Review Article

Depression and Heart Failure

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A healthy mind in a healthy body (νοῦς ὑγιὴς ἐν σώματι ὑγιεῖ - Thales of Miletus). An ancient saying that still resonates powerfully in the modern era for health-related matters. The relationship between body and psyche is a two-way one. When someone is suffering from depression, then the whole body may suffer, with the result that it can be afflicted more easily by diseases and convalescence is more difficult.

Introduction

There is a wealth of literature to confirm the relation between psychiatric disorders and cardiovascular diseases. Most of the initial studies concerned the impact that mental illness, such as chronic stress and depression, may have on the clinical course and outcome of cardiac diseases, including myocardial infarction, worsening of angina, the occurrence of dangerous arrhythmias, and sometimes even sudden cardiac death.[1-3] Apart from the possible unfavourable effects on clinical manifestation and prognosis, depression is recognised by epidemiologists as an independent risk factor for coronary artery disease, with the same weight as smoking, arterial hypertension and hyperlipidaemia.[4]

The concept that depression also exerts an unfavourable effect on heart failure (HF) was not studied and documented until quite a lot later. Depression is a chronic condition, and is associated with a restriction of physical and social function equal to or even greater than that caused by other common chronic disorders. It is also associated with increased mortality. Reviews of the literature confirm that depression is more common in patients with HF than in the general population.[1]

The aim of this review is to describe the relation that may exist between depression and HF. The analysis of this relation was based on various studies and was steered by an attempt to answer three basic questions:

1. What are the pathophysiological mechanisms responsible for this relationship?
2. How should we clinically evaluate this population and what is the prognosis?
3. Prevention and therapy: what is the target?

Pathophysiological mechanisms and causes

The possible pathophysiological mechanisms and aetiological factors for the simultaneous manifestation of the two diseases may be investigated with the aid of various scientific studies. So far, there is a relative consensus among investigators as to the fact that no specific aetiological factor has been isolated, but rather that many factors have been found to contribute to the development of depression in individuals with HF.

In more detail, certain genetic, pathophysiological, psychosocial and environmental factors have been recognised and

designated as possible links in the chain (Table 1).[5-7] An important question that arises from the study of these factors is whether and to what extent depression has an aetiological relationship with the appearance and development of the HF syndrome, or whether it is a coexistent entity and simply one of the many clinical manifestations of the syndrome. From the analysis of the individual factors that arise in turn, it appears that this relationship is a two-way one. Namely, sometimes HF leads to the occurrence and development of depression, and sometimes the same pathophysiological mechanisms lead to the appearance of both conditions. Despite the plethora of data available so far, it seems that further studies are probably necessary for the full investigation of the this relationship.

As regards the genetic factors, recent studies have determined that the same genetic polymorphisms are involved in the development of depression and cardiovascular disease. The G protein beta 3 825T-allele has been connected with depression[8] as well as with arterial hypertension,[9] one of the most significant risk factors for HF. An interaction between the G protein beta 3 825T-allele and the D allele of the angiotensin-converting enzyme gene probably plays a role in the genesis of both diseases.

As regards the pathophysiological factors, an increase in circulating catecholamine levels has been observed in both diseases, with the result that depression is aggravated in patients with HF. A basic common mechanism is the consequent inflammation, with high levels of circulating proinflammatory cytokines, which cause and are caused by the depression syndrome and subsequently play a decisive role in the development of HF.[10] Specifically, increased levels of cytokines, especially interleukin-6 (IL-6), interleukin-1 (IL-1), and tumour necrosis factor alpha (TNF-α), have been found to have an unfavourable effect on cardiac function. Of interest is a study by Parissis et al,[11] who studied the expression of circulating proinflammatory (TNF-α and IL-6) and anti-inflammatory cytokines (IL-10), and of the soluble apoptosis mediator Fas ligand in patients with chronic HF and symptoms of depression. According to the findings of the study, patients with symptoms of depression showed significantly higher levels of TNF-α and soluble Fas ligand, as well as significantly lower levels of IL-10, compared with patients who did not have depression. In the authors' opinion, a dysregulated cytokine network, together with the activation of signalling molecules for the apoptosis mechanism, appears to be involved in the pathophysiology of chronic mental stress and depression in patients with HF.

Table 1. Indicative common pathophysiological mechanisms of depression and heart failure.

