, and in the remainder, both depression and CVD are part of a broader underlying process. Figure 1 summarizes the relationships between depression and CVD, as well as their pathophysiological basis.

In our opinion, this chicken-and-egg dilemma is far from being solved. To minimize morbidity and mortality, it is crucial to understand that MDD and CVD are frequently co-morbid and that both conditions should be treated concomitantly, as the treatment of depression improves the patient's quality of life and their adherence to a regimen of medication for CVD. Although there is preliminary evidence supporting the idea that the treatment of MDD with serotonin reuptake inhibitors (SSRIs) may be useful to reduce the risk of CVD and death, especially in those patients with recurrent and severe depressive symptoms, convincing evidence based on large, randomized control trials is clearly needed. Until such evidence becomes available, is it not justifiable to prescribe SSRIs as a prophylactic for depression in non-depressed patients with CVD.

Acknowledgements

Our work has been supported by NIH grants GM61394, RR017365, MH062777, RR000865, RR16996, HG002500, and DK063240, and by the Australian National University.

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Disclosures

Writing group member	Employment	Research grant[1]	Other research grant of medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Gilberto Paz-Filho	Australian National University	NH	-	-	-	-	-
Julio Licinio	Australian National University	NIH	-	-	-	-	Editor of the Molecular Psychiatry and the Pharamacogenomics Journal
Ma-Li Wong	Australian National University	NIH	-	-	-	-	-

* Modest

** Significant

*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author

Note: NIH = National Institutes of Health.

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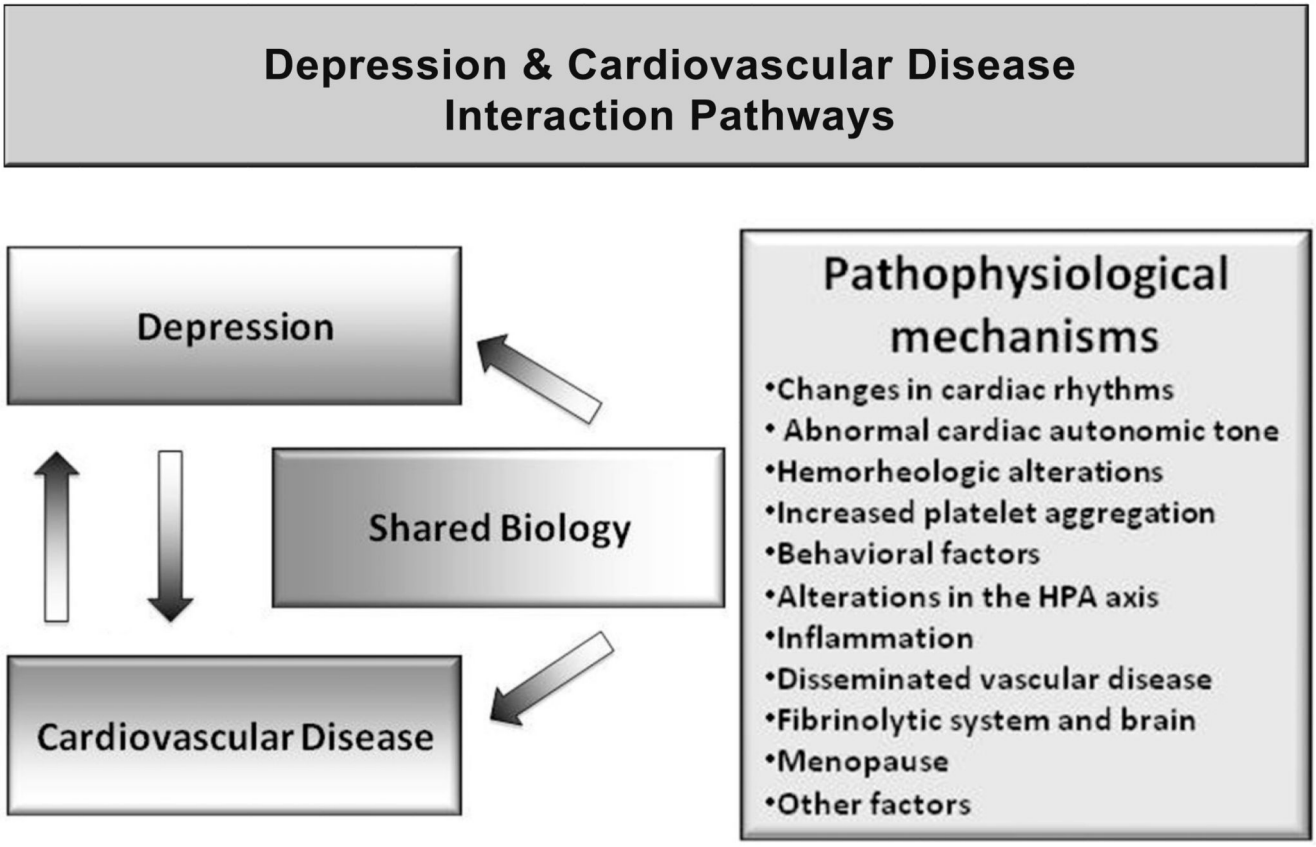

Figure 1.
A proposed conceptual framework for the pathways connecting depression and cardiovascular disease with a summary of the pathophysiological basis for such connections.