Psychiatric Disorders and Cardiovascular System: Heart-Brain Interaction

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Abstract

Depression and anxiety are psychiatric disorders that often coexist with coronary artery disease (CAD) and other cardiovascular diseases (CVD). Both depressive symptoms and anxiety are currently recognized as risk factors for CAD and CVD, and present complex pathophysiological processes that seem to adversely influence the prognosis of patients with these comorbidities. These symptoms include hypercortisolism, sympathetic hyperactivity, complex platelet abnormalities, immune activation leading to inflammatory response, common genetic factors and association with behaviors that predispose to cardiovascular disease. Strategies for treating depression such as using selective serotonin reuptake inhibitors (SSRI), have the potential to contribute to reducing the risk of acute coronary events. From a clinical perspective, instruments and protocols for screening and evaluating depression and anxiety are intended to counteract the negative effects of these disorders on the quality of life and cardiovascular health.

Keywords: Cardiovascular diseases; Mental disorders; Coronary disease

Introduction

Patients with psychiatric disorders have mortality rates two to three times higher than the general population, including cardiovascular diseases (CVD) – primarily responsible for this information. These include the coronary artery disease (CAD)³.

Depression and anxiety are highly prevalent in patients with CAD and other CVD. Despite being frequent, these psychiatric disorders are usually ignored²³. They have also been considered independent risk factors for CAD and CVD and believed to change its natural history⁴⁵. Early identification and effective treatment of these disorders may contribute to the increased survival of patients with heart diseases⁶.

This review is intended to discuss the prevalence and impact of depression and anxiety in patients with CAD or other forms of CVD. It discusses the mechanisms by which they change the prognosis of CVD. In addition, the instruments for screening and handling patients with CAD and concomitant depression will be addressed.

Epidemiology

CAD is the leading cause of death and disability in the world, including in developed countries⁷⁸. It is estimated that, each year, about 935,000 people in the United States have acute myocardial infarction (AMI) and approximately 1/3 will die as a result of AMI. In 2011, one in seven deaths in the United States was due to CAD, which has an annual mortality rate higher than
Depression is a mental disorder with high incidence. It is estimated that 5.8% of men and 9.5% of women experience at least one episode of depression throughout life and its prevalence corresponds to 14.6% and 11.1% in developed and developing countries, respectively. According to the World Health Organization (WHO), more than 340 million people suffer from depression worldwide and in 2020 it will be the second leading cause of lost years of healthy life.

The National Comorbidity Survey revealed that anxiety disorders are the most common mental disorders in the general population. One in four people meets the diagnostic criteria for an anxiety disorder with a prevalence rate of 18.1%. One-year prevalence for phobias is 8.7%; for generalized anxiety disorder, 3.1%; and panic disorder, 2.7%. United States data reveal that the prevalence of panic disorder is 2.1% in 12 months and 5.1% over life, mainly in women and in the age group of 20 to 29 years.

Based on that study, literature review of papers published on PubMed, Medline and Google Scholar up to November 2, 2015 was conducted. The following terms were used: major depression, anxiety, panic disorder, cardiovascular disease and coronary heart disease. The combined search of all terms resulted in 1418 papers. The filters were: manuscripts of international relevance, published after 1995. Through the review of abstracts, papers were excluded if they did not address the issue or if they were repeat papers, resulting in 79 manuscripts, which were the subject of this review.

Depression
Depression is a term used to describe a variety of clinical phenomena. According to Manual Diagnóstico e Estatístico dos Transtornos Mentais, 5a ed. (DSM 5), the two main symptoms of major depression are depressed mood and a markedly diminished interest or pleasure in nearly all activities that once motivated the patient (anhedonia). For the existence of a major depressive episode to be confirmed, at least one of these main symptoms must be present and be accompanied by other typical symptoms, totaling at least five symptoms. The minimum duration of a depressive episode is two weeks.