- common genetic predisposition
- increased platelet activation
- inflammatory agents
- increased catecholamine levels
- increased serotonin levels
- non-compliance with medication
- deviation from dietary guidelines
- refusal to exercise/sedentary lifestyle
- poor familial and social support
- ischaemia due to stress

A similar study by Ferketich et al[12] investigated the correlation between the proinflammatory cytokines IL-6, IL-1β and TNF-α in patients with and without symptoms of depression, as evaluated by the Beck Depression Inventory (BDI) scale, taking a score ≥10 as the threshold for the presence of depression. After applying appropriate multiple linear regression models, the investigators found that TNF-α had a significant positive correlation with BDI score, as well as with a subparameter of BDI score that estimates the depressive disposition independently of physical signs and symptoms. They concluded that there is a dependency between depression and the activation of proinflammatory cytokines, which may promote disease progression and increase mortality in patients with HF.

In addition, major depression seems to be correlated with disturbances of platelet function, with an increase in the expression of the 5HT2 and IIβ/IIIα receptors, elevated levels of β-TG PF4, and increased calcium mobilisation, contributing to a condition of hypercoagulability and hyperviscosity, which exacerbate HF.[13] Moreover, there seems to exist a broader and more generalised disturbance affecting the immune system, which reinforces immunological stimulation and cellular immunity, as indicated by a disturbance of the T1:T2 lymphocyte ratio; the latter is also correlated with the prognosis in patients with depression and HF.[14]

On the other hand, it has been shown that psychosocial factors, such as stressful everyday situations, non-compliance with drug therapy, deviation from dietary guidelines, refusal to exercise, may unfavourably affect depression, with the additional result of further exacerbating HF.[15]

Finally, environmental factors, such as familial and social surroundings, often contribute significantly to the occurrence of depression in patients with HF. Family members and associates may not understand

the temperament of HF patients and can end up imposing a further emotional burden upon them, with feelings of insecurity and rejection.

Clinical data

Evaluation of depressed patients with HF

The frequent appearance of a depressive symptomatology, as well as its exacerbating effect on the prognosis of patients with HF, means that its diagnosis should be made without delay and patients with such a significant mental disturbance should undergo a thorough evaluation.[16] The diagnosis of a depressive syndrome requires the presence of five or more of the following symptoms, according to the recommendations of the Diagnostic and Statistical Manual of Mental Disorders:[17] a) insomnia or hypersomnia; b) diminished interest or pleasure from activities; c) excessive or inappropriate guilt, feelings of worthlessness; d) loss of energy or fatigue; e) diminished concentration or indecisiveness; f) decrease or increase in appetite and resulting weight loss or gain; g) psychomotor retardation/agitation; h) recurrent thoughts of death, suicidal ideation, or suicide attempt (see Table 2 for mnemonic).

These symptoms should be present almost daily for a period of about two weeks, and at least one of the symptoms should be either bad mood, or loss of interest or enjoyment and should represent a pathological change in the mental sphere in relation to a previously healthy mental state. The evaluation of depression in the patient with HF requires an understanding of the risk factors. These risk factors include: female sex, previous episode of depression, family history of depression, lack of social support, and loss of an important role in life. This information may be obtained during a full interview with the patient.[18]

The official diagnosis of depression is made after the patient is interviewed personally by the psychiatrist; however, there are many available questionnaires that are completed by the patient or the clinical physician with a view to detecting any depressive symptomatology (Table 3).[16] For example, Zung's Self-rating Depression Scale,[19] with the 20 questions shown in Table 4, is one of the most reliable scales and is used in most studies and research. It is also available in more than 30 languages and has wide cultural applications.[20] These study instruments are sensitive to changes arising from depression and are thus useful for the processing and quantification of the depressive burden. Despite these benefits, the greatest risk of diagnosis associated with the selection of depressed patients includes the likely recording of false positive results. In patients with HF, the difficulty in diagnosis is even greater, because the physical symptoms of depression can be confused with the symptomatology of HF. To reduce this danger, patients with a positive depression result should undergo a more through interview with a specialist, in order to confirm or to rule out depression.

Table 2. Symptoms of depression (SIG E CAPS + MOOD mnemonic).

