Chapter 9

Neuroimmune Mechanisms of Depression in Adults with Heart Failure

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Abstract

Heart failure (HF) is a major and costly public health concern, and its prognosis is grim—with high hospitalization and mortality rates. HF affects millions of individuals across the world, and this condition is expected to become "the epidemic" of the twenty-first century (Jessup et al., 2016). It is well documented that individuals with HF experience disproportionately high rates of depression and that those who are depressed have worse clinical outcomes than their nondepressed counterparts. The purpose of this chapter is to introduce the reader to the study of depression in HF, and how psychoneuroimmunologic principles have been applied to further elucidate mechanisms (i.e., neurohormonal and cytokine activation) linking these comorbid disorders.

Key words Heart failure, Depression, Inflammation, Renin-angiotensin-aldosterone system, Sympathetic nervous system, Gut microbiota and metabolites