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Depression and heart failure: An overview of what we know and don't know

ABSTRACT

Depression is prevalent in patients with heart failure, and the two conditions share underlying physiologic mechanisms. The prevalence of depression increases sharply with the severity of heart failure symptoms, an important consideration when confronting patients with worsening heart failure. Depression leads to poorer outcomes in patients with heart failure, including increased risk of poor functional status, hospital readmission, and death. Although beta-blockers are often implicated in the development and exacerbation of depression, evidence for this association is lacking, so withholding beta-blocker therapy is not recommended for patients with heart failure and depression. Evidence on whether therapy for depression also improves cardiac outcomes in heart failure patients is inconclusive, and further research on this question is needed. Nevertheless, early identification of depression in heart failure patients is imperative, as it can facilitate intervention attempts.

The relationship between depression and heart failure is not as obvious as the one between depression and coronary artery disease. Myriad questions on the subject are open to research:

- Does depression occur in heart failure at higher-than-expected rates?
- Does heart failure severity influence depression?
- Is depression a risk factor for heart failure? If so, why?
- How should we screen for depression in patients with heart failure?
- Do we have an evidence-based approach to treatment?

Part of the challenge in clarifying the relationship between depression and heart failure is that heart failure is a disease of chronically ill, elderly patients—a population in which adjustment disorder with depressed mood and major depression are also common diagnoses, with rates recently found to be 22.3% and 13.3%, respectively.[1] Nevertheless, interest in examining the relationship between heart failure and depression is long-standing, and many clinical studies have examined this relationship.[2–16] Unfortunately, measures are not standardized, so comparisons between studies are difficult.

DEPRESSION IS COMMON IN PATIENTS WITH HEART FAILURE

Many studies show that rates of depression among patients with heart failure are higher than expected among other elderly, chronically ill patients. Furthermore, depression has been linked to more severe heart failure symptoms and worse outcomes in some studies.

In a 2001 study, Jiang et al screened 374 hospitalized patients with heart failure using the Beck Depression Inventory score and found that 35% had scores of 10 or higher (indicative of at least mild depression).[12] Further testing showed that 14% met criteria for major depression.

A 2006 meta-analysis of 27 studies by Rutledge et al found a 21% incidence of clinically significant depression in patients with heart failure.[17] Rates of depression depended heavily on the rigor of screening criteria for classifying participants as depressed: rates were as high as 38% with the use of liberal criteria and as low as 14% with strict criteria. New York Heart Association (NYHA) functional status correlated strongly with the prevalence of depression, which increased steadily from 11% in patients with NYHA class I (mild) heart failure to 20% in those with class II, 38% in those with class III, and 42% in those with class IV (severe) heart failure.

In one of the studies included in the meta-analysis, Freedland et al found that the prevalence of major depression was strongly associated with age and functional status in hospitalized patients with heart failure.[18] In patients younger than age 60 years, rates of major depression rose particularly sharply as heart failure symptoms worsened.

