SPECIAL ARTICLE

ANXIETY AND DEPRESSION IN HEART FAILURE: SPECIAL ARTICLE

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Abstract

Background/Objective: Anxiety and depression are closely associated with heart failure (HF) and contribute to its development and progression through multiple biological and behavioral pathways.

Summary: The shared biological and behavioral pathways among depression, anxiety and HF include dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, reduced heart rate variability, elevated levels of pro-inflammatory cytokines, platelet dysfunction, endothelial dysfunction and metabolic disorders. Behavioral factors such as smoking, physical inactivity, poor diet, and low medication adherence also contribute significantly to this reciprocal relationship. Together, these factors may interact to the progression of cardiac dysfunction.

Conclusion: Anxiety and depression may coexist or deteriorate HF through interconnected neuroendocrine, inflammatory, vascular, and behavioral mechanisms, highlighting the importance of integrated clinical management. Understanding these interactions is essential for developing personalized treatment strategies aimed at improving both mental health and HF outcomes.

Keywords: Heart failure, anxiety, depression

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INTRODUCTION

Heart failure (HF) is widely regarded as a significant global health burden, affecting approximately 64 million individuals, worldwide. HF is often described as a pandemic due to its high prevalence and clinical impact. The number of HF patients is expected to rise substantially in future, largely as a result of population ageing, better diagnosis and improved survival from other cardiovascular conditions.[1-5]

HF prevalence varies across populations with epidemiological data from European and international registries highlighting geographic differences in disease burden. According to the 2019 European Society of Cardiology Heart Failure Association atlas, the HF prevalence across participating European countries was estimated at 17 cases per 1,000 individuals, with lower rates reported in Greece and Spain, and higher rates observed in Lithuania and Germany. National studies also highlight this variability. For example, in Germany, healthcare data indicated a HF prevalence of approximately 4%, while population-based data from the United Kingdom reported prevalence of 1.6% (age and sex-adjusted). In the United States, self-reported national survey data estimated HF prevalence at approximately 2.5% while projections indicated that HF prevalence may increase by nearly 46% between 2012 and 2030, accompanied by a dramatic rise in healthcare expenditures.[1]

HF is challenged by several limitations which include variability in diagnostic criteria, differences in sampling and a lack of data from certain regions of the world. Furthermore, studies depend on the International Classification of Diseases coding and/or administrative databases which may not capture all cases of HF and lack detailed clinical information such as left ventricular ejection fraction (LVEF). Other data sources, such as self-reported diagnoses or hospital-based records, also present limitations (inaccuracies and/or exclusions of outpatients).[1]

This clinical syndrome is encompassing a heterogeneous group of underlying causes rather than a distinct disease entity. It is characterized by the heart's impaired ability to fill and/or eject blood effectively, or by an insufficient cardiac output resulting from structural or functional cardiac abnormalities.[1,2] Although several definitions of HF exist, LVEF is the fundamental parameter for diagnosis, phenotypic classification, prognostic assessment, and therapeutic decision-making. Natriuretic peptides, released by the myocardium in response to inflammatory activation and elevated wall stress play an important role in both the diagnosis and risk stratification of HF patients.[1,2]

A universal definition and classification system for HF was introduced in 2021 to provide greater standardization in clinical practice. According to this definition, HF is a clinical syndrome characterized by the presence of symptoms and/or signs resulting from structural and functional cardiac abnormalities, and supported by objective evidence of pulmonary or systemic congestion and high natriuretic peptide concentrations.[1]

The updated staging system categorizes individuals into four progressive phases which include: stage A (at risk for HF), stage B (pre-HF), stage C (symptomatic HF) and stage D (advanced HF).[1] The classification based on LVEF was refined to reflect the heterogeneity of this clinical syndrome. This includes HF with: a. reduced ejection fraction and LVEF ≤40% (HFrEF), b. mildly reduced with LVEF 41–49% (HFmrEF) and c. preserved with LVEF ≥50% (HFpEF). A new HF category with improved LVEF (HFimpEF) was introduced to describe HF patients who had at baseline LVEF ≤40% and showed improvement of 10 percentage points, accompanied by a follow-up LVEF>40%. This new term acknowledges the dynamic nature of HF and the potential for functional recovery after treatment.[1] Data from major international HF registries, showed the HFrEF as the most commonly reported phenotype, accounting for 39–60% of cases while HFpEF accounted for 16-47%, depending on the sample studied.[1]

