Pathophysiological Relationships Between Heart Failure and Depression and Anxiety

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Depression and anxiety are common comorbid conditions in patients with heart failure. Patients with heart failure and depression have increased mortality. The association of anxiety with increased mortality in patients with heart failure is not established. The purpose of this article is to illustrate the similarities of the underlying pathophysiology of heart failure, depression, and anxiety by using the Biopsychosocial Holistic Model of Cardiovascular Health. Depression and anxiety affect biological processes of cardiovascular function in patients with heart failure by altering neurohormonal function via activation of the hypothalamic-pituitary-adrenal axis, autonomic dysregulation, and activation of cytokine cascades and platelets. Patients with heart failure and depression or anxiety may exhibit a continued cycle of heart failure progression, increased depression, and increased anxiety. Understanding the underlying pathophysiological relationships in patients with heart failure who experience comorbid depression and/or anxiety is critical in order to implement appropriate treatments, educate patients and caregivers, and educate other health professionals. (Critical Care Nurse. 2014;34[2]:14-25)

Heart failure is an epidemic with national and global implications. Compared with the situation in other cardiac diseases, the incidence and prevalence of heart failure continue to increase despite recent advancements in understanding and treatment. Increased survival after myocardial infarction, aging of the population, and increased incidence of diabetes are contributing factors. In the United States, heart failure is...
the primary diagnosis in more than 1 million hospitalizations, and the estimated cost is $40 billion annually.1

Depression is a common comorbid condition in patients with heart failure.2 Prevalence of depression was 23.8%3 to 67%4 in 8 studies of inpatients with heart failure5-10 and 16.7%11 to 70%12 in 22 studies of outpatients with heart failure.11-32 The wide range reflects the inpatients and outpatients assessed and the methods used to determine depression, including diagnostic interviews and a variety of both brief and extensive symptom inventories. The prevalence of depression in all studies of patients with heart failure is greater than the prevalence in the general population.33

Compared with depression, anxiety is less commonly examined in patients with heart failure.2 The prevalence of anxiety in patients with heart failure was determined in 14 studies.2,16-31,25-35 Prevalence was 14.8% in the 1 study21 of inpatients and 11%25 to 54%34 in the 13 studies of outpatients. A total of 8 different instruments were used to assess anxiety in these 14 studies, resulting in the wide range of prevalence. The Brief Symptom Inventory was used in the 3 studies16,28,34 with the highest prevalence rates. The Hamilton Anxiety and Depression Scale was used in 5 studies26,29-31,35; the prevalence of anxiety was 21% to 30%. Regardless of the method of assessment, the prevalence of anxiety in patients with heart failure was greater than the prevalence of 11.3% in the general population.33

The association between depression and mortality in patients with heart failure was examined in 9 studies.13,22,25,31,36-40 In most studies (7 of 9),13,22,25,31,36-40 in depression symptoms were significantly predictive of higher mortality rates. In 2 studies35,37 no relationship was detected between depressive symptoms and mortality. In one of these studies,37 a questionnaire with only 4 items was used to assess both anxiety and depression, a method that decreases sensitivity and specificity of the assessment. In the other study,31 the sample size was small (n=111), mortality was low, and none of the patients had indications of severe depression. The association between anxiety and mortality was recently examined in only 2 studies.31,34 In one study,31 the investigators found no relationship between anxiety and mortality. This study was underpowered, and only 10% of the sample reported moderate to severe symptoms of anxiety. In the other study,34 patients with heart failure and high anxiety had a significantly shorter period of event-free survival than did patients with heart failure and lower anxiety. Event-free survival was defined as the period without rehospitalization or death. The results did not indicate a direct association between anxiety and mortality in patients with heart failure.

Depression contributes to increased mortality in patients with heart failure. The association between increased anxiety and mortality has not been established. More studies on the association in patients with heart failure are needed.

In this article, we use the Biopsychosocial Holistic Model of Cardiovascular Health to describe the relationships of the underlying pathophysiology of heart failure, depression, and anxiety. Patients with heart failure who

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are depressed or anxious may be trapped in a harmful loop in which depression and anxiety symptoms might be worsened by the synergistic pathophysiological changes associated with heart failure.

