Broken heart: depression in cardiovascular disease

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Heart disease and depression are among the most common diseases seen in developed countries. The relationship between heart disease and depression has been the subject of both popular interest and scientific research. Sadness is often portrayed as a feeling of heaviness in the chest or as a "broken heart." Interestingly, as we learn more about the expression of emotions, it appears that these perceptions may simply be the language representation of somatic feelings. Large, prospective, longitudinal studies that have examined the relationship between depression and development of coronary artery disease (CAD) have shown that depression is a risk factor for the development of CAD. Depression also increases mortality in patients with stable CAD or myocardial infarction compared with patients without depression. The recent Sertraline AntiDepressant HeARt attack Trial (SADHART) has shown that selective serotonin reuptake inhibitors like sertraline can be safely used in patients with depression following myocardial infarction. There is also intriguing evidence that treating depression with antidepressants may improve outcomes, including mortality.

Dialogues Clin Neurosci. 2003;5:167-174.

Heart disease and depression are among the most common diseases seen in developed countries. The relationship between heart disease and depression has been the subject of both popular interest and scientific research. Sadness is often portrayed as a feeling of heaviness in the chest or as a "broken heart." Interestingly, as we learn more about the expression of emotions, it appears that these perceptions may simply be the language representation of the somatic feelings. In this article, I will review the scientific literature on the relationship between heart disease and depression. (For a more comprehensive discussion, the interested reader is referred to an article by Jiang et al[1]). There are three questions that I will address: first, whether depression is a risk factor for heart disease; second, whether depression can worsen the prognosis of heart disease; and third and finally, the treatment of depression in the context of cardiac disease. The cardiac disease that is the most common and where the literature is the clearest is coronary artery disease (CAD). The focus of this article will thus be primarily on this condition.

How common is depression among cardiac patients?

Depression is not a surprising finding after an acute medical event such as a heart attack. What is a surprise is that the frequency is not higher. Cassem and Hackett[2] found depressed mood to be common in 50% of patients immediately following a myocardial infarction (MI). What is of interest is that this is persistent, ie, more than 70% of patients remain depressed a year after the event. Not only was the depression present, but it also had functional consequences such as being related to inability to return to

Keywords: *depression; myocardial infarction; heart disease; sertraline; mortality*

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work or previous activities, sexual difficulties, and readmission to hospital. This risk of developing depression was highest among patients who had prior episodes of depression.[3] Those with a prior history of major depression account for 44% to 56%[4] of post-MI patients with major depression. Dovenmuehle and Verwoerdt[5] found that, among cardiac patients who experienced moderate-to-severe depressive symptoms, what was interesting was the absence of expected biological symptoms of depression. This is seen when more formal evaluations for depression are conducted.

More formal psychiatric evaluations for diagnosing disorders based on standardized criteria report lower rates. Carney et al[6] examined 50 patients with documented CAD (by coronary angiography); they found the prevalence of major depression to be only 18%. Similarly, Schleifer et al[7] performed structured psychiatric interviews in 283 patients admitted for MI 8 to 10 days after infarction and then again 3 to 4 months later. Initially, nearly a fifth met criteria for major depression, but nearly half the patients met diagnostic criteria for either minor or major depression. The persistence of depression was also documented: 3 to 4 months later, a third of patients continued to meet criteria for depression, including 75% of those who had initially met criteria for major depression. To summarize, depressive symptoms are common, but full-blown major depression is seen only in 20% of patients. This depression is persistent.

What are the risk factors for the development of depression among cardiac patients?

The risk factors that have been identified include negative life events unrelated to the cardiac condition and lowered subjective or perceived social support.[8] Another possible risk factor is the development of silent ischemic strokes in critical regions of the brain.[9] We and others have shown that these strokes are common as people age, and that, when these strokes occur in critical regions of the brain such as the orbital frontal cortex (OFC), they can lead to depression.[10] The OFC is important in regulating mood, and impairment in OFC function can lead to persistent problems with negative reinforcement making an individual vulnerable to depression.[11]

Can depression early in life lead to cardiac disease or can you die from a broken heart?

