The Role of Depression in Coronary Artery Disease

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General considerations

The concept of depression encompasses a series of psychopathological disorders that differ in regard to symptomatology, severity, course and prognosis. It is important to individualize these disorders for a better understanding of the following studies and of their diagnostic management.

Major depressive disorder, as defined by CID X ¹ and DSM IV², may have different clinical characteristics (table I). A specifier that may be employed in diagnosing the major depressive episode is the presence of melancholic symptoms (melancholia), whose main characteristic is the loss of interest and pleasure in all or almost all activities and a lack of reactivity to usually pleasant stimuli. In these circumstances, the depressive mood does not improve, not even temporarily, when something positive happens. Yet, at least three of the following symptoms should be present for the diagnosis of major depression to be made: depressive mood qualitatively different from the normal, worsening in the morning, terminal insomnia (to wake up at least two hours before the usual time), psychomotor retardation or agitation, anorexia or significant weight loss (5% of the body weight per month), excessive or inappropriate guilt. Sometimes, however, the depressive disorder is atypical with mood reactivity, i.e., enhancement of the mood in response to real or potential positive events, significant weight gain, increase in appetite, hypersomnia, sensation of heaviness in the upper and lower limbs, in addition to a prolonged pattern of sensitivity to interpersonal rejection resulting in significant social or occupational impairment ³,².

The dysthymic disorder (dysthymia) is characterized by a chronically depressed mood lasting for most of the day, for the majority of days, and lasting for at least two years ³,². The individual may note significant reduction in usual interests and in self-criticism, frequently seeing himself or herself as uninteresting and incapable. As these symptoms become part of daily life, usually they are not mentioned by the patient unless directly inquired about by the physician ³. Minor depression is characterized by depressive episodes of at least two weeks that do not fulfill the 5 criteria required for major depression ². An adjustment disorder with depressive mood, however, is directly associated with identifiable psychosocial stressing factors and occurs within three months of the onset of the stressors and persists for up to 6 months after the end of the stressing factors, not fulfilling the criteria for major depression ³. On the other hand, secondary depression is a direct physiological consequence of a general medical condition or may result from the abuse (or withdrawal) of any substance ².

Studies point to a prevalence of 13% and 5% for major depression and dysthymia, respectively ⁴, and of 23% for minor depressive symptoms ⁵ in the general population. Recent studies show that depression and anxiety play a preponderant role in the genesis and course of cardiovascular diseases (fig. 1). Severe depressive symptoms have been associated with an increase in the risk of the development of acute myocardial infarction (AMI) ⁵,⁶, as well as in early post-AMI mortality ⁵,⁶. The role of stress, excessive preoccupations and aggressive behavior in the development of cardiovascular diseases has also been investigated ⁵,⁹.

The present study aims to address the main features of the association of depression-coronary artery disease (CAD), considering the great prevalence of these two entities in the overall population and their significant impact on patients’ quality of life.

Depression. Risk factor for the development of ischemic heart disease

In a follow-up study of patients with no history of cardiac disease, an increased fatal or nonfatal risk for CAD was demonstrated in the patients with depressive symptoms ⁹. Another study also verified a risk of the development of AMI two times higher in patients with episodes of dysphoria (at least two weeks of deep sadness) and four times higher in those patients with major depression, as compared with individuals with no antecedents of depression ¹¹. In addition, it has been demonstrated that depression is an independent risk factor for the development of ischemic heart disease, even when the risk factors considered traditional (smoking, hypertension, hyperlipidemia, sex, age, obesity, sedentary lifestyle) are controlled ⁵,⁶,¹²,¹³.
Post-AMI depression. Epidemiology (table II) and prognostic factors