**Biopsychosocial Holistic Model of Cardiovascular Health**

Thomas et al have proposed a holistic model of cardiovascular health based on the biopsychosocial model. Engel believed that treatment directed at the biological factors alone would not restore health. The biopsychosocial holistic model is an interactive biological, psychological, and social model in which factors work together within a person to affect cardiovascular health (Figure 1).

Unlike the situation in a biomedical model of disease, health is considered a process in which acute and chronic shifts in each realm interact to either enhance or inhibit pathological processes and thus affect health. Interaction between the biological and psychological realms is illustrated by increased mortality in patients with depression and heart failure. An example of the interaction between the psychological and the social realms is the independent association between increased anxiety and low social support that is predictive of readmission of heart failure patients. Another example of the interaction of all 3 realms is the relationship of dog ownership and cardiovascular health.

Depression and anxiety affect biological processes of cardiovascular function in patients with heart failure by altering neurohormonal function via activation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic dysregulation, and activation of cytokine cascades and platelets. Conversely, neurohormonal dysfunctions due to heart failure may increase the risk for depression and anxiety in patients with this cardiovascular abnormality.

**Role of Neurohormones**

Heart failure is a progressive, complex pathophysiological state. The usual clinical manifestation of heart failure is left ventricular dysfunction that occurs after some index event, such as myocardial infarction, uncontrolled hypertension, or hereditary causes, in which damage to heart muscle impairs the heart’s pumping or filling ability. Current understanding of heart failure involves a neurohormonal model. Many of the neurohormones involved in heart function, such as norepinephrine, angiotensin II, aldosterone, and tumor necrosis factor α (TNF-α), are synthesized both within endocrine organs, from which they are released into the circulation, and within the myocardium, where they cause interactions between and within myocardial cells. The Table lists the major neurohormones involved in heart failure, depression, and anxiety and their effects. Increases in neurohormones initially are an adaptive physiological response. However, in heart failure, long-term activation of these biochemical messengers results in direct end-organ damage to the heart and vasculature. Neurohormone dysregulation also occurs in depression and anxiety. In many instances, the pathological processes of anxiety parallel those of depression, although some cardiac effects of anxiety are thought to be due to an exaggerated sensitivity to exogenous stress.

Figure 2 is a simplified representation of the complex pathophysiological mechanisms that link depression, anxiety, and heart failure. An overview of the pathophysiological mechanisms that link the elements of the model together are discussed in the following sections.

**Activation of the HPA Axis**

In response to mental and physical stress, activation of the HPA axis occurs, leading to the following reactions.
The hypothalamus releases corticotropin-releasing factor. This factor signals hypothalamic neurons to synthesize and release corticotropin from the anterior part of the pituitary gland. Corticotropin then stimulates release of cortisol and aldosterone.59 Corticotropin stimulates release of cortisol and aldosterone from the adrenal cortex.60 Hypercortisolemia contributes to abdominal obesity,61 hypertension,62 insulin resistance,63 and inflammation. Aldosterone promotes water reabsorption, conservation of sodium, and secretion of potassium, increasing circulating blood volume and ultimately increasing blood pressure.64,65

The HPA axis is activated by a failing ventricle. Therefore, with increased severity of heart failure, production of aldosterone increases. Aldosterone is also produced within the heart and works directly on heart tissue at the sites where the hormone is produced.66 Increased levels of aldosterone in the circulation or in heart tissue stimulate excessive production of collagen, which leads to cardiac fibrosis and cardiac remodeling.66 Further, cortisol may mimic the effects of aldosterone in patients with heart failure because of changes caused by damage to myocardial tissue.66 Elevated serum levels of cortisol and aldosterone are independent predictors of mortality in patients with heart failure.67 Aldosterone level is also elevated in patients with depression and may precipitate depression.67 Little is known about the relationship between aldosterone and anxiety. No studies on the relationship and changes of aldosterone level and anxiety or aldosterone in heart failure, depression, and anxiety are available.