This is an intriguing question. *Table I* summarizes results of large studies that have attempted to address this question.[12-20] All these studies were longitudinal in nature. The first study was a 12-year follow-up in a group of Swedish women.[12] The first US population study was reported in 1993, with a similar follow-up duration, but a much larger sample that included both men and women.[14]

An illustrative study is that of Ford et al,[19] who prospectively followed all male medical students who entered

Study	Age (years)	Follow-up (years)	RR*
Hallstrom et al[12]	38-54	12	Severity of depression, predicted angina only
Appels and Mulder[13]	39-65	4.5	RR=2.28 for nonfatal MI; no association with fatal MI
Anda et al[14]	45-77	12.4	RR=1.5 for depressive affect
Aromaa et al[15]	40-64	6.6	RR=3.36
Wassertheil-Smoller et al[16]	≥60	4.5	Deaths: RR=1.26 MI or stroke: RR=1.18 MI: RR=1.14, but not significant*
Barefoot and Schroll[17]	50	24	Death: RR=1.59 MI: RR=1.71
Pratt et al[18]	>18	13	MI: RR=4.54 for major depressive episode MI: RR=2.07 for dysphoria
Ford et al[19]	26±2	37	MI or CAD: RR=2.12
Mendes de Leon et al[20]	65-99	9	Mortality: RR=1.03

Table I. Studies of the relationship between depression and prognosis of coronary artery disease (CAD), in people without preexisting CAD. *Adjusted for multiple factors (varies between studies, in general age, conventional cardiovascular risk factors, such as smoking, cholesterol, weight, or body mass index, and physical conditions at entry of the study). MI, myocardial infarction; RR, relative risk.

Johns Hopkins Medical School from 1948 to 1964. At entry, the students completed a questionnaire about their personal and family history and health status, and underwent a routine medical examination. They were followed yearly with a variety of questionnaires. The lifetime prevalence of clinical depression in this population was 12%. Clinical depression was associated with an almost twofold higher risk for later CAD. The usual risk factors, such as smoking, alcohol use, body mass index, baseline cholesterol level, hyperlipidemia, hypertension, and diabetes, were all examined. The study also addressed the question of whether there was a temporal relationship between CAD and depression. Just showing an association between depression and CAD is insufficient. The question is how long after depression develops one can demonstrate a risk for CAD. Ford suggested a broad range from 1 year to 44 years. The one major limitation was that the study was confined to men.[21]

However, Hallstrom et al[12] had similar results in a study of a community sample of women. Their study was conducted in a wide age range of women between 38 and 54 years in Gothenburg, Sweden. The women were followed for 12 years for the occurrence of angina pectoris, MI, and death. Clinical depression was again associated a higher risk for angina pectoris. The study did not show a clear relationship between depression and other cardiovascular outcomes.

Of particular importance is the Epidemiologic Catchment Study (ECA). This study was conducted by the National Institute of Mental Health (NIMH) to assess the incidence and prevalence of psychiatric disorders in the USA.[18] A structured psychiatric interview, the Diagnostic Interview Schedule, was used for the clinical diagnosis of major depression according to *Diagnostic and Statistical Manual of Mental Health Disorders, Third Edition (DSM-III)*[22] criteria. There were 5 sites in the initial study. One of the sites in Baltimore followed up patients 13 years later. Patients with major depression had a 4.5-times higher risk of suffering a heart attack than did those without major depressive disorder. Even depressed mood alone increased the risk for MI. The finding that dysphoria alone correlated with significantly increased relative risks[13] for heart attack during a 13-year follow-up is extremely interesting and brings up the question of whether it is clinical depression that is important and needed, or would just minor features of depression suffice in increasing the risk for CAD. There are also negative studies that have shown no relation between depression and the development of CAD.[16,20,23,24] Some of these showed effects in one gender, but not in the other. For example, in the Established Populations for the Epidemiological Studies of the Elderly (EPESE) project,[20] there was an association between depressive symptoms and CAD in women, but not among men. The fact that women develop CAD at an older age than men might explain the results of this study. Also, the effect seems to be less as people age, suggesting that this relationship may be more evident when depression is seen in younger populations.[19]

What we do know is that the preponderance of evidence suggests that depression and possibly (modest levels of evidence) just feeling sad may increase the risk for CAD. Although the studies suggest that depression occurs before the onset of clinically significant CAD, it is possible that atherosclerosis, which is the basis of CAD and is known to begin at very young ages, may precede clinical depression or may arise at the same time.[25] Therefore, the possibility that both diseases may have a common origin remains open.