The Psychosocial Factors Outcome Study found that

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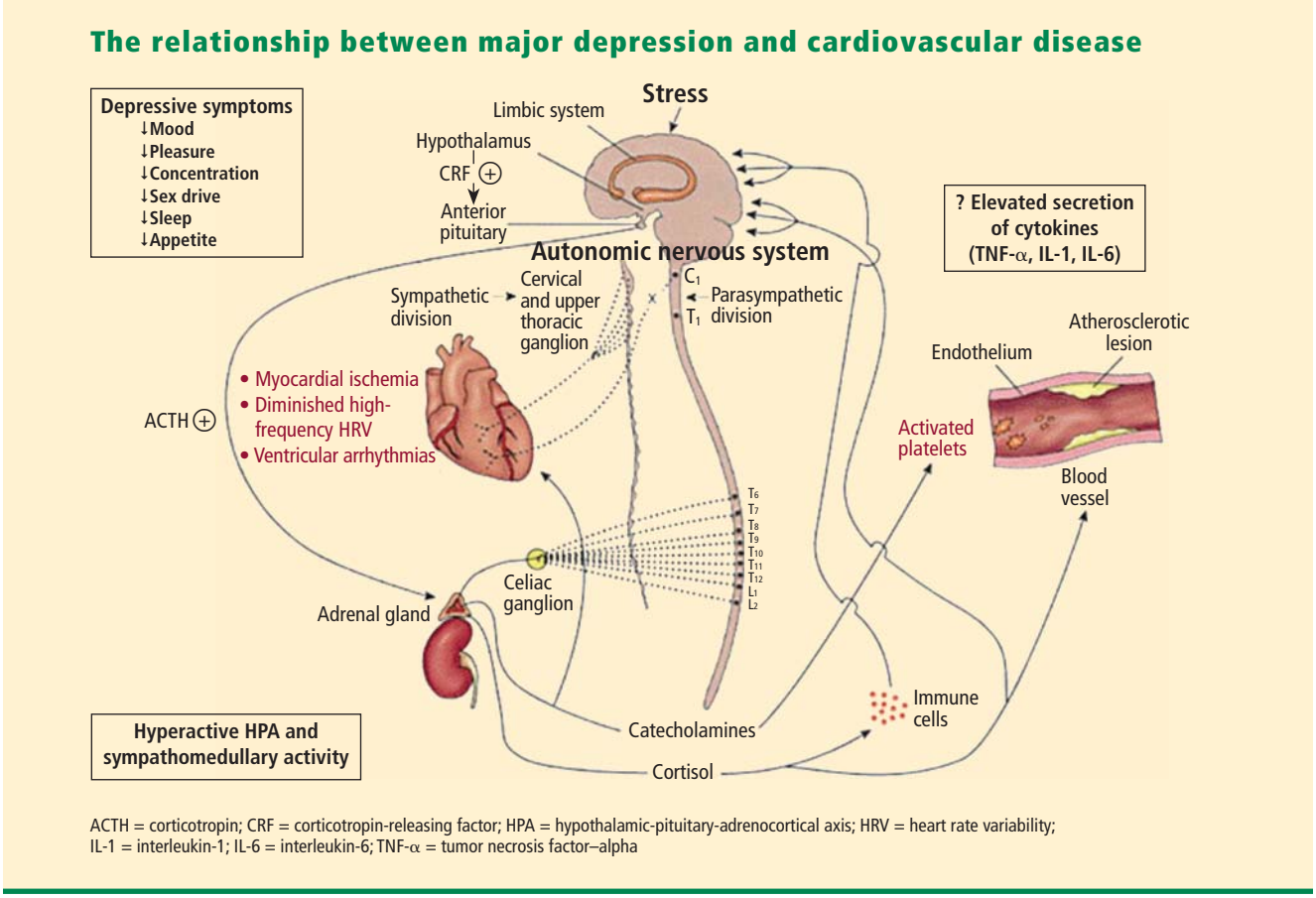

FIGURE 1. Numerous alterations in biologic markers observed in depressed subjects may contribute to their increased vulnerability to cardiovascular disease, including sympathoadrenal hyperactivity, diminished heart rate variability, ventricular instability and myocardial ischemia in response to mental stress, and alterations in platelet receptors and platelet reactivity.

the prevalence of depression in patients with heart failure who participated in the community-based Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was 36%, based on a score of 13 or greater on the Beck Depression Inventory-II.[19] Similarly, unpublished preliminary data from the Heart Failure Adherence and Retention Trial (HART) show that about one-third of community-based patients with heart failure have depression.[20]

DEPRESSION AND HEART FAILURE ARE CLOSELY LINKED PHYSIOLOGICALLY

The underlying relationship between depression and cardiovascular disease is depicted in **Figure 1**.[21] It shows the commonality of pathophysiologic mechanisms for the two conditions.

The likely psychological and physiologic mechanisms leading to depression in patients with heart failure are almost identical to the list of mechanisms proposed for the development of heart failure itself **(Table 1)**, including autonomic dysregulation, hyperproduction of cortisol, and a prothrombotic and proinflammatory state. One interesting line of study involves a polymorphism in the serotonin transporter gene, which increases the amount of catecholamine secretions secondary to stress in mice. The serotonin transporter gene has also been found to be associated with depression during stress in humans.[22] Likewise, norepinephrine has been found to be a risk factor for adverse outcomes in patients with coronary artery disease and heart failure.[23]

The evidence, therefore, strongly suggests a common pathway between heart failure and depression, and this evidence of a relationship favors a new paradigm that integrates the treatment of the two conditions.

BETA-BLOCKERS DO NOT RAISE RISK OF DEPRESSION

Pharmacotherapy is often implicated as a related factor in the development or exacerbation of depression in patients with heart failure, especially in those taking

beta-blockers. Meta-analyses of the incidence of depression associated with various beta-blockers have been conducted in patients with hypertension, heart failure, and recent myocardial infarction. A 2002 meta-analysis of eight trials that randomized patients to treatment with a beta-blocker or placebo found no difference in the incidence of depressive symptoms between the active treatment and placebo groups, or between patients in the two groups who withdrew from the trial, presumably because of depression or other symptoms.[24] An additional study not included in that meta-analysis found no differences in rates of depression among hypertensive patients according to the type of antihypertensive medication they were taking (ie, beta-blockers, diuretics, reserpine, or no drug therapy).[25]

Based on the evidence, I see no reason to avoid a trial of beta-blockers in patients who have depression at baseline or to be overly concerned that patients without depression will develop it as a result of beta-blocker treatment.