<table>
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<tr>
<th>Chart 1: Diagnostic criteria for depression</th>
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<tr>
<td>1. Depressed mood during most of the day, nearly every day.</td>
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<tr>
<td>2. Markedly reduced interest or pleasure in all or nearly all activities for most of the day, nearly every day.</td>
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<td>3. Significant weight loss or gain (about 5%) without a specific diet or decreased/increased appetite nearly every day.</td>
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<td>4. Insomnia or oversleeping, nearly every day.</td>
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<td>5. Psychomotor retardation or agitation, nearly every day, observed by others.</td>
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<td>6. Fatigue or loss of energy, nearly every day.</td>
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<td>7. Feelings of worthlessness, self-devaluation or excessive guilt, nearly every day.</td>
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<td>8. Difficulty thinking, concentrating or making decisions, nearly every day.</td>
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<tr>
<td>9. Recurring death thoughts/desire; ideation, planning or attempting suicide.</td>
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The symptoms cause clinically significant social and occupational distress or problems. The symptoms are not better explained by general medical condition, use of drugs or substances.

Source: adapted from Manual diagnóstico e estatístico de transtornos mentais: DSM 5.
Five or more of the following criteria must be present for at least two weeks and must characterize a change in previous functioning. At least one between criteria (1) and (2) must be present.

**Depression and CAD: a two-way connection?**

Epidemiological studies indicate that depression is disproportionately more frequent among patients with CAD with an estimated prevalence between 20% and 40%.[15] It is also reported that depression is prospectively associated with an increased risk of developing CAD over life.[16] Regardless of the direct or indirect effects on CAD, early recognition and treatment of coronary artery disease patients are known to be important, as they can contribute to restoring the quality of life and promoting well-being.[17]

CAD often coexists with depressive disorders. It is possible that this comorbidity does not reflect just a random co-occurrence of two independent diseases with high prevalence.[15] Controlled study indicated that some depressed populations have an increased risk of CVD and are at risk of death three times greater than paired control groups.[18]

Depressed patients have risk 1.6 times higher than those not depressed of presenting cardiac event in the first 24 months after diagnosis of CAD[19] and are significantly more likely to die in the year following diagnosis.[20] Rugulies[21] examined 11 cohort studies evaluating the association between depression and CAD, finding that people with depression had a 2.5 times higher risk of AMI or death from coronary causes than the general population.[21] A recent cohort was confirmed increased risk of AMI in patients who met the criteria for depression.[22]

Epidemiological evidence also support the existence of an association between depression and increased mortality after AMI.[23] A follow-up study for 60 months in 158 patients who had AMI revealed that major depression was a significant predictor of mortality and adverse cardiac events.[24] Another follow-up study with 896 patients showed that the increased risk was not only restricted to patients with major depression. The severity of depressive symptoms during hospitalization, assessed using the Beck Depression Inventory, showed a dose-response relationship with mortality of cardiac origin. Even patients affected by relatively mild depressive disorders at the beginning of follow-up, showed increased cardiac mortality five years later.[25] Welin et al.[26], in turn, followed 275 patients who had their first AMI and found that the increased risk of mortality associated with depressive symptoms at baseline was noticeable nine years later.[26]

In recent years, there has been increased evidence that depression is not only more prevalent in patients with CVD than the general population; it is also a risk factor for the development of CVD and is associated with poor prognosis in patients with CAD[23-26].

As depression appears to be a significant risk factor for cardiac mortality and/or morbidity, both in healthy people and in those with CVD, it has been suggested that the relationship between the two could be casual.[27] However, one cannot simply say that a disease causes the other, but the mechanisms by which CVD can contribute to the development of depression and vice-versa should be clarified.[28]

The main mechanisms proposed are: 1) hypercortisolism; 2) sympathetic hyperactivity; 3) complex platelet abnormalities leading to thrombotic phenomena; 4) activation of the immune system promoting inflammation; 5) common genetic factors; and 6) association of depression with behaviors that predispose to CVD (Figure 1).