Why would depression increase the risk for CAD?

The most parsimonious explanation is that depression reduces motivation and that individuals do not take care of their general health, and this leads to the increased risk for depression. In support of this, it is noted that depressed patients exercise less,[26,27] eat poorly, do not take aspirin,[28-30] smoke more, and in general exhibit behaviors that increase the risk for cardiac disease. A more interesting explanation is that depression increases platelet aggregation. Increased platelet aggregation, which plays a significant role in coronary occlusion, is another recently uncovered biological abnormality in depression.[31] Depressed ischemic heart disease patients showed elevated β-thromboglobulin levels, increased plasma levels of platelet factor 4, and increased expression of the platelet surface receptors for glycoprotein IIb/IIIa and P-selectin compared with non-depressed subjects.[32] It is possible that these factors play a mediating role on the effect of depression in the development of CAD.

Can depression increase the chances of dying?

Dying from a broken heart is a common tale and one that is accepted in the stories and literature of all cul-

tures. But what is the scientific evidence? *Table II* summarizes the results of several studies investigating the relationship of depression and mortality in patients with recent MI (<2 months).[4,33-39] These studies clearly document that depression increases the risk of dying among patients who have just had an MI. The relative risk ratio attributable to depression differs among studies, but it is clear that depression increases the risk of dying among patients who have just had an MI. The relative risk ratio for dying within 6 months among post-MI patients with versus without major depressive disorder was reported as 3.1 both by Schleifer in 1989[34] and by Frasure-Smith in 1993.[37] At 1 year, the relative risk ratio ranges remain high. The long-term impact of major depression on mortality after MI has not been as well studied. Frasure-Smith et al[38] showed that the mortality rate of patients with major depression remained elevated at 18 months, but not after adjustment for cardiac risk variables.

Of particular interest is the finding that subclinical depression (Beck Depression Inventory [BDI] score ≥10) increases mortality after MI. This raises the question of whether the criterion-based diagnosis is the predictor or whether just the symptoms were sufficient. It also raises the question of whether there is a particular profile of symptoms necessary, or if just the will to live is the factor. Besides mortality, the factor that is of interest is other cardiac events. The data for cardiac events are sparse. Ladwig et al[40] noted that depressed post-MI patients had a threefold higher rate of chest pain than nondepressed patients. This could reflect angina or just increased awareness of pain, but it probably contributes to increased costs due to the need for increased assessment.[28,41-43] Few studies have evaluated mortality following CAD rather than MI. Carney et al[44] noted the relative risk of a cardiac event was 2.2 times higher in patients with major depression compared with no depression. Barefoot and Schroll[17] from Duke University in their study of 1250 patients who had undergone their first angiogram noted that the Zung Depression Scale score was significantly associated with increased risks for cardiac mortality and all-cause mortality. Moderate-to-severe depression increased the odds of cardiac death by nearly 70%. Even mild depression increased the odds by 38% compared with nondepressed patients. The effect was most pronounced in the first year and then decreased over the next 4 years, and then remerged.

Study	n	Follow-up (months)	RR*
Stern et al[4]	68	12	7.5 (OR)
Schleifer et al[34]	282	6	3.1
Ahern et al[35]	265	12	-
Ladwig et al[36]	552	6	4.9 2.8
Frasure-Smith et al[37]	222	6	3.1
Frasure-Smith et al[38]	218	18	6.64
Frasure-Smith et al[39]	896	12	3.66
Kaufman et al[33]	361	12	2.33

Table II. Studies of the relationship between depression and prognosis in coronary artery disease (CAD), in people with preexisting CAD. RR, adjusted relative risk ratio for mortality after myocardial infarction with versus without depression; OR, odds ratio.

Can depression provoke ischemia?