S	sleep (insomnia or hypersomnia)
I	interests (diminished interest or pleasure from activities)
G	guilt (excessive or inappropriate guilt, feelings of worthlessness)
E	energy (loss of energy or fatigue)
C	concentration (diminished concentration or indecisiveness)
A	appetite (decrease or increase in appetite, weight loss or gain)
P	psychomotor retardation/agitation
S	suicide (recurrent thoughts of death, suicidal ideation, or suicide attempt)

Clinical outcome

For almost two decades now, the correlation between depression and cardiovascular disease has been recorded in the international literature.[4,7] Published studies provide ample data that define the relationship between depression and cardiac disorders. There are data highlighting the incidence of depression in patients with coronary artery disease (CAD), showing correlations between depression and mortality in patients with documented CAD and between depression and mortality in populations with and without CAD.[21,22] Significant depression has been reported in 15-22% of patients who suffer from cardiovascular disease, while 65% of the same population show mild symptoms of depression.[2] In other studies, depression has been established as an independent risk factor that contributes to a poor outcome and to mortality in patients with CAD.[23] However, more recent research interest has turned towards the possible connection between depression and HF. From recent reviews of the literature it appears that 5 million Americans suffer from HF and around 400,000 new cases of HF are diagnosed annually, while the incidence of depression among HF patients ranges from 24-42%. Other studies suggest that depression is common in patients with chronic HF, with a prevalence that ranges from 13% to 77%, according to the diagnostic method used and the population characteristics.[24,25]

In Greece, the prevalence of HF reaches 0.3-2%

Table 3. Most important questionnaires for the evaluation of depression in patients with heart failure.

Evaluation scales	Description	Score
Zung Self-Rating Depression Scale (ZSDS)	Provides quantitative evaluation of depression. Includes 20 questions that assess emotional, psychological, and physical "burden". Five of the 20 questions determine physical symptoms.	<50: no depression 50-59: mild depression 60-69: moderate to strong depression >70: severe depression
Beck Depression Inventory (BDI)	Consists of a questionnaire with 21 questions designed to monitor depressive symptoms. Only 5 of the questions refer to physical symptoms, while the remaining 16 reflect non-physical symptoms of depression.	0-13: normal range 14-19: mild form 20-28: moderate 29-63: severe depression
Center for Epidemiologic Studies Depression Scale (CES-D)	One of the most common questionnaires for the detection of depression, which assists in determining the depressive burden.	>20: evaluates depressive feelings and behaviours during the preceding week
Geriatric Depression Scale (GDS).	Consists of 15 questions; developed as a basic measure for the assessment of depression in subjects of advanced age.	0-14: no depression 15-30: denotes depression
Hamilton Depression Rating Scale (HDRS)	One of the most widely accepted scales for the evaluation of depression. Includes 17 questions that assess symptoms of depression that last more than 1 week.	0-7: normal range (or in clinical remission) ≥20: at least moderate degree of depression
Hospital Anxiety And Depression Scale (HADS)	Consists of 14 questions, of which 7 assess anxiety and the remaining 7 assess depression. A basic innovation that comes with HADS is that it can easily rule out symptoms that might arise from other illnesses.	0-7: normal range 8-10: borderline value for depression ≥11: depression

Table 4. Zung self-rating depression scale.[19] The patient's choices are scored in accordance with the numbers given.

Make check mark (√) in appropriate column	A little of the time	Some of the time	Good part of the time	Most of the time
1. I feel down-hearted and blue	1	2	3	4
2. Morning is when I feel the best	4	3	2	1
3. I have crying spells or feel like it	1	2	3	4
4. I have trouble sleeping at night	1	2	3	4
5. I eat as much as I used to	4	3	2	1
6. I still enjoy sex	4	3	2	1
7. I notice that I am losing weight	1	2	3	4
8. I have trouble with constipation	1	2	3	4
9. My heart beats faster than usual	1	2	3	4
10. I get tired for no reason	1	2	3	4
11. My mind is as clear as it used to be	4	3	2	1
12. I find it easy to do the things I used to	4	3	2	1
13. I am restless and can't keep still	1	2	3	4
14. I feel hopeful about the future	1	2	3	4
15. I am more irritable than usual	1	2	3	4
16. I find it easy to make decisions	4	3	2	1
17. I feel that I am useful and needed	4	3	2	1
18. My life is pretty full	4	3	2	1
19. I feel that others would be better off if I were dead	1	2	3	4
20. I still enjoy the things I used to do	4	3	2	1

Scoring: <50 – normal values; 50-59 – mild form of depression; 60-69 – moderate to strong depression; >70 – severe depression.

in the general population and 8-16% in those aged over 75 years, while 1-5 new cases per 1000 population are added each year. At the same time, a large percentage of the general population without cardiovascular disease also seems to suffer from depression. More specifically, a recent study by Panagiotakos et al found that 21% of men and 27% of women had mild depression, while 4% of men and 6% of women had a symptomatology of severe depressive syndrome.[26] As regards the coexistence of depression and HF, although data for Greece are lacking, the international literature in recent years has shown a great focus of research interest, with an increased number of publications involving patients with depression and HF. Vaccarino et al[27] found that 35%, 33.5% and 9% of a sample of HF patients aged over 50 years had mild, moderate, or deep depression (old definition), respectively, while Jiang et al[28] found that 13.9% of patients with HF satisfied the criteria for significant depressive syndrome during an 18-year follow up.