Depressive syndrome has been commonly found in patients in the post-AMI period, reaching a prevalence of 45% \(^{14,15}\). Among the patients who developed depressive symptoms, 15% to 33% fulfilled the criteria for major depression \(^{14,16}\). This finding persisted after a 3-month follow-up, in which 33% to 44% of the patients still fulfilled these criteria \(^{14,15}\). Another study carried out with patients in the post-AMI period showed a prevalence of 18% to 27% for major and minor depression, respectively (according to the Research Diagnostic Criteria). From these patients, 77% and 36% still had depressive symptoms after 3 months \(^{14}\). In addition, it was also observed that 17% to 18% of the patients with coronary artery disease angiographically diagnosed, with no history of AMI, have findings of major depression \(^{17-19}\) and 17% of minor depression \(^{19}\). It is described in the literature that patients with associated comorbidities, negative experiences during life and familial history of psychopathologies comprise a risk group for the development of post-AMI depression \(^{15}\) (table II). However, severity of the cardiac disease does not seem to be directly related to an increased risk of post-AMI depression \(^{14}\). Other psychosocial factors that also seem to influence the post-AMI depression are stress, social isolation \(^{17}\), and low educational level \(^{20,21}\) (table III).

Studies have shown that depression is also an important prognostic factor in post-AMI patients relating to a significant increase in CAD morbidity and mortality \(^{7-9,22,23}\). Depression may double the risk for fatal outcomes in individuals in the age range of 40-60 years with cardiovascular diseases \(^{8}\). Reports in the literature show that major depression \(^{7,8}\) and depressive symptoms \(^{8}\) have an important impact on the prognosis of hospitalized patients in the post-AMI period during the first 6 to 18 months \(^{7,8,24}\). This higher risk of

<table>
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<tr>
<th>Table 1 – Diagnostic Criteria  Depressive Episode</th>
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<tr>
<td>✓ Five or more of the following symptoms present during the same period of 2 weeks; at least, one of the symptoms is (1) depressive mood or (2) lack of interest or pleasure in the activities</td>
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<td>✓ Depressive mood lasting for most of the day, almost every day</td>
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<tr>
<td>✓ Marked lack of interest or pleasure in the usual activities</td>
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<td>✓ Significant weight loss or gain (5% of the body weight / month)</td>
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<td>✓ Insomnia or hypersomnia, almost every day</td>
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<td>✓ Thinking and concentration difficulty or indecision</td>
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<td>✓ Sensation of uselessness or excessive or inappropriate guilt</td>
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<tr>
<td>✓ Fatigue or lack of energy</td>
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<tr>
<td>✓ Agitation or psychomotor retardation</td>
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<tr>
<td>✓ Recurrent thoughts about death or suicide ideations</td>
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Adapted from ref. \(^{1}\)

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Fig. 1 – Relation between major depression and cardiovascular disease
death seems to be equivalent to or even higher than that of the already known risk factors for mortality in ischemic heart disease. Studies have shown that an intense depressive symptomatology in the post-AMI period is a very good predictor of mortality 7,8,15,27, even after exclusion of other prognostic factors (left ventricular dysfunction and previous AMI) 7,8. Recent studies suggest that depressive symptoms may influence the functionality of CAD more than the number of impaired arteries 26.

Major depression and the depressive symptoms exert a negative impact, not only on the physical recovery of the patients but also on their functionality. In a follow-up study of patients with CAD, 38% of those who had fulfilled the criteria for major depression returned to work in 3 months, compared with 63% of the patients who had not had previous depression 14.

The association of depressive symptoms and CAD seems to be different between the sexes. Two studies have shown a higher prevalence of depression among women with or without CAD 14,25. An increased trend toward post-AMI mortality in the female sex has also been observed 27. This fact may be related to the occurrence of more severe depression in women with ischemic heart disease 28.