A recent study evaluated the impact of depression on ischemia using a laboratory model. Mental stress, which can be provoked by a number of strategies, such as asking an individual to speak publicly, do mental arithmetic, etc, has been shown to provoke ischemia that can be reliably measured. Patients with established CAD and depressive symptoms showed more ischemia during mental stress testing.[45] Another way is to look for silent ischemia during daily living. During the day when subjects with CAD are evaluated using Holter monitoring to record ischemic events, it is not uncommon to find evidence of ischemia of which the patient is unaware. A recent study used a rating scale to show that sadness and feeling tense is associated with the silent ischemia.[46] This suggests that even emotions within the normal range can play a role.

Why would depression lead to increased chances of dying?

Patients with depression have been found to have elevated plasma norepinephrine, increased heart rates, and reduced heart-rate variability.[28,47-50] Reduced heart-rate variability has been associated with increased mortality in both CAD and chronic heart failure.[45,51] In fact, an association between ventricular arrhythmia and depression has been noted. Clearly, motivational problems due to depression probably play a role by reducing adherence to medical treatment and possibly by increasing platelet aggregation. All these factors could also play a role in increasing mortality. The best evidence so far is that there is an interaction with ventricular arrhythmia and depression.[37]

Can we treat depression in heart disease and will it affect prognosis?

First, it is important to know that treatment studies are very limited. Second, it is important to note that the treatment of depression in this context remains limited. Only 10% to 25% of those with CAD and major depression receive treatment.[34,52] There are essentially three ways to treat depression in cardiac patients: psychotherapy; medication; and, in rare cases, electroconvulsive therapy. The evidence for safety and efficacy for these treatments is limited. Veith et al[53] in a small study of 24 depressed patients with chronic heart disease showed that depression was significantly improved with either imipramine or doxepin, but not placebo, after 4 weeks of treatment. However, imipramine, doxepin, and other tricyclics may not be the best option. Imipramine can, for example, induce severe orthostatic hypotension, especially in patients with impaired cardiac ventricular function.[54] These drugs also have quinidine-like cardiotoxic side effects. This can be seen as QTc prolongation, conduction delay, and block of the AV conjunction and bundle branches, and can lead to atrial or ventricular arrhythmia, ST-T abnormalities, and death.[55,56] These factors were illustrated by a recent comparison of the selective serotonin reuptake inhibitor (SSRI) paroxetine with nortriptyline.[57,58] Both drugs were effective in treating depression. However, 25% of the patients on nortriptyline terminated the study early because of adverse events, compared with 5% of those on paroxetine. Also, cardiac events were more frequent among patients on nortriptyline (18%) compared with paroxetine (2%). Moreover, other antidepressants, such as tianeptine, are also known to be free of deleterious cardiovascular effects and interactions in polymedicated patients due to lack of action on cytochrome P-450; tianeptine can thus be freely administered in depressed patients with concomitant cardiovascular disease.

The data on newer drugs are very limited, as are the data with regard to treatment of depression following MI. A large, randomized trial has been recently completed, the Sertraline AntiDepressant HeARt attack Trial (SADHART), in which 369 patients from 40 sites were identified at hospitalization for an acute MI or unstable angina. They were enrolled within 30 days of diagnosis of acute coronary syndrome[59]; 64% were male; 74% had MI. The primary (safety) outcome measure was change from baseline in left ventricular ejection fraction (LVEF); secondary measures included surrogate cardiac measures and cardiovascular adverse events. Patients were randomized to sertraline or placebo. There was no minimum Hamilton Depression (HAMD) score for entering the study. The mean baseline HAMD score was 19.6±5.3. A prespecified population was identified for evaluating the efficacy of sertraline. These were patients with a HAMD score >18 and two previous episode of depression. The study lasted 24 weeks. On the Clincial Global Impression (CGI) scale, sertraline was more effective than placebo (P<0.05). The CGI-Improvement responder rates for sertraline were significantly higher than for placebo in the total sample (67% vs 53%). For the efficacy evaluable population, the effect of sertraline was more clear.[59] Sertraline had no significant effect on mean LVEF, treatment-emergent increase in ventricular premature complex (VPC) runs, QTc interval >450 ms at end point, or other cardiac measures. Mortality, rehospitalization, and occurrence of peripheral edema were all numerically lower in patients on sertraline compared with those on placebo. The incidence of severe cardiovascular adverse events was 14.5% with sertraline and 22.4% with placebo. The study was not powered to detect a reduction in cardiac events. The results of the trial provide the first evidence that depression can be treated following an MI with an antidepressant. The ENhancing Recovery In Coronary Heart Disease (ENRICHD) study[60] examined the efficacy and safety of cognitive behavioral therapy (CBT) in depression as well as patients with low social support after MI. This study showed that CBT was effective in treating depression following MI, but did not reduce cardiac events. Another study provided some support to the notion that treating depression may improve cardiac outcomes.[61] This was a case-control study of depressed patients who were receiving antidepressants, electroconvulsive therapy, or both. Both MI and all-cause mortality were lower among patients who were adequately treated for depression compared with the inadequately treated patients.