1. **Hypercortisolism**

Hypercortisolism is caused by conditions that chronically activate the hypothalamic-pituitary-adrenal (HPA) axis and usually occurs in major depression, panic disorder and generalized anxiety disorders, and may accelerate the development of CVD.[29] In response to stress, hypothalamic neurons containing corticotropin releasing factor (CRF) increase the release of adrenocorticotropic hormone (ACTH) and other products from the anterior pituitary gland. A significant proportion of patients with major depression have hyperactivity evidence of the HPA axis, such as high levels of CRF in the cerebrospinal fluid, non-suppression of cortisol secretion after administration of dexamethasone and hypercortisolism.[30-32] Chronically high cortisol levels tend to damage vascular endothelial cells and accelerate the development of atherosclerosis and systemic hypertension.[31,33] In addition, the hyperactivity of the HPA axis enhances sympathetic mechanisms, resulting in increased levels of circulating catecholamines, inflammatory markers, endothelial dysfunction and heart rate variability.[31]
2. Sympathetic hyperactivity
Depression often co-exists with sympathetic hyperactivity. Thus, in combination with chronically high levels of cortisol, sympathetic hyperactivity could contribute to the fast development of atherosclerosis. The sympathetic excitation mechanism in patients with depression or anxiety disorder remains unclear, but an autonomic deregulation can increase sympathetic nerve activity, leading to left ventricular dysfunction, has been proposed. Using direct cardiac catheterization techniques with noradrenaline isotope dilution, it was demonstrated that the activity of the cardiac sympathetic nervous system in patients with depression follows a bimodal distribution, with high levels in some patients (about 30%).

3. Platelet abnormalities
The negative effects of depression on CVD can also be measured by abnormal platelet function. Depression has been associated with complex functional alterations of platelets, such as increased concentrations of glycoprotein IIb/IIIa functional receptors and hyperactivity of 2a serotonin receptor signal transducing system. These findings are of great interest, considering the role that the abnormalities of the serotonergic systems are believed to have in the pathophysiology of depression. Depressed patients also have decreased platelet aggregation in response to serotonin.

4. Activation of the immune system
Depression may also contribute to the development of CVD via alterations of the immune system. Depressed patients have high levels of inflammatory markers and depression is associated with increased C-reactive protein (CRP) and fibrinogen. Individuals with depressed mood have higher plasma levels of interleukin-6 (IL-6), interleukin 1 (IL-1) and CRP.

5. Common genetic factors
There is evidence on the genetic contributions common to depression and CAD. In studies with twins, both depression and CAD showed genetic contribution. McCaffery et al. investigated both diseases combined and the genetic correlation was 0.42, indicating that nearly 20% of the variability of depressive symptoms and CAD could be attributed to common genetic factors. The authors concluded that the co-variation of depressive symptoms and CAD can be partially attributed to common genetic vulnerability.

6. Behavioral factors
In addition to the direct pathophysiological effects, depression may indirectly contribute to the onset of CAD through its known association with behaviors that place individuals at increased risk for developing CVD. In general, patients with depression may live with unhealthy lifestyle habits, tending to be less physically active.
active and more prone to smoking and alcohol abuse – situations that are known to be risk factors for the development of CVD and AMI.

**Screening depression in patients with CAD**

There is no consensus on the need and the ideal method of screening depression in patients with CAD. The American Heart Association, in a concerted effort with the American Psychiatric Association, recommend routine screening for depression in all patients with CAD.

The recommendations made by the American Heart Association committee were summarized in Chart 2.

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**Chart 2**

**Recommendations of the American Heart Association**

Routine screening of depression in patients with CAD in different contexts, including hospitals, clinics and doctors' surgeries and in cardiac rehabilitation centers.

Patients whose screening results positive should be examined by a qualified professional in the diagnosis and treatment of depression.

Patients with heart disease who are being treated for depression should be continuously monitored for adherence to treatment, efficacy of pharmacotherapy and safety to cardiovascular and mental health.

It is essential to coordinate cardiovascular and psychiatric treatments in patients with comorbid conditions.

Source: adapted from Lichtman et al.