<table>
<thead>
<tr>
<th>Neurohormone</th>
<th>Site</th>
<th>Action/effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing factor</td>
<td>Synthesized in hypothalamus and peripheral cells such as T lymphocytes</td>
<td>Signals hypothalamic neurons to synthesize and release adrenocorticotropin from the anterior part of the pituitary gland. Corticotropin then stimulates release of cortisol and aldosterone.</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Produced in the adrenal cortex</td>
<td>Increases glucose through gluconeogenesis. Suppresses the immune system. Aids in fat, protein, and carbohydrate metabolism. Decreases bone formation. Inhibits peripheral utilization of glucose (insulin resistance). Increases blood pressure by increasing sensitivity of the vasculature to epinephrine and norepinephrine. Promotes anti-inflammatory mechanism that reduces histamine secretion.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Produced in adrenal medulla and released from cells in adrenal medulla and postganglionic parasympathetic neurons</td>
<td>Increases blood pressure by increasing vascular tone. Directly increases heart rate. Causes release of glucose from energy stores. Increases blood flow to skeletal muscle. Increases oxygen supply to the brain.</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Produced and released mainly in adrenal medulla but also heart and brain</td>
<td>Increases heart rate. Increases blood vessel diameter. Promotes bronchodilation. Stimulates glycogenolysis in the liver and muscle. Inhibits insulin secretion. Increases levels of blood glucose and fatty acids.</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Produced by adrenal cortex</td>
<td>Promotes conservation of sodium. Promotes secretion of potassium. Increases water retention. Increases blood volume and therefore blood pressure.</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Produced by conversion of angiotensin I by angiotensin-converting enzyme</td>
<td>Causes vasoconstriction of systemic arterioles, resulting in elevated arterial blood pressure. Aids in norepinephrine release and reuptake. Increases circulating levels of antidiuretic hormone, resulting in increases in vasoconstriction and inhibition of water excretion.</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Produced by macrophages</td>
<td>Promote immunosuppression. Promote inflammation. Promote cardiac remodeling.</td>
</tr>
</tbody>
</table>

The table above provides a summary of major hormones involved in heart failure, depression, and anxiety.
Hyperactivity of the HPA axis mediates hyperactivity of the sympathetic nervous system and increases circulating levels of norepinephrine and epinephrine. Levels of circulating norepinephrine and epinephrine fluctuate in patients with heart failure. In patients with heart failure, high norepinephrine levels are predictive of poor prognosis. Patients with decompensated heart failure have increased levels of norepinephrine and epinephrine. However, patients with chronic but stable heart failure usually have increased levels of circulating norepinephrine but no marked changes in levels of circulating epinephrine. Myocardial levels of norepinephrine may be reduced in the later stages of heart failure.

Patients with depression and anxiety also have increased levels of norepinephrine and epinephrine. Emerging evidence on norepinephrine in depression indicates that the hormone has a determinant role in regulating cognition, motivation, and intellect, providing the fundamentals for social relationships. Epinephrine also regulates attention, mental focus, arousal, and cognition. One-quarter to one-half of individuals with anxiety or depression have both abnormalities, and this combination is also associated with increased severity of anxiety and depression.

Patients with heart failure who have signs and symptoms of depression and increased levels of norepinephrine and epinephrine have greater than normal responsiveness to β-adrenergics such as epinephrine. Increased β-adrenergic sensitivity is postulated to be associated with cardiac remodeling and progression of heart failure. Anxiety reduces compliance with medications, resulting in shorter event-free survival. No published studies on the combination of anxiety, epinephrine, and heart failure are available.