Several recent studies have assessed the effects of SSRIs on platelet activity and heart-rate variability in depressed patients, with or without heart disease.

Serebrauny et al, with other members of the SADHART group including my own group, have recently shown that, consistent with previous reports from the Columbia, Pittsburgh, and Emory groups, platelet activation increased in depression is reduced by sertraline. A significant advantage for sertraline over placebo was seen for B thromboglobulin and P-selectin.[62]

SSRIs appear to reduce the platelet aggregation in a vari-

ety of studies that have examined platelet function.[63-66] It is possible that one of the mechanisms by which SSRIs have a benefit is by their effect on platelet aggregation.

Conclusion

Depression is common among patients with heart disease. It increases the risk of developing CAD. It also worsens the prognosis of patients following MI or even in those with CAD. The recent antidepressant study has clearly shown that we can treat depression following an MI. The overriding imperative should be to recognize depression as early as possible and intervene appropriately. It is critical to continue to investigate whether the treatment of depression can improve the poorer prognosis in patients with CAD. ❑

"Corazón roto": depresión en la enfermedad cardiovascular

La cardiopatía y la depresión están entre las enfermedades más frecuentemente observadas en países desarrollados. La relación entre la cardiopatía y la depresión ha sido motivo de interés tanto de la población general como de la investigación científica. La tristeza a menudo es representada como un sentimiento de pesadez en el pecho o como un "corazón roto." Es interesante considerar que a medida que se tiene un mayor conocimiento acerca de la expresión de emociones, pareciera que estas percepciones pudieran ser simplemente la representación, mediante el lenguaje, de sentimientos somáticos. Grandes estudios prospectivos y longitudinales que han examinado la relación entre depresión y desarrollo de enfermedad coronaria (EC) han mostrado que la depresión constituye un factor de riesgo para el desarrollo de EC. La depresión también aumenta la mortalidad en pacientes con EC estable o infarto al miocardio en comparación con pacientes sin depresión. El reciente ensayo SADHART (Sertraline AntiDepressant HeARt attack Trial) *ha mostrado que los inhibidores selectivos de la recaptación de serotonina como la sertralina pueden utilizarse con gran seguridad en pacientes con depresión post infarto al miocardio. También hay interesantes constataciones que indican que el tratamiento de la depresión con antidepresivos podría mejorar su evolución incluyendo la mortalidad.*

Cœur brisé : dépression dans la maladie cardio-vasculaire

La cardiopathie et la dépression font partie des maladies les plus courantes des pays développés. Les liens entre cardiopathie et dépression intéressent tant le grand public que la recherche scientifique. La tristesse est souvent représentée comme un sentiment de pesanteur dans la poitrine ou comme un « cœur brisé ». De façon intéressante, notre meilleure connaissance de l'expression des émotions suggère que ces perceptions puissent être la représentation par le langage des sensations somatiques. De grandes études prospectives, longitudinales qui ont étudié la relation entre dépression et développement de la maladie coronaire (MC) ont montré que la dépression est un facteur de risque pour le développement de la MC. La dépression majore aussi la mortalité chez les patients atteints de MC stable et chez les patients atteints d'infarctus du myocarde comparés aux patients non dépressifs. L'essai récent SADHART (Sertraline AntiDepressant HeARt attack Trial) *a montré que les inhibiteurs sélectifs de la recapture de la sérotonine comme la sertraline pouvaient être utilisés en toute sécurité chez les patients ayant eu une dépression après un infarctus du myocarde. D'intéressantes constatations indiquent que le traitement de la dépression par les antidépresseurs pourrait améliorer l'évolution, y compris la mortalité.*

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