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The screening tool recommended in the report of the American Heart Association (AHA) is the Patient Health Questionnaire (PHQ-9). The AHA recommends that the first two items of the PHQ-9 be asked to the patient. If the answer is yes to one or both questions, the other items should be asked. Scores ≥ 9 appear to represent greater likelihood of depression among adults in the general population, with sensitivity of 77.5% and specificity of 86.7%, which should be referred to a psychiatrist.

**Anxiety and panic disorder**

Normal anxiety has an adaptive function, representing a signal that motivates the individual to act in situations that require an intervention. Anxiety is said to be pathological when there are exaggerated or inaccurate assessments of the supposed danger.

The main anxiety disorders listed in ICD-10 are: social phobia, obsessive-compulsive disorder, specific phobia, panic disorder to (with and without agoraphobia) and generalized anxiety disorder, the latter two being the most related to increased risk of adverse cardiovascular and cerebrovascular events.

The central manifestation of panic disorder is the panic attack itself: an episode of acute anxiety accompanied by abundant physical symptoms. Typical physical symptoms are: palpitations, chest pain, choking, shortness of breath, sweating, trembling, sensations of heat or cold, dizziness, nausea or diarrhea, fear of losing control or going crazy and sensation of imminent death.

The main symptom of generalized anxiety disorder is apprehensive expectation or exaggerated concern. Patients report feeling excessively worried most of the time.

**Anxiety, panic disorder and CAD**

The relationship between anxiety and CAD is not as studied and understood as depression. However, it is currently possible to establish an increased incidence of cardiovascular events in individuals with this disorder.

A meta-analysis involving 20 prospective studies with an average of 11.2 years follow-up has shown that individuals with generalized anxiety disorder are at increased risk of CAD and cardiovascular death, regardless of demographic variables, biological risk factors and health behaviors.
Recently, a large prospective study associated anxiety with increased incidence of CAD. A study with nearly 50,000 men evaluated for anxiety showed that the diagnosis of any anxiety disorder was strongly associated with CAD and AMI during 37 years of follow-up with HR: 2.17 (CI 95%: 1.28-3.67) and 2.51 (CI 95%: 1.38-4.55), respectively\textsuperscript{53}. In other studies, generalized anxiety disorder was associated with increased risk of recurrent cardiovascular events and cardiac death\textsuperscript{54,55}.

A cohort study involving more than 57,000 individuals diagnosed with panic disorder concluded that there was a significant increased risk of AMI in patients younger than 50 and CAD in all age groups\textsuperscript{56}.

In 2015, a meta-analysis proposed correlating panic disorder and the incidence of CVD in patients with no evidence of coronary impairment\textsuperscript{57}. That study included papers on intrinsic factors for cardiovascular disease that could be changed, such as heart rate variability\textsuperscript{58}, QRS complex changes and QT interval on electrocardiogram\textsuperscript{59,60}, reduced flow in the coronary arteries\textsuperscript{61} and microvascular angina\textsuperscript{62}. The analysis of inflammatory cytokines was also positive, with evidence that panic disorder results in a pro-inflammatory state: serum increase was found in 18 of the 20 cytokines evaluated\textsuperscript{63}.

These data indicate that anxiety disorders represent an independent risk factor for CAD, although the pathophysiological mechanisms involved in this relationship cannot be affirmed yet\textsuperscript{64}.

**Mechanisms proposed for a connection between anxiety and CAD**

Some hypotheses capable of justifying the impact of anxiety on the onset or progression of CAD are described in the literature (Figure 2). A study from 2005\textsuperscript{65} reports that from a random telephone survey with noninstitutional population \(\geq 18\) years of age in the United States of America (USA), the authors estimated a 15% prevalence of symptoms of anxiety in the study population.

A cross-sectional study of 2012\textsuperscript{66} with 453 men and 400 women showed that patients with anxiety disorders had an increased risk for cardiovascular events compared to the healthy population.

An additional effect of anxiety on the sympathetic nervous system and hemodynamic control is currently proposed. Hence, there is excessive activation of the HPA axis and the sympathetic nervous system. Release of plasma catecholamine and endothelial damage contribute to the development of atherosclerosis, occurrence of CAD and cardiovascular events\textsuperscript{64}.