TABLE 1
Possible psychophysiologic mechanisms for depression in heart failure

High sympathetic tone (cardiovascular autonomic dysregulation)
- Reduced heart rate variability
- Elevated levels of circulating catecholamines

Platelet activation (prothrombotic)
- Dysfunctional serotonin signaling
- Elevated levels of platelet factor 4 and beta-thromboglobulin

Elevated levels of cortisol (atherosclerosis)
- Elevated levels of free fatty acids

Inflammation (atherosclerosis)
- Elevated production of inflammatory cytokines

DEPRESSION LEADS TO WORSE OUTCOMES, HIGHER COSTS IN HEART FAILURE

Not only is depression prevalent in patients with heart failure, but depression adversely affects heart failure outcomes. One study of hospitalized patients older than 70 years found readmission rates to be 67% among heart failure patients with depression versus 44% among heart failure patients without depression.[26] Patients in this study were three times as likely to die if they had heart failure than if they did not have heart failure, and they were twice as likely to die if they had depression than if they did not have depression. The mortality rate was 21% for patients with both heart failure and depression versus 15% for patients with heart failure without depression.[26]

Depressive symptoms also correlate with poorer quality of life in patients with heart failure. Gottlieb et al found that quality-of-life scores were significantly worse in heart failure patients if they had a diagnosis of depression on the basis of the Beck Depression Index.[27]

The 27-study meta-analysis by Rutledge et al discussed earlier found that the presence of depression in a patient with heart failure predicts worse outcomes in terms of hospital readmission rates, functional status, and walk times.[17] This analysis also found twice the rate of death in heart failure patients with depression compared with heart failure patients without depression.

In a large community-based trial involving more than 48,000 patients with heart failure, Macchia et al found that survival was markedly reduced in patients who had a history of depression.[28] This study also showed that depressed patients were less likely to adhere to medication regimens with angiotensin-converting enzyme inhibitors and beta-blockers, which may offer a potential explanation for the reduction in survival among depressed patients.

In a study of patients with coronary artery disease who had no diagnosis of depression or heart failure, May et al demonstrated that those who subsequently developed depression had more than four times the risk of also developing heart failure.[29]

The combination of heart failure and depression also is costly. In a 3-year retrospective study of community-based patients following a first hospitalization for heart failure, Sullivan et al found that annualized adjusted total costs were nearly 30% greater in patients diagnosed with depression and that inpatient and outpatient service utilization was also greater in those with depression.[5]

DIAGNOSIS AND TREATMENT

One simple question can effectively screen for depression

Numerous tools are available for the diagnosis of depression, but developing a tool that is readily useful to a busy clinician is challenging. Simply asking the single question, "Are you depressed?" has fairly high sensitivity (55%) and specificity (74%) for diagnosing depression in palliative care patients, a population even more seriously ill than heart failure patients.[30] A variation on the question from British studies—"Do you feel that your life is empty?"—is considered to be a better screening question for elderly patients.[31,32]

Effect of depression therapy on heart failure still unclear

Unfortunately, evidence for the best treatment for depression in patients with heart failure is lacking. Some guidance may be gleaned from studies in patients with coronary artery disease. The Sertraline Antidepressant

Heart Attack Randomized Trial (SADHART) was a multicenter, randomized, placebo-controlled study of the safety and efficacy of treating major depressive disorder with sertraline for 24 weeks in patients hospitalized for acute coronary syndrome.[33,34] No significant differences were found between treatment groups in left ventricular ejection fraction, blood pressure, resting electrocardiogram, and cardiac arrhythmias. Although the trial was not powered to detect an effect of treatment on mortality, there were fewer deaths and severe cardiovascular adverse events in the active treatment group.

A later study was designed to evaluate 12 weeks of treatment with sertraline in patients with major depression and heart failure.[35] Although symptoms of depression improved with treatment, no beneficial effect on heart failure was found.[36] A nursing intervention that was included for both the treatment and placebo groups may have served to limit the impact of sertraline on heart failure surrogate end points.

The abovementioned HART study randomized patients with systolic or diastolic dysfunction and NYHA class II or III functional status to receive either heart failure education (comprising 18 American Heart Association tip sheets and 18 phone calls) or heart failure education plus self-management strategies (comprising the tip sheets, 18 group sessions, and problem-solving and self-management skills) following hospital discharge.[37] Over 3 years, no difference between the two groups was found in the rates and timing of deaths or heart failure hospitalizations.

The best treatment strategies for depression in heart failure are still unclear, and more research is needed. Although guidelines exist for the management of depression in patients with coronary heart disease,[38] no such guidelines have been issued for the management of depression in heart failure.

CONCLUSIONS

Although evidence is strong that treatment with medication or cognitive therapies improves symptoms of depression, evidence is lacking for a significant effect of such interventions on cardiac outcomes.[39] Because depression and heart failure are so closely linked and appear to share a genetic and pathophysiologic basis, greater understanding of the relationship between these diseases across the stages of heart failure should be pursued.

Any patient with heart failure who is symptomatic has advanced disease, and is therefore closer to death than to health. The same is probably true of depression. Patients with heart failure and depression must be identified early, and interventions must be tried at these early stages of disease. Better depression screening tools and heightened awareness of the relationship between heart failure and depression are essential.

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