With regard to prognosis, in a meta-analysis[29] that included 36 studies of patients with depression and HF, although there was heterogeneity in the diagnostic methods used for the evaluation of depressive syndrome (self-rating questionnaire, interview with psychiatrist, medical history), in the follow-up duration (from 6 months to 4 years), and in the endpoints (mortality, need for transplant, readmission to hospital), it appeared that patients with depression and HF are associated with a twofold risk of cardiac death and any cardiac event. In another interesting study of prognosis in patients with HF, 302 of the 1006 patients qualified as depressed based on the Beck Depression Inventory (BDI), with a BDI total >10. After a mean follow-up time of 971 ± 730 days, patients with BDI totals 5-9, 10-18 and >19 had 21%, 53% and 83% greater mortality, respectively, compared with those who had a total <5 ($p<0.001$). In this study, too, depression was shown to be an independent prognostic index of mortality, together with advanced age, HF of ischaemic aetiology, a history of diabetes mellitus, and a higher New York Heart Association (NYHA) class.[30]

A recent study by Parissis et al[31] assessed the clinical and prognostic value of depression measurement scales (Beck Depression Inventory, Zung Self-rating Depression Scale) in combination with levels of brain natriuretic peptide (BNP) in patients with HF. A total of 155 HF patients completed questionnaires for the evaluation of depression and functional capacity, and underwent BNP measurement and a 6-minute walk test. They were then followed for 6 months for cardiovascular events, including death from any cause or rehospitalisation for HF decompensation. The authors concluded that patients with HF and symptoms of depression have impaired physical activity associated with excessive hormonal activation. Of the scales and questionnaires studied, the Zung SDS appeared to be an independent predictor of the clinical outcome, especially in patients with elevated BNP levels. The combination of these two methods offers a practical means for risk stratification in patients with congestive HF.

Prevention and treatment

As described above, depressive symptoms in patients with HF are strongly associated with a drop in functional capacity, with an increase in the risk of hospitalisation and high mortality. Given such evidence, experts suggest that reducing the depression load in HF patients can improve their health and quality of life.[32] Even among HF patients who are not depressed, it would be useful and valuable to determine which patients have a high risk of developing depression, in order to make it easier to determine the need for intervention to reduce the incidence of the condition. Recent studies support the concept that depression prevention programmes can be effective and can prevent inauspicious developments.[33]

Psychosocial therapy

The most effective psychosocial therapy for depression is cognitive-behaviour therapy (CBT).[34] CBT presupposes that patients are active participants in the treatment and that there are mutual interactions between events around them, their thoughts, and their behaviour. With CBT, clinical physicians are encouraged to control both thoughts and those events that can lead to depression. Patients are more easily guided to discover their problem, to understand the depressed condition in which they live, with the ultimate aim of taking appropriate measures against it. It appears that depressed patients with HF often have difficulty evaluating their own functional capacity.[35] The clinical physician should assist those patients to reveal the irrational thoughts they often express and should encourage them to counter those thoughts by providing precise information about the real functional possibilities that are associated with their physical and social activity.[36] All such efforts can amelio-

rate the pathological psychological condition and lead to a more positive approach to improving health and quality of life.

Pharmaceutical therapy

Before the selection of an antidepressant drug for a patient with HF, the efficacy, adverse effects, and possible interactions must all be taken into consideration. Specific studies report that there are only slight differences in efficacy, not only between drugs within the same category, but also between the categories themselves. In addition, no difference has been found between the treatment of mild and moderate depression.[37,38] Consequently, efficacy plays a secondary role, while the side effects of antidepressant drugs and their interactions with other medications become of primary importance. This is particularly true in patients with HF, given that they are more likely to be elderly, and to suffer from other morbid conditions whose treatment involves the use of additional medication.[39]

Two large categories of antidepressants are the tricyclic antidepressants and the selective serotonin reuptake inhibitors. The standard tricyclic antidepressants should be avoided because of adverse effects, such as hypotension, arrhythmias, and disturbances of myocardial contractility (Table 5). Hypotension has a special place as an adverse effect of antidepressant drugs.[40,41] In a study by Glassman et al, of the 15 patients with HF who were given imipramine, 7 developed severe orthostatic hypotension. A severe proarrhythmic reaction, resulting in the appearance of life-threatening arrhythmias, has also been reported as a complication of tricyclic antidepressants.[43] Finally, for the patient with HF the effect of an antidepressant drug on myocardial contractility is of particular importance. However, in the small number of patients included in the various studies, antidepressant medications were not proven to have any significant effects on left ventricular contractility.[40,44,45]

Table 5. Side effects of antidepressant drugs on the cardiovascular system.

