

# Heart Failure and Depression, an Often Neglected Combination

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## General Considerations

The rate of depression in the general population with heart failure is 25%, and in patients where this is advanced or serious, depression or depression-anxiety disorder rates are more than 50%.<sup>1</sup>

The association between the onset of depression and a longer evolution of heart disease supports the already classical hypothesis that suffering from chronic stress is a risk factor for depression-anxiety disorder<sup>2</sup>. In these patients, heart disease involves marked emotional stress over several years, with the need to successively adapt to changing physical and psychosocial situations that generally entail a progressive loss of autonomy.

For these reasons, depression is a first-order problem that should be approached within a comprehensive care program for the patient with heart failure patients. However, it is not always viewed in this way. The causes for this imbalance between the real relevance of depression for the patients with heart failure and the actual care they receive are complex. No group of professionals, whether psychiatrists or cardiologists should be blamed; rather, what is needed is to circulate the evidence available on the topic of matter and look for new and robust findings that clarify the real relationship between the 2 diseases and, especially, offer solutions to improve the current situation.

Thus, we draw attention to the work of Guallar-Castillón et al,<sup>3</sup> published in this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA. The authors emphasize the importance that the final prognosis has on detecting depression in an especially vulnerable subpopulation of patients with heart failure, as well as the significance of identifying the clinical risk factors

for depression. Both can be obtained from a good medical record and via the administration of simple scales to quantify depression. This would facilitate beginning therapy with new specific antidepressants that have proved more efficacious than placebo in the treatment of depression and which have very few side effects or interactions with other drugs.

It is known that depression itself reduces the quality of life of our patients, both in those exclusively presenting a psychiatric disease and in those with a medical disease plus a psychiatric disorder.

## Relationships Between Depression and Heart Failure

Regarding heart disease, it is known that depression<sup>4</sup> and anxiety<sup>5</sup> are independent risk factors for the onset of coronary artery disease, and that subthreshold depressive symptoms are also correlated with a greater risk of cardiovascular mortality. A long-term evaluation has even found that a negative state of mind can predict mortality following a myocardial infarction, regardless of the severity of heart disease.<sup>6</sup>

The biological factors that underlie this relationship are based on the multiple changes in neuroimmunoendocrines and proteins that occur in depressive patients in the acute phase of the inflammation. Thus, it has been found that patients with depression experience greater platelet activation which predisposes them to episodes of thromboembolism. These patients also experience immune activation (NK cells, leukocytes, etc) and hypercortisolemia, together with increases in adrenocorticotrophic hormone (ACTH) and ACTH-releasing factor, with less resistance to insulin, as well as an increase in endogenous steroid production and catecholamine release, plus an increase in blood pressure and coronary vasoconstriction.

It is not easy to specify the way in which these factors determine the clinical worsening that increases mortality, however the way it impacts cardiovascular health is well established but in fact their importance regarding cardiovascular health is well-known. From a strictly symptomatic perspective regarding depression in patients with heart failure, some clinical

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characteristics have been associated with a poor vital prognosis, such as appetite loss, weight loss, losing the will to struggle and live, and noncompliance with medical advice. The latter factor is especially relevant, since it can be modified by managing the patient in a suitable and comprehensive manner (medical-psychological) and the patient should always be evaluated concerning the degree of acceptance and compliance with the treatment, lapses regarding medical visits and complementary tests, control over self-care such as blood pressure and diet, tobacco, alcohol and other drug use, and physical exercise.

Finally, there is also evidence that heart failure itself could have a causal relationship with the onset of depression in these patients, since there are areas in the brain, such as the medial temporal region, which are especially vulnerable to perfusion deficits which arise in a heart failure context.<sup>7</sup> It has been known for several decades that these areas are involved in the pathophysiology of depression.

### Diagnostic Difficulties

The close relationship between the 2 diseases, however, does not facilitate its diagnosis. This occurs because, in the first place, the presence of comorbidity would necessitate a meeting point between professionals, which does not always occur, in order to lay the groundwork for such collaboration. Furthermore, psychiatrists and cardiologists still share much common ground: it is believed that the decline in vital status and mood is part of serious heart disease, which can be confused with psychological reactions to life-threatening diseases and with the beginning of a real depressive syndrome. That thus, it is not easy to define the group of emotional changes and “mental schema” aimed at suitably adapting to a disease, and to differentiate this from what is a form of “claudication” or alterations in the functioning of the limbic-cortical cerebral areas, that constitute depression.