Autonomic Dysregulation and Sudden Cardiac Death

The autonomic nervous system regulates cardiovascular homeostasis via sympathetic and parasympathetic nerves. Norepinephrine and epinephrine are the major catecholamines released by the autonomic nervous system (see preceding section on activation of the HPA axis).
Heart rate varies frequently over time in response to changes in the physical and mental needs of the body. Ventricular rate can be calculated by measuring the RR interval on an electrocardiogram. Changes in the RR interval are described as either an increase or a decrease in heart rate variability. Therefore, heart rate variability, a measure of beat-to-beat alterations in heart rate, is used to measure autonomic neurocardiogenic dysfunction. Dysregulation of the autonomic nervous system is a predictor of progression of heart failure, mortality, and sudden cardiac death. Decreased heart rate variability is associated with increased severity of heart failure and increased dysrhythmia in patients with depression and anxiety. In patients with depression, an imbalance exists between sympathetic and parasympathetic tone. Induction of depression, defined as anhedonia in a rodent model, increased susceptibility to ventricular arrhythmias.

Risk of sudden cardiac death may be increased in patients with anxiety because of an increased risk for ventricular arrhythmias. Higher anxiety scores have been related to lower heart rate variability and increased risk of sudden cardiac death. The combined impact of autonomic dysregulation in patients with heart failure who have depression or anxiety disorders has not been established. According to the biopsychosocial holistic model, the biological factor of autonomic dysregulation is associated with heart failure and with depression and anxiety.

Renin-Angiotensin-Aldosterone System

The release of aldosterone is also initiated by the renin-angiotensin-aldosterone system (RAAS). The release of renin, an enzyme synthesized, stored, and released by juxtaglomerular cells in the kidney, is stimulated by the sympathetic nervous system, renal artery hypotension, and decreased amounts of sodium delivered to the distal tubules of the kidney. After release by juxtaglomerular cells, renin moves into the bloodstream, leading to conversion of the inactive plasma protein angiotensinogen to angiotensin I. Then, angiotensin-converting enzyme converts angiotensin I to angiotensin II. After this conversion, angiotensin II stimulates the adrenal cortex to release aldosterone. Aldosterone is metabolized in the liver. In patients with heart failure and resulting liver congestion, aldosterone levels are increased. Angiotensin II also causes vasoconstriction of systemic arterioles, resulting in elevated arterial blood pressure. Other potent effects of angiotensin II in patients with heart failure are inhibition of the release and reuptake of norepinephrine and increases in circulating levels of anti-diuretic hormone, which also increase vasoconstriction and inhibition of water excretion.

Other important pathophysiological complications due to angiotensin II and aldosterone are release of inflammatory cytokines, activation of macrophages at sites of injury, attraction of neutrophils and macrophages, increased growth of fibroblasts, and synthesis of collagen fibers. Deposition of fibroblasts and collagen results in ventricular hypertrophy and fibrosis of the myocardial wall, leading to inappropriate heart remodeling and subsequent systolic and diastolic ventricular dysfunction.

The RAAS is activated in both patients with depression and patients with anxiety. In a study by Häfner et al, depressive symptoms alone were not linked to increased activation of RAAS, but patients with chronic stress and depressive symptoms had activation of the system. No investigators have examined the RAAS and depression and heart failure or RAAS and anxiety and heart failure.

Activation of Cytokine Cascades

Cytokines are widely secreted peptides that mediate and regulate cellular immune function. Cytokines exert both proinflammatory and anti-inflammatory control over physiological conditions. Like the neurohormones previously discussed, under normal physiological conditions, cytokines limit the potentially injurious effects of sustained inflammatory reactions. When proinflammatory cytokines are unchecked by anti-inflammatory cytokines, illness such as heart failure may result. Proinflammatory cytokines have direct toxic effects on the heart and are hypothesized to be responsible for myocardial remodeling and progression of heart failure.

TNF-α and interleukin-6 (IL-6) are proinflammatory cytokines that produce abnormal endothelium-dependent vasodilation and myocardial dysfunction. High levels are independent predictors of mortality in patients with...
heart failure. Increased plasma levels of IL-6 in patients with heart failure are associated with activation of the sympathetic nervous system. TNF-α initiates processes that result in left ventricular dysfunction, pulmonary edema, and cardiomyopathy. Elevated levels of peripherally circulating TNF-α are associated with increased severity of heart failure. Three sources of TNF-α after myocardial injury in heart failure are proposed: (1) TNF-α produced locally in the myocardium triggers the HPA axis and leads to secondary activation of the immune system in the periphery; (2) decreased cardiac output causes underperfusion of systemic tissues and leads to elaboration of the factor; and/or (3) activation of the immune system occurs in response to injury from some index event.