Hypotension
Hypertensive crisis
Arrhythmias
Prolongation of QT interval
Bradycardia/tachycardia
Increase/decrease in prothrombin time
Disturbances of myocardial contractility

In contrast, the newer category of selective serotonin reuptake inhibitors—which includes fluoxetine, fluvoxamine, citalopram and paroxetine—appears to guarantee safer treatment, without the adverse effects described above for tricyclic antidepressants, and should be considered the treatment of choice, since these drugs have no anticholinergic properties and so their proarrhythmic action is very limited.[39,46]

Nevertheless, there are scant data regarding the efficacy and safety of antidepressant treatment in cardiovascular diseases, and they mainly concern coronary artery disease, whereas studies of the treatment of depression in HF are at a very early stage. The first report of the administration of serotonin reuptake inhibitors to patients with HF was published quite recently and involved paroxetine. The study showed the benefit on the levels of depression and quality of life in the paroxetine group compared with controls (69% reversion from depressive syndrome vs. 23% in controls).[47] Another randomised trial (SADHART), which examined the administration of sertraline to patients with acute coronary syndromes, showed that the treatment of depression in those patients could be successful, without complications or any troubling increase in cardiovascular events.[48]

Also of interest is the SADHART-CHF (safety and efficacy of sertraline for depression in patients with congestive HF) trial, a multi-centre, prospective, randomised, double-blinded study that was designed to evaluate the safety and efficacy of sertraline in the treatment of major depression in patients with HF, as well as the effect of antidepressant therapy on cardiac events and the morbidity and mortality of those patients.[49] The study enrolled 469 patients aged ≥45 years with major depression and chronic HF (left ventricular ejection fraction ≤45%, NYHA class ≥II), who were randomised to sertraline or placebo (treatment duration 12 weeks) combined in both groups with psychological support from nursing staff specialised in depression. The patients were followed for a period of 6 months. The primary clinical endpoints were a change in the severity of symptoms of depression, mortality and morbidity. The first results were presented at the 13th annual congress of the Heart Failure Society of America,[50] where the investigators reported that, while sertraline was safe with respect to major cardiac events, patients with HF and depression did neither better nor worse with the treatment in question than with placebo. As regards secondary clinical endpoints, the sertraline group had better scores on the Kansas City Cardiomyopathy Question-

naire and the Hamilton Depression Scale. The sertraline group had a lower incidence of HF deterioration leading to hospitalisation (8% vs. 12% for placebo, p:NS). However, the study did not have the statistical power to evaluate overall mortality, hospital readmissions, or mortality from HF.

In view of the above findings concerning adverse effects and interaction between antidepressant drugs and those used to treat HF, the choice of drug should by definition be made with care.

Choice of treatment methods

CBT is preferable when most of the following conditions apply: 1) the depression is not severe; 2) the depression is not chronic; 3) the characteristic features of psychosis are absent; 4) there was a positive response to CBT during a previous and transient depressive period; 5) CBT services are available; 6) there is a medical contraindication for drugs; 7) drug treatment alone has not been effective; and 8) there are complicated psychosocial factors.[18]

In contrast, administration of antidepressant medication should be considered under any of the following terms: 1) the depression is severe; 2) the depression is chronic or repeated; 3) the characteristic features of psychosis are present; 4) there has been a previous positive response to medication; 5) there is a history of hereditary depression; and 6) the patient is incapable of participating in the work required for psychotherapy.

Conclusions

The determination of risk factors, an understanding of the pathophysiological mechanisms, evaluation of the clinical data, and prevention through optimisation of the cardiological and psychiatric therapeutic strategies emerge as crucial for these patients. Prompt diagnosis and treatment of both HF and depression can avert further pathophysiological consequences for the heart and brain. Special emphasis should be given to the inspection of such a case, with primary aim the improvement of this damaging physical and psychosocial condition. Additional attention should be paid to the cardiac consequences of antidepressant medication and often the psychosocial therapy of patients with HF. Thus, taking into account the incidence of adverse effects of tricyclic antidepressants in relation to selective serotonin reuptake inhibitors, the latter should be considered the treatment of choice.

Finally, perhaps today we should adopt the following motto: a healthy mind and a healthy heart.

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