Obviously, there are clinical aspects that justify this difficulty, such as the vegetative symptoms characteristic of heart disease identical to those which depressive patients present (weight loss, fatigue, weakness, anorexia, dyspnea, sweating, trembling, etc). Thus, diagnosis should be based on more specific areas of evaluation, such as the state of mind (persistent sadness, hopelessness, lack of affect, i.e., no change of mood in the face of good or bad news) and “cognitive style,” i.e., the type of thinking that the patient presents to us (negative ideas, loss of trust in the future, ideas related to death, not being able to see any way out of the current situation, etc). Another factor that hinders clinical diagnosis is psychomotor slowdown and the “mental dullness” common to both diseases, which is the reason why authors such as

Endicott<sup>8</sup> give more weight to symptoms such as crying, depressed appearance, social isolation, reduced talkativeness, melancholic-self-pitying-pessimistic attitude or lack of response to the environmental events than to the set of somatic symptoms that can accompany depression.

### Evaluation of Depression in Patients With Heart Failure

At present, in addition to the clinical aspects mentioned, instruments are available that facilitate the task of detecting depression in medical patients, or in patients attended to by other specialists. The Hospital Anxiety and Depression (HAD) scale can be used,<sup>9</sup> which has been translated into Spanish and validated regarding its psychometric properties. The questionnaire is self-administered by the patient in a few minutes and can be scored by the physician in less than 1 min. It provides excellent diagnostic performance regarding depression and anxiety disorders, the 2 most common in these patients. The cut-off point to diagnose a “probable psychiatric case” would involve scoring more than 10 points in 1 of the subscales (anxiety or depression).

Although they remain untranslated, 2 brief questionnaires are available which evaluate depression in medically ill patients (Depression in the Medically Ill [DMI]) specifically validated for patients with recent heart disease.<sup>10</sup> The 2 questionnaires, DMI-10 and DMI-18, are largely free of questions specific to medical disease by excluding those related to the physical-somatic aspects of depression.

These simple and reliable questionnaires, together with currently available instruments for measuring the overall quality of life, or this as perceived by the patients,<sup>11</sup> can facilitate the work of the cardiologist regarding a more careful evaluation of the relevant aspects of the prognosis in patients with heart failure and depressive comorbidity.

These instruments can help the clinician who is not an expert in psychiatry to familiarize him/herself with the detection of psychiatric disease in order to subsequently initiate suitable treatment, if necessary.

These issues have been raised because every physician who interacts with several colleagues from other specialties knows how difficult it is to first, detect, and second, to treat, diseases that do not belong to their specialty. Various studies that have a bearing on this issue have demonstrated that many patients with congestive heart failure and major depression had not been treated for their psychiatric disease.<sup>12</sup> It has also been found that quality of life questionnaires can be of great clinical usefulness by showing that factors such as attitude in the face of the disease or social support as perceived by the patient, are those more strongly correlated with depressive disease.<sup>13</sup>

## Considerations Regarding the Treatment of Depression in Patients With Heart Failure

After depression has been diagnosed, an important and difficult factor is how to initiate treatment. The first problem faced by the physician unaccustomed to psychiatric disease in the context of medical disease is that not all the drugs are suitable! Choosing a psychoactive antidepressant that does no or as little as possible harm is a crucial step.

One of the points worth considering is the capacity of drugs used in the normal treatment of the heart failure to produce psychopathological alterations (depression, psychosis, etc) and neuropsychological alterations (delirium or confusion, loss of orientation, changes in attentional functions, amnesia, vagueness, alterations in conceptual relationships, calculation, language functions, etc). Specifically, digoxin can produce neuropsychiatric side effects, even in therapeutic serum concentrations. Neuropsychiatric symptoms include disorientation, confusion, and visual hallucinations (seeing contours or white halos around dark objects, or seeing colors modified by yellow or green tones) up to the induction of states similar to depression.

### *Heart Disease and Psychotherapy*

Cardiac rehabilitation programs have become the key to secondary prevention following episodes of myocardial damage for reducing mortality and improving tolerance to exercise, functional capacity, blood pressure, and symptoms of angina and dyspnea, as well as psychosocial functioning. Most rehabilitation programs contain elements such as physical exercise training, modifying risk factors, providing information, medical supervision, labor rehabilitation and psychological counseling.