Considering the high prevalence of depression among patients with heart disease, as well as its prognostic impact on CAD, it is important to appraise the depressive symptoms in these cases, because the fact of not recognizing these disturbances implies an even worse prognosis for these patients. It is worth stressing that some patients may have atypical depressive symptoms, either predominating symptoms such as excessive fatigue and pain, or with complaints such as hypersomnia, hyperphagia, weight gain, and restlessness. Another finding that may help in recognizing and diagnosing depressive disorders is the anxiety component. A study indicates that two thirds of the patients with depression have symptoms of anxiety and that this association leads to an increase in the severity and chronicity of the disease, in addition to a decrease in the therapeutical response 29.

### Depression and ischemic heart disease. Mechanisms of association

Two types of mechanisms may explain the relation between depression and cardiovascular disease: the psychosocial or behavioral and the physiopathological mechanisms. The latter involve increase in platelet aggregation, reduction in the heart rate (HR) variability, and alterations in the regulation of the autonomic nervous system and of the hypothalamic-pituitary-adrenal (HPA) axis.

### A. Psychosocial mechanisms

Depressed patients tend to adhere less to medicamentous treatment, to programmed exercises 30, to smoking cessation 31, and to dietary changes 6,7,11. Some studies have also shown a greater prevalence of women and unmarried individuals in the depressed group 6,31,32, in addition to a greater abuse of and dependence on alcohol 11 and tobacco 6. These factors may significantly contribute to the increase in cardiovascular morbidity and mortality in patients with depressive symptoms.

### B. Pathophysiological mechanisms

At least 4 possible factors may be related to the pathophysiological mechanisms: increase in the platelet activity, alteration in the regulation of the autonomic nervous system, decrease in the HR variability, and dysfunction of the HPA axis.

#### 1. Increase in platelet activity

A recent study using flow cytometry showed an increase in platelet activity in depressed patients as compared with healthy individuals. In this study, an increase in the basal platelet activity of 41% in the depressed group was observed. In addition, an increment of 24% in the binding of a specific substance to sites of the platelet glycoprotein IIIa induced by proclotting endogenous ligands, such as fibrinogen (MoAb anti-LIBS1), after changing from dorsal decubitus to the orthostatic position, was also observed 32. Another study also observed a higher platelet activation in patients with CAD and major depression as compared with healthy individuals and nondepressed individuals with CAD, through the increase in the plasma levels of products secreted by platelets 33. The mechanism by which this hyperactivity occurs remains unknown. One hypothesis is related to serotonin (5-HT). Platelet serotonergic stimulus is known to induce platelet aggregation and coronary arterial vasoconstriction through 5-HT2 receptors. This vasoconstriction occurs preferentially when a disorder exists in the regulatory endothelial mechanisms, as occurs in CAD 33,35. Even though serotonin, when isolated, is a weak platelet-aggregating agent, it promotes amplification of platelet reactivity to several substances, such as thromboxane A2, catecholamines and thrombin. In addition, through the 5-HT2 receptors, serotonin increases the area of platelet aggregation and the release of metabolites of arachidonic acid in response to low levels of other platelet agonists 35.

The fact that depressed patients have an increase in the density of platelet 5-HT2 receptors 36-40 and a decrease in the

### Table III – Predisposing factors for Post-AMI depression

| ✓ Associated comorbidities |
| ✓ Negative experiences in life |
| ✓ Prevalence of post-AMI minor depression: 27% |
| ✓ Familial history of psychopathologies |

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| ✓ Associated comorbidities |
| ✓ Negative experiences in life |
| ✓ Familial history of psychopathologies |
| ✓ Stress |
| ✓ Social isolation |
| ✓ Low educational level |
density of platelet and cerebral serotonin transporters has also been described in the literature. Therefore, this causes a greater susceptibility of the depressed patients to platelet activation and to coronary arterial vasoconstriction by serotonergic stimulus through the prolonged exposure of this higher number of receptors to serotonin action.

2. Sympathetic hyperactivity

Several clinical and experimental studies point out that in patients with preexistent CAD ventricular fibrillation is the most common cause of sudden death, which occurs when an electrical stimulus reaches the myocardium during the repolarization period and surpasses the excitability threshold, triggering an electrical myocardial instability. This threshold is decreased in cardiomyopathies, especially in myocardial ischemia. Another factor related to reduction in the excitability threshold, in human and animal models, is the stimulus of the sympathetic nervous system.