In spite of the development of effective evidence-based therapies that improve survival, HF is a significant clinical burden, with one-third of patients experiencing rehospitalization within the first year after diagnosis or hospital discharge.[1-3]

Anxiety and depression

Anxiety and depression are among the most common mental health disorders, worldwide. The comorbidity of mental disorders with physical illnesses is considered a major public health issue as it negatively affects disease progression, reduces patients' quality of life and increases healthcare costs.[4-9]

Anxiety is considered a fundamental human experience that historically served as a survival mechanism. Early

descriptions of anxiety are traced back to Hippocrates. Walter Cannon (1939) introduced the response «fight-or-flight» which explains anxiety as psychophysiological reaction involving activation of the sympathetic nervous system and release of the hormones epinephrine and norepinephrine. Throughout human history, anxiety has evolved from responses to immediate physical threats, such as wild animals or natural disasters to more persistent concerns related to social, existential, and cultural factors.[9,10]

As already articulated, anxiety serves as a normal adaptive response to real or perceived threats. However, when its intensity or duration exceeds adaptive limits, it may develop into pathological anxiety, characterized by disproportionate physiological responses. From the neurobiological perspective, anxiety involves neurotransmitters, including norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA), while the amygdala plays a central role in fear processing. For example, increased amygdala activation and dysfunction in prefrontal-limbic neural circuits have been observed in individuals with anxiety disorders, though they improve through treatment.[9]

Clinically, anxiety may manifest through cognitive symptoms such as: a. fear of losing control, fear of death, intrusive thoughts, difficulty concentrating, b. physical symptoms including tachycardia, dyspnea, chest pain, sweating, tremor, muscle tension and c. behavioral symptoms such as avoidance, hypervigilance, or escape responses. Severe anxiety may impair daily functioning as well as social and professional life, treatment adherence, and lifestyle modifications. [6,9,10,11]

Depression is a common mental health disorder and a major contributor to the global burden of disease. Depression is not considered a temporary emotional state, but rather a clinical syndrome with clearly defined diagnostic criteria, duration, and outcomes. Depression is characterized by persistent sadness, loss of interest or pleasure and a broad range of psychological and physical symptoms Distinguishing between depressive feelings, depressed mood, and clinical depressive disorder is essential for accurate diagnosis and treatment.[10]

Descriptions of depression date back to ancient Greece when Hippocrates recognized the biological basis of «melancholia». Nowadays, depression is understood as a multifactorial disorder influenced by genetic, biological, and psychosocial factors. It is also linked to alterations in neurotransmitters such as serotonin and norepinephrine, which play key roles in neural communication. The «kindling model» explains depression as a process of progressive sensitization, in which recurrent episodes become increasingly autonomous over time. Initial episodes are often triggered by major stressful life events such as severe loss or illness, whereas recurrent episodes may occur more easily over time due to lasting neurobiological changes caused by prior episodes. Moreover, psychosocial and medical factors including bereavement, chronic illness, infections, medication use, malignancies, may contribute to depression onset. [2,10,11]

Neurobiological mechanisms involve disturbances in neurotransmitters such as serotonin, norepinephrine, dopamine, glutamate, and brain-derived neurotrophic factor, as well as alterations in receptor sensitivity and gene expression. The effectiveness of selective serotonin reuptake inhibitors (SSRIs) supports the important role of serotonin in its pathophysiology. Brain circuits involved in emotional regulation, including the prefrontal cortex, striatum, amygdala, and limbic system, also play a significant role in depression. Seasonal affective disorder is a subtype of depression associated with changes in serotonin levels, circadian rhythm disturbances and reduced exposure to sunlight. Despite availability of effective treatments, around 60% of individuals with depression do not seek professional help due to perceived stigma, misconceptions and fear of consequences.[11]

Diagnosis

Diagnosing anxiety and depression requires a systematic clinical approach due to their frequent coexistence with physical illness and their impact on prognosis.[2,12,13] In patients with chronic illness, diagnosis of mental disorder is essential since it may influence functionality.[14] HF patients often experience significant physical and psychological burden, including fatigue, dyspnea, reduced health-related quality of life. [15] All these factors should be carefully considered during the diagnostic process, as they may influence the diagnosis of depression and anxiety in patients with HF.