Complex and not fully understood, depression is accompanied by moderate activation of proinflammatory cytokines, in particular TNF-α, IL-1, and IL-6. Receptors for these cytokines have been found in the hippocampus and hypothalamus. Levels of TNF-α were significantly higher in outpatients with depression and heart failure than in outpatients with heart failure and no depression. In addition, levels of IL-6 were higher in patients with depression and heart failure who were hospitalized. Cytokines can be also triggered by mental stress and are associated with anxiety and fear in healthy people without heart failure. Administration of cytokines to patients can produce "sickness behavior," which is characterized by marked behavioral symptoms of depression and anxiety that include increased sleep, decreased appetite, malaise, decreased motivation, impairment in cognition, and depressed memory.

C-reactive protein is found in the blood and is known as an acute-phase protein, or a marker of inflammation. The release of IL-6 triggers the synthesis of C-reactive protein by the liver. Serum levels of C-reactive protein are elevated in cardiovascular disease, and research on C-reactive protein in patients with heart failure is increasing. Increased levels of C-reactive protein are associated with increased severity of heart failure and can independently increase morbidity and mortality in patients with heart failure. After an episode of acute heart failure, levels of C-reactive protein increase and contribute to a poor prognosis at 30 and 180 days. Patients with depression and anxiety have elevated levels of C-reactive protein. According to the biopsychosocial holistic model, the biological factors of cytokines, levels of C-reactive protein, and heart failure interact with the psychological factors of depression and anxiety, compounding the possibility for a poor prognosis in patients with heart failure who are depressed or anxious or both.

Platelet Activation

The biological factor of heart failure and the psychological processes of depression and anxiety increase platelet reactivity. In heart failure, through a complex process that includes a cascade of neurohormones, activated platelets interact with leukocytes to adhere to endothelial cells in the vasculature and promote thrombosis. Through stimulation of platelet receptors for norepinephrine and epinephrine, elevated levels of circulating catecholamines potentiate platelet responses. Platelet activation is increased in depression. No published articles on platelet activation in anxiety or on platelet activation in depression and heart failure are available.

Summary of Pathophysiological Mechanisms That Link Depression and Anxiety to Heart Failure

Increased activation if the HPA axis, autonomic dysregulation, activation of RAAS, and cytokine cascades occur in patients with heart failure who are depressed or anxious. Because of the combined effects of emotional distress and heart failure, patients with heart failure who are depressed or anxious may be at greater risk than patients who are not depressed or anxious for progression of heart failure. The substantial research supporting increased mortality in depressed patients with heart failure provides noncausal evidence of the relationship.

Effects of Selective Serotonin Reuptake Inhibitors and Exercise

A recent systematic review of studies from 1996 to 2011 provided an evaluation of the effects of intervention on depression in patients with heart failure. Evidence was strong for the use of selective serotonin reuptake inhibitors, and moderate evidence supported use of exercise to reduce depression in patients with heart failure. Disease management programs for patients with heart failure did not improve depressive symptoms.
The effect of selective serotonin reuptake inhibitors on depression in patients with heart failure was examined in 4 double-blind, placebo-controlled randomized trials.97-100 Use of paroxetine98 and sertraline99 reduced depression in 2 of the trials, whereas use of sertraline97 and citalopram100 yield no improvement in 2 other trials. The limitation of the 2 studies in which no difference occurred was that the control groups in both studies inadvertently received therapeutic interventions. The strength of the evidence is high that paroxetine and sertraline are effective in treating depression in patients with heart failure.96

The effects of an exercise program on depression in patients with heart failure were examined in 7 studies.101-107 The exercise programs varied by type, intensity, frequency, duration, and patients’ adherence. Despite the differences, the strength of the evidence was moderate that exercise is effective at decreasing depressive symptoms in patients with heart failure. The recently completed HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) indicated that regular exercise confers a modest reduction in the risk for all-cause mortality or hospitalization in patients with heart failure.108 The same trial indicated a significant reduction in depressive symptoms, illustrating that exercise may be an effective intervention for reducing depressive symptoms and preventing worsening of depressive symptoms of patients with heart failure.109 Physical activity also enhances anti-inflammatory responses and reduces proinflammatory responses.110 Currently, physical activity is recommended as safe and effective in patients with heart failure.111