The cognitive-behavioral model of psychotherapy is the one most studied in this population and has become the reference model. Cognitive-behavioral psychotherapy is very effective in improving quality of life and reducing the frequency of subsequent coronary events. Studies have found that the psychological treatment of depression in cardiovascular patients does indeed improve quality of life even if, in the worst cases, this does not influence the natural history of disease, and thus should be given high therapeutic priority.<sup>14</sup>

Within this group of psychosocial measures, the attitude of the physician during follow-up visits is crucial. An empathetic attitude, attempting to understand the patient's difficulties regarding compliance with medical advice, their acceptance of their disease, the apparently paradoxical behavior of "not taking sufficient care of themselves," all this helps to improve communication and obtain

information, as well as increasing the patient's confidence in the physician. An example could be as follows: "patient X does not quit smoking, does not lose weight, etc," this normally increases the anxiety of the patient, while increasing the need to deny the existence of disease. Then the physician may get slightly annoyed, and tells the patient (sometimes non-verbally) that the disease is self-induced, that it is the result of an indulgent lifestyle, undisciplined and self-destructive, so the patient feels blamed, abandons the physician and persists in his/her irrational but unstoppable lifestyle.

### *Psychoactive Drugs in the Context of Heart Failure*

Benzodiazepines are the drugs most frequently prescribed in the context of heart failure. These improve well-being and it is thought that they could reduce morbidity in coronary patients. The clinical advantages are due to their anxiolytic effects and their ability to attenuate the physiological response to sympathetic activation. Possible complications arising from their chronic use are: habituation, tolerance, respiratory depression, and excessive sedation.

Buspirone is a non-benzodiazepine anxiolytic that does not give rise to the complications that can occur when benzodiazepines are used chronically. However, one of their main problems is that the therapeutic effect appears 2 weeks after beginning treatment, similar to all the antidepressants. One strategy is to begin administration at the same time as a benzodiazepine or neuroleptic is given and, later, to gradually tail this off when the buspirone begins to take effect.

Antidepressant agents have demonstrated efficacy in the remission of depressive episodes and prevention of later relapse. This double effect, which could be added to the treatment of subacute chronic anxiety disease, makes them the drugs of choice in almost all medical patients with comorbid psychiatric disorder.

Selective serotonin reuptake inhibitors (SSRI) (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram) would currently be the drugs of choice for depression in cardiopathy patients with heart disease. Paroxetine should not be used initially due to its great potential for interacting with cytochrome 3A4 of the P450 cytochrome system, which is the metabolic route of many other psychoactive drugs, immunosuppressants, and other drugs commonly used in cardiology.

There is vast experience with sertraline. Double-blind multicenter studies have shown that sertraline is an innocuous drug and constitutes an effective treatment for recurrent depression in patients who have had a recent myocardial infarction or unstable angina, when

no other life-threatening medical diseases present.<sup>15</sup>

In heart disease secondary to myocardial infarction, it is currently considered that the 6-week wait until beginning antidepressant treatment is reasonable even though, unlike the old tricyclic antidepressants, which had high anticholinergic and arrhythmogenic potential, the new SSRI do not have such cardiotoxic effects.

Indications for antidepressant treatment before 6 weeks following myocardial infarction are: depression with suicidal ideation, the appearance of depressive symptoms during hospitalization in a patient with a background of serious depression, and serious depression that inhibits involvement in rehabilitation or self-care.

Despite their safety, concentrations of warfarin and acenocoumarol should closely be controlled whenever a patient begins SSRI treatment. Citalopram would be the safest to use with these drugs, but there is still insufficient evidence regarding escitalopram.

Currently, the cardiovascular safety and efficacy of SSRI offer clinical advantages in contrast to the old tricyclic antidepressants (imipramine, clomipramine, amitriptyline) and monoamine oxidase inhibitors that require the doses to be carefully adjusted, drug and food interactions controlled, blood concentrations adjusted, serial electrocardiograms done, and blood pressure monitored. For these reason they should never be used as first-choice drugs.