Anxiety represents an adaptive response to illness, whereas depression is considered a maladaptive condition requiring careful diagnostic evaluation. Assessment includes the patient's subjective interpretation of illness, coping mechanisms, vulnerability to stress, personality traits, as well

as several other biological, demographic and psychosocial factors.[1,9,12]

The diagnostic process is complicated by the overlap between psychological and physical symptoms, such as fatigue, sleep disorders, dyspnea, tachycardia, thus making the differential diagnosis essential. Clinical evaluation is based on medical history, structured clinical interviews and information from family members.[1,9,12]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5-TR) by the American Psychiatric Association, the diagnosis of major depressive disorder requires the presence of at least one of two core symptoms: depressed mood or loss of interest/pleasure (anhedonia) along with at least five total symptoms, including changes in appetite, sleep disturbances, fatigue, feelings of worthlessness, impaired concentration, or suicidal thoughts. These symptoms must persist almost daily for at least two consecutive weeks and cause clinically distress or functional impairment. Suicide risk assessment is an essential part of diagnostic process, and severe cases require immediate referral to specialized mental health services. [2,7,9,12].13

Given the complexity of the diagnostic process, clinicians are advised to carefully evaluate HF patients to determine whether they meet full DSM-5 criteria for major Depression or an anxiety disorder. Early and accurate diagnosis based on DSM-5 criteria helps to ensure that symptoms such as sleep disturbance, fatigue, or poor concentration are not misattributed to psychiatric illness when they may be related to HF itself.[12,16]

Despite available diagnostic criteria and several tools, anxiety and depression remain underdiagnosed. Contributing factors include limited cultural validity of screening tools, time constraints, lack of routine implementation in clinical settings, and the tendency of healthcare professionals to focus primarily on physical symptoms. On the other hand, patients may hesitate to report emotional symptoms due to self-perceived stigma, prioritization of physical complaints, and the perception that these symptoms represent a normal emotional response to stressful life circumstances.[2,6,9,12,16]

Therefore, improving early diagnosis requires better training of healthcare professionals, especially nurses, use of culturally appropriate and validated screening tools, and the adoption of a holistic biopsychosocial approach in everyday clinical practice.[2,9,16]

Therapy

The treatment of anxiety and depression includes both pharmacological and non-pharmacological interventions, with treatment selection based on patient's clinical history, previous treatment response, comorbidities, adverse effects and healthcare resources.[2,6,7,9]

In terms of pharmacological treatment, benzodiazepines are mainly used for short-term management of acute anxiety due to the risk of dependence and cognitive side effects. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are considered first-line treatments for both anxiety and depression, as they regulate neurotransmitter activity and improve mood. Their therapeutic effects usually appear after 4–6 weeks, while common side effects include nausea, insomnia, sexual dysfunction, and weight gain. [2,9,10,16]

Regarding non-pharmacological treatment, Cognitive Behavioral Therapy is one of the most evidence-based psychotherapeutic approaches, helping patients to identify and modify dysfunctional thoughts and behaviors. Combination of psychotherapy and medication has been shown to be more effective than treatment alone, particularly in severe depression.[2]

Psychological interventions may reduce symptoms of depression and anxiety and improve mental health-related quality of life, although they appear to have limited effects on mortality, physical quality of life, or major cardiovascular events.[15]

Effective management of anxiety and depression requires a holistic approach, involving healthcare professionals, the patient, and family, with the ultimate goal of improving treatment adherence, reducing relapse rates and enhancing quality of life.[1,15]