Multidisciplinary, multicomponent disease management programs for patients with heart failure were examined in 7 studies.112-118 The results were strong evidence that disease management programs do not decrease depressive symptoms in patients with heart failure. The objective of disease management programs is not reduction in depression, and these programs may have other benefits for patients with heart failure. Currently no clinical guidelines for diagnosing and treating depression in patients with heart failure are available.119 Further research is needed to establish effective treatments for depression in patients with heart failure.

Nursing Implications

Screening and Assessment

Development of a comprehensive evidence-based assessment tool that includes depression, anxiety, and physical activity patterns for patients with heart failure is essential. Nurses who care for patients with heart failure can benefit from an understanding of pathophysiology, signs and symptoms, depression, and anxiety. Signs and symptoms of heart failure can mimic signs and symptoms of depression and anxiety, and shared pathophysiological mechanisms may potentiate comorbid progression. Improvement in depression and anxiety is associated with improvement in medication compliance and health outcomes in patients with cardiovascular disease.115

Patient and Family Education

Patients and their families may lack understanding of the diagnoses of depression and anxiety, the underlying pathophysiology, and the interrelationships between depression, anxiety, and heart failure. Patients and their family members also require education about treatment options for depression that include selective serotonin reuptake inhibitors (paroxetine and sertraline), exercise, and physical activity. Important information for patients and families about these treatments includes the side effects, the length of treatment required for anticipated benefits to begin, and the possibility that more than 1 treatment may be required to obtain effective results. Patients and their families should be encouraged by the knowledge that an improvement in quality of life often accompanies improvement in the signs and symptoms of depression and anxiety.119

Implications for Nursing Research

Similar pathophysiological processes in depression, anxiety, and heart failure suggest that the onset and progression of these conditions may be linked. Although anxiety in heart failure is common, few investigators have evaluated anxiety in patients with heart failure. More research on anxiety in patients with heart failure is needed. Research on the pathophysiological changes that occur in patients with heart failure who are depressed and anxious is critical. Evidence-based treatments for depression and anxiety in patients with heart failure have not been established. Research is needed to determine which treatments are most effective and whether the treatment
of depression and anxiety will improve morbidity and mortality in patients with heart failure.

Conclusion

Increasing evidence supports depression and anxiety as frequent comorbid conditions in patients with heart failure. Major pathophysiological changes that occur in depression and anxiety have potentially deleterious effects on the heart. Using a holistic model to understand the integration of mind and body in health status, nurses can improve assessment and treatment of patients with heart failure who are depressed and anxious. The most effective treatments for depression and anxiety in patients with heart failure have not been established. Research is needed on the physiological changes that occur in patients with heart failure who are depressed and anxious. Research is needed to determine which treatments are most effective and whether the treatment of depression and anxiety will improve morbidity and mortality in patients with heart failure, depression, and anxiety. CCN

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None reported.

References


1. Which of the following are the neurohormones involved in heart failure (HF)?
   a. Glucagon, acetylcholine, aldosterone, and cortisol
   b. Aldosterone, growth hormone releasing factor, oxytocin, and TNF-α
   c. Angiotensin II, cortisol, somatostatin, and glucagon
   d. Norepinephrine, angiotensin II, aldosterone, and TNF-α

2. Which of the following statements best reflects the biopsychosocial holistic model of cardiovascular health?
   a. Depression and anxiety are usually only increased in HF patients with a lower socioeconomic status.
   b. Neurohormonal dysfunction from HF is the primary cause of depression and anxiety.
   c. The interaction of physiologic and psychological factors affects HF patients and may lead to increased depression and anxiety.
   d. The holistic model of depression/anxiety/HF indicates that pet therapy always alleviates anxiety.