Among patients with CAD, those with major depression have a higher prevalence of ventricular tachycardia as compared with nondepressed patients. One study showed a mortality rate five times higher in patients undergoing treatment for supraventricular and ventricular tachyarrhythmias, who had depressive symptoms at the moment of the diagnosis as compared with those who did not have the symptoms. Increase in the plasma levels of norepinephrine in patients with major depression and bipolar affective disorder (depression and mania), as well as high urinary levels of norepinephrine metabolites were also observed when compared with the levels in healthy individuals. Other studies have shown that the presence of melancholic symptoms increases even more the plasma levels of norepinephrine as compared with levels in patients with dysthymia and major depression without history of melancholia. In addition, an 8-times higher mortality rate due to heart disease was found in patients with episodes of melancholia as compared with the general population.

This sympathetic hyperactivity of the HPA axis may correspond to the main mechanism through which depression is associated with an increase in sudden death due to ventricular tachycardia in patients with CAD.

3. Decrease in the heart rate variability

Recent studies have reported that patients with depression have a reduction in the HR variability due to an increase in the autonomic tone. This type of alteration of the HR is an independent risk factor for mortality in post-AMI patients. A decrease in the vagal tone reduces the HR variability and predisposes a patient, therefore, to the development of ventricular fibrillation, findings that were confirmed in animal studies with AMI experimentally induced.

4. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis

It is long established and well known that excessive plasma levels of corticosteroids cause hypertriglyceridemia, hypercholesterolemia, and hypertension. A series of studies reports that alterations in the HPA axis of depressed patients cause high plasma levels of cortisol. The stress status caused by depression may lead to a hyperactivity of the HPA axis due to an increase in the secretion of the corticotropin releasing hormone (CRH) by the hypothalamus and a hyperresponsiveness of the adrenal cortex to adrenocorticotropic hormone (ACTH). Non-suppression of the cortisol secretion after administration of exogenous dexamethasone in depressed patients was observed for the first time by Carrol et al in 1968. The dexamethasone suppression test (DST) is more often altered in melancholic patients than in patients with minor depression or with adjustment reactions. Depressed patients without suppression on the DST have serum levels of noradrenaline significantly higher than depressed patients with suppression on the DST.

Depression and CAD. Therapeutical management

The strong evidence that patients with depressive symptoms more often develop symptomatic and fatal ischemic cardiac events generates the following basic questions: Will the treatment of depression alter these superior indices of mortality and morbidity in depressed patients with CAD? Which is the best antidepressant for the treatment of these patients?

A. Psychosocial treatment

Psychosocial interventions have proved efficient for the emotional improvement of patients and for the reduction in post-AMI mortality. Studies have shown that psychological support in coronary units and stress management programs for post-AMI patients have reduced the depressive and anginal symptoms of these patients. The symptomatic reduction obtained through a psychosocial approach may significantly contribute to the clinical and psychological improvement of these patients.

B. Pharmacological treatment

Tricyclic antidepressants (TAD) have proved to be cardiotoxic, and their most common noxious cardiovascular effect is orthostatic hypotension (table IV). In two previous studies, this noxious effect caused interruption of the antidepressant treatment in approximately 10% of the patients without heart disease and in 25% to 50% of the patients with preexistent heart disease. This orthostatic hypotension caused by TAD is more marked in patients with disorders of heart conduction, mainly bundle-branch block, and in patients with heart failure. Other studies report a strong association between the use of TAD and hip fractures and a 4% increase in the incidence of lacerations and fractures in patients treated with imipramine. In
addition, orthostatic hypotension may be a precipitant factor for AMI and stroke.