Anxiety, Depression, Heart Failure

Among HF patients, depression and anxiety is more frequent than in the general population. Meta-analytic evidence indicates that approximately 19-21.5% meet diagnostic criteria for depression, while about one-third report clinically significant depressive symptoms. Anxiety disorders are present in around 13% of patients, with nearly 30% reporting elevated anxiety levels. These rates are approximately two to three times higher than those in the general population.[16]

Depression and anxiety are associated with HF through shared biological and behavioral mechanisms. These include

dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, reduced heart rate variability, elevated levels of pro-inflammatory cytokines, platelet dysfunction, poor adherence to treatment recommendations, sedentary behavior and limited social interaction. All these interacting factors contribute to cardiac dysfunction.[1,12,16-18]

Excessive cortisol secretion can lead to cardiovascular consequences, including hyperglycemia, hypertension, insulin resistance, dyslipidemia and elevated intravascular volume. Prolonged inflammatory activity, involving cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) is associated with poorer prognosis in patients with depression and HF.[1,18]

The autonomic nervous system plays a critical role in regulating cardiac function and vascular tone. Increased sympathetic nervous system activity contributes to tachycardia and vasoconstriction, whereas parasympathetic activity promotes bradycardia and vasodilation. Anxiety and depression are associated with increased sympathetic tone and reduced parasympathetic activity, resulting in decreased heart rate variability. This autonomic imbalance may accelerate coronary atherosclerosis, contribute to myocardial ischemia, to arrhythmias and promote HF development.[1]

Chronic and prolonged psychological distress promote systemic inflammation and neuroinflammation. These processes interact with HPA and glucocorticoid receptors in the hippocampus, enhancing the pro-inflammatory state and disrupting the balance between oxidative stress and antioxidant defense mechanisms. This creates a self-perpetuating cycle that contributes to the persistence of depressive symptoms. [1,12,16-18]

Endothelial function is essential for maintaining hemodynamic homeostasis by regulating vascular tone, leukocyte adhesion and platelet activity. Endothelial dysfunction, characterized by reduced nitric oxide production, promotes atherosclerosis and is associated with increased morbidity and mortality. At the same time, increased platelet activation and abnormal serotonin release promote thrombotic activity. [1,12,16-18]

Metabolic disorders such as metabolic syndrome, obesity, and excessive caloric intake represent another shared pathway linking depression, anxiety, and HF. These conditions enhance inflammatory activity and create a vicious cycle of physical and psychological burden. [1,12,16-18]

In addition, several behavioral changes associated with depression may indirectly increase the risk of HF. Patients with depression are more likely to engage in unhealthy behaviors such as smoking, alcohol consumption, and physical inactivity. They are less likely to adhere to medication regimens, maintain a healthy diet and participate in rehabilitation programs. These behaviors may worsen overall health status and contribute to the development of HF. Depression may also indirectly contribute to HF development through comorbidities, as it is a recognized risk factor for diabetes mellitus, hypertension, and coronary artery disease, all of which increase the risk of HF.[2,12,16-18]

This concept is further supported by findings from relevant studies. A study conducted by Harshfield et al.,19 among 563,255 participants showed increased risk of developing cardiovascular disease among those with depressive symptoms. A systematic review and meta-analysis by Cao et al.,20 of prospective cohort studies (1950–2019) with 131,282 participants and 4,727 HF events showed that individuals with depression had a 23% higher risk of developing HF compared to those without depression. Rome et al.,21 support that women with incident or established coronary heart disease show a higher prevalence of depression compared with men. Sex-specific mechanisms include psychosocial, cardiometabolic, behavioral, inflammatory, hormonal, and autonomic factors. Lin et al.,22 showed an association between depression and increased coronary artery calcification. Depression is linked to adverse clinical outcomes in patients undergoing artery bypass graft surgery and percutaneous coronary intervention.

CONCLUSIONS

Overall, the interaction between anxiety, depression, and HF involves autonomic nervous system dysregulation, HPA axis dysfunction, chronic inflammation, endothelial dysfunction, platelet activation, and metabolic abnormalities. These mechanisms act together to worsen cardiac function and negatively affect patient prognosis.

Given the global HF burden, high-quality research is still needed to clarify the causal relationship between mental health and HF development in order to implement targeted preventive and therapeutic interventions.

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