3. Which of the following statements best describes activation of the hypothalamic-pituitary-adrenal (HPA) axis in cardiovascular function?
   a. Neurohumoral dysfunction in HF decreases the incidences of depression and anxiety through decreased activation of the HPA axis.
   b. Mental and physical stress leads to a release of cortisol and aldosterone, which leads to increased inflammation and hypertension and cardiac remodeling.
   c. The HPA axis is only activated by a failing ventricle, which increases aldosterone production.
   d. Hypoactivity of the HPA axis increases the production of circulating levels of norepinephrine and epinephrine, which leads to decompensated HF.

4. Which of the following statements best reflects the effects of psychological status on HF patients?
   a. Depression in HF patients is less prevalent than in the general population.
   b. HF patients with depression symptoms have higher mortality rates.
   c. Anxiety in HF patients causes increased platelet activation.
   d. Psychological effects from neurohormonal dysregulation cause HF through inhibition of serotonin secretion.

5. Which of the following statements uses the biopsychosocial holistic model to address cardiovascular health?
   a. Medication management in HF prevents the progression of disease.
   b. Psychological therapy as a single modality decreases anxiety in HF patients.
   c. Increased readmission rates for HF patients can be related to social support and medication management.
   d. Neurohormonal dysfunction in HF is a short-term problem.

6. Which of the following statements best reflects the effect of autonomic dysregulation and HF?
   a. Heart rate variability is caused by the release of pro-inflammatory cytokines.
   b. PR intervals are used to measure heart rate variability in HF patients.
   c. Depressed patients experience heart rate variability due to sympathetic and parasympathetic tone imbalances.
   d. The renin-angiotensin-aldosterone system (RAAS) increases cardiac arrhythmias leading to sudden cardiac death.

7. Which of the following statements best describes the role of the cytokine cascade in HF?
   a. TNF-α is a pro-inflammatory cytokine that leads to left ventricular dysfunction.
   b. Decreased interleukin-6 in HF patients is a predictor of mortality.
   c. Pro-inflammatory cytokines are not implicated in toxic effects on heart muscle.
   d. The cytokine cascade is mediated by C-reactive protein in depressed patients.

8. Nursing management of HF patients with depression and anxiety includes which of the following?
   a. Frequent vital signs, visitor restrictions, and medication education
   b. Enrollment in out-patient disease management program
   c. Fluid restriction, a psychiatric consult, and frequent vital signs
   d. Education regarding treatment options for depression including selective serotonin reuptake inhibitors and exercise.

9. Which of the following statements summarizes the pathophysiological processes of depression, anxiety, and HF?
   a. Neurohumoral dysregulation in depressed and anxious patients causes worsening HF.
   b. Increased sodium and water retention and increased catecholamine levels lead to increased anxiety.
   c. Activation of the HPA axis, cytokine and platelet cascade, and autonomic dysfunction in depressed and anxious patients affects cardiovascular function in HF patients.
   d. Aldosterone production and cytokine cascade are the primary connection of HF to depression and anxiety.

10. Which of the following statements reflects the role of norepinephrine in depression and HF?
    a. Mental focus and attention are regulated in depressed patients by norepinephrine.
    b. Patients with depression and HF have increased circulating norepinephrine.
    c. Hyperactivity of the parasympathetic nervous system is mediated by norepinephrine in HF.
    d. High circulating norepinephrine levels are associated with improved prognosis in HF.

11. Which of the following statements best reflects research regarding patients with HF, depression, and anxiety?
    a. Current evidence indicates the most effective treatments for patients with HF and depression are based on biologic factors.
    b. The progression of HF is not linked to anxiety.
    c. The similar pathophysiological changes for HF, depression, and anxiety would benefit from nursing research to determine treatment guidelines.
    d. Qualitative research on quality of life for the depressed and anxious HF patient is robust.

12. Which of the following statements is true regarding the RAAS?
    a. The parasympathetic nervous system regulates the release of renin.
    b. Angiotensin II and aldosterone promote release of inflammatory cytokines.
    c. The RAAS is inhibited in patients with depression and anxiety.
    d. The activation of angiotensin II in HF causes the release of norepinephrine.