Recent studies have shown that TADs have an antiarrhythmic effect similar to that of the class IA agents (calcium channel blockers), such as quinidine (table IV). Therefore, TADs may cause an extension of the QT, PR and QRS intervals in patients with myocardial ischemia and an arrhythmogenic effect or exacerbation of the degree of the bundle-branch block in patients with disorders of heart conduction. The results of the Cardiac Arrhythmia Suppression Trials I and II (CAST I and II) showed that patients after an AMI, prophylactically treated with certain types of antiarrhythmic agents, including class IA agents, showed a morbidity and mortality rate higher than those treated with placebo. Considering this, we may attribute these effects to the TADs, because they also act through that mechanism. It is generally agreed that the use of TADs in the first 2 or 3 months after an AMI should be avoided whenever possible because, during this recovery period, patients are more sensitive to the noxious cardiovascular effects of these drugs.

Due to the lowest potential of noxious cardiovascular effects and to the highest safety of their use even in overdoses, the selective serotonin reuptake inhibitors (SSRIs) may show advantages in the therapeutical management of patients with CAD and depression. Among the drugs of this class are fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram. Incidence of noxious cardiovascular effects of SSRIs is around 0.0003%, ranging from 0.00001%-0.0003%. This could increase the potential cardio toxicity of these drugs. In addition, SSRIs may interfere with the cardiovascular integrity through amplification of the platelet aggregation and vasoconstriction in response to serotonergic stimuli, due to an increase in the serotonin concentration in platelet and cerebral sites.

It is also necessary to consider the risk:benefit ratio of the use of antidepressant drugs in the treatment of patients with CAD and associated depression. For example, studies have shown that SSRIs have antidepressant efficacy similar to that of the TADs in patients under 65 years of age with moderate to severe depression, but little is known about the efficacy of the SSRIs in the elderly and patients with heart disease. On the other hand, TADs have been widely studied and have proved to be greatly effective in the treatment of depression in the elderly. A study in depressed older patients treated with nortriptyline (TAD) or fluoxetine (SSRI) showed a superior index of response in the first group (67% versus 23%), and this index was even higher in the patients who had melancholia (83% versus 10%) .

Another recent double-blind multicenter randomized study compared the efficacy of nortriptyline (TAD) with that of paroxetine (SSRI) in depressed patients with CAD. Both antidepressants showed similar efficacy in the treatment of depression but the patients treated with nortriptyline showed a significantly higher rate of cardiac side effects, such as increase in the heart rate and reduction in the heart rate variability.

Atypical antidepressant agents (with mechanisms of action different from those of the TADs and SSRIs), such as bupropion, venlafaxine, mirtazapine, nefazodone, trazodone, and tianeptine, still lack controlled studies for a better assessment in regard to the safety of use of these drugs in patients with heart disease. Bupropion does not have major effects on myocardial conduction or contractility, but may cause light orthostatic hypotension and increase in blood pressure (BP). Venlafaxine has been associated with an increase in BP and HR, in addition to hypertriglyceridemia. Mirtazapine seems to be a relatively safe drug because the indices of hypertension, orthostatic hypotension and tachycardia reported were similar to those of the placebo group. Until the present moment, there are no reports on cardiac alterations with the use of nefazodone; we stress, however, the need for controlled studies. Trazodone, on the other hand, does not seem to have effects on the cardiac conduction when used in therapeutic doses or even toxic doses; however, there are reports of cases of nonsustained ventricular tachycardia and orthostatic hypotension with the use of this drug. Tianeptine seems to be a relatively safe drug even though there is no study of depressed patients with underlying heart disease.

Evidence exists that the antidepressant treatment in patients with depression and CAD has a significant prognostic impact on the evolution of heart disease. A study reports a higher recurrence of AMI in depressed patients with CAD, who undergo inadequate antidepressant treatment, as compared with those who undergo correct treatment. However, further studies regarding the risk: benefit ratio of the use of the diverse classes of antidepressants in patients with CAD are required for the adoption of standardized therapeutic management of these patients.
References