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**Figure 2**

Relationship between anxiety and CAD: assumptions that justify the impact of anxiety for progression of CAD.

CAD – coronary artery disease
Rozanski et al. showed that chronic stress and affective disorders evoke central responses, such as hypercortisolism, increased circulating catecholamines and behavioral changes, directly related to cardiovascular outcomes. The authors also showed that the patients had reduced heart rate variation, baroreflex dysfunction and increased variation of the QT interval.

A cohort study of individuals with symptoms of anxiety revealed, after 32 years of follow-up, 402 cases of CAD, including fatal and non-fatal AMI, angina and sudden death. Those with two or more symptoms of anxiety showed increased risk of fatal CAD and sudden death, after multivariate analysis to adjust for confounding variables.

These factors may explain the increased incidence of CAD as well as arrhythmias and sudden death in patients with anxiety disorders (Figure 3).

**Figure 3**
Cardiac response to acute stress: cardiovascular outcomes related to acute episodes of anxiety.

- Increased cardiac reactivity to stress
- Increased baseline heart rate
- Baroreflex failure
- Greater variation of ventricular repolarization

**Treatment of depression and anxiety in cardiovascular disease**

In the current therapeutic setting, the combination of drug treatment with psychotherapy for both depression and anxiety disorder represents an alternative.

From the pharmacological point of view, selective serotonin reuptake inhibitors (SSRIs) are the drugs of choice for treating depression and anxiety. In a meta-analysis of patients with CAD and depression, SSRIs reduced depressive symptoms and demonstrated the potential to improve cardiovascular prognosis. Potential beneficial mechanisms of this class of antidepressants are smaller platelet activation and coronary vasoconstriction.

A case-control study examined the correlation between the use of antidepressants and lower risk of AMI. It also showed that discontinuing the use of SSRIs makes the individuals more vulnerable.

Another class of drugs indicated for the treatment of depression and anxiety disorders are tricyclic antidepressants (TCA). Their cardiovascular side effects...
are well recognized: increased heart rate, orthostatic hypotension, cardiac conduction delay and increased variability of the QT interval.\footnote{72}

A study from 2014, which followed 956 patients with coronary artery disease for 7.2 years, evaluated the incidence of cardiovascular events in those treated with TCA or SSRI, showing that the first class resulted in lower heart rate variability and higher serum levels of norepinephrine compared to the other. At the end of follow-up, the use of TCA was clearly associated with increased mortality compared to SSRI: 52.3\% vs. 38.2\%, respectively. In the same study, the control group had a mortality rate of 37.3\%.\footnote{73}

Another important group of antidepressants are the monoamine oxidase inhibitors (MAOI), whose most worrisome cardiovascular effects are orthostatic hypotension and hypertensive crises, the latter associated with stroke and acute aortic dissection. Because of their profile of adverse effects, they should be avoided in patients with CAD.\footnote{74}

Dual inhibitors of serotonin and noradrenaline reuptake have been recently added to the range of therapies. The first to be used in medical practice is venlafaxine, which is associated with severe cardiotoxicity only if administered in high doses. Left ventricular failure, even in patients with no previous history of CVD, is also reported in the literature.\footnote{75}

Benzodiazepines are drugs for the management of panic and anxiety attacks. In 2014, a study examined the relationship between benzodiazepines and stroke in patients with a history of AMI. The study included 7419 patients and revealed a lack of increased risk of future cardiovascular events using low doses of benzodiazepines after the ischemic episode.\footnote{76}

In addition to drug treatment, it is of paramount importance to prescribe non-drug therapies to improve the prognosis and quality of life of patients, and reduce the risks of progression of CAD and CVD, such as physical activity, especially aerobic exercise and cardiac rehabilitation.

It can be concluded that depression and anxiety are prevalent conditions that present important interconnection with cardiovascular diseases. A better understanding and early recognition of these, as well as greater interaction between cardiologists and psychiatrists can be of great benefit in clinical cardiology care.

\textbf{Potential Conflicts of Interest}
This study has no relevant conflicts of interest.

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\textbf{Academic Association}
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