Bupropion is a norepinephrine and dopamine reuptake inhibitor, with a favorable profile regarding cardiovascular side effects, although it would be necessary to monitor hypertension, which is serious in some cases and requires intensive treatment. Treatment with bupropion only or when combined with nicotine-substitution therapy to quit smoking can trigger hypertension.

Venlafaxine inhibits uptake of serotonin and norepinephrine and is a weak dopamine reuptake inhibitor. Its most relevant side effects are sustained increases in blood pressure, especially diastolic, which is dose-related in some patients. However, it does not seem that this drug has adverse effects on blood pressure control in patients with preexisting hypertension.

Mirtazapine affects the alpha-2 adrenergic autoreceptors and increases norepinephrine and serotonin activity. Its side effects are drowsiness, increased appetite, and weight gain. It is a good anxiolytic and sleep regulator if it is administered in low doses in cardiopathy patients.

Trazodone, at 200 mg/day or more, gives rise to conduction problems, ventricular arrhythmias, and orthostatic hypotension. Priapism is a rare side effect.

The decision to begin treatment with antidepressants should be taken by a psychiatrist. Nevertheless, the suitable timing of administering antidepressants after

myocardial infarction is something better decided with the help of a cardiologist. In general, we can say that not all antidepressants are the same and that, until we gain more experience, we should be cautious when administering new antidepressants to patients with heart disease and depression.

Therapeutic success is only achieved when this is perceived by the patient, and not when the physician believes that it has been achieved. Thus, we should work in a multidisciplinary manner such that effective interventions by different specialists can achieve optimal quality of life as perceived by the patient.

## REFERENCES

- Gottlieb SS, Khatta M, Friedmann E, Einbinder L, Katzen S, Baker B, et al. The influence of age, gender and race on the prevalence of depression in heart failure patients. *J Am Coll Cardiol.* 2004;43:1542-9.
- Kupfer DJ, Frank E. The minimum length of treatment for recovery. In: Montgomery SA, Rouillon F, editors. *Longterm treatment of depression.* London: John Wiley & Sons LTD; 1992b. p. 33-52.
- Guallar-Castillón P, Magariños-Losada MM, Montoto-Otero C, Tabuenca AI, Rodríguez-Pascual C, Olcoz-Chiva M, et al. Prevalencia de depresión, y factores biomédicos y psicosociales asociados, en ancianos hospitalizados con insuficiencia cardiaca en España. *Rev Esp Cardiol.* 2006;59:770-8.
- Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med.* 2004;66:305-15.
- Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol.* 2003;42:1801-7.
- Frasure-Smith N, Lesperance F. Depression and other psychological risks following myocardial infarction. *Arch Gen Psychiatry.* 2003;60:627-36.
- Alves TC, Rays J, Fraguas R Jr, Wajngarten M, Telles RMS, de Souza Duran FL, et al. Association between major depressive symptoms in heart failure and impaired regional cerebral blood flow in the medial temporal region: a study using 99tc-HMPAO single photon emission computerized tomography (SPECT). *Psychological Med.* 2006;36:597-608.
- Endicott J. Measurement of depression in patients with cancer. *Cancer* 1984;53 Suppl 10: 2243-9.
- Herrero MJ, Torres X, Blanch J, Peri JM, Pintor L, Bulbena A, et al. A validation study of the Hospital anxiety and depression scale (HADS) in a Spanish population. *General Hospital Psychiatr.* 2003;25:277-83.
- Hilton TM, Parker G, McDonald S, Heruc GA, Olley A, Brotchie H, et al. A validation study of two brief measures of depression in the cardiac population: the DMI-10 and DMI-18. *Psychosomatics.* 2006;47:129-35.
- Parajón T, Lupón J, González B, Urrutia A, Altimir S, Coll R, et al. Aplicación en España del cuestionario sobre calidad de vida "Minnesota Living With Heart Failure" para la IC. *Rev Esp Cardiol.* 2004;57:155-60.
- Koenig HG. Depression outcome in inpatients with congestive heart failure. *Arch Intern Med.* 2006;166:991-6.
- Turvey CL, Klein DM, Pies CJ. Depression, physical impairment, and treatment of depression in chronic heart failure. *J Cardiovasc Nurs.* 2006;21:175-8.

14. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289: 3106-16.
15. Carney R, Jaffe A. Treatment of major depression following acute myocardial infarction [editorial]. *JAMA* 2002;288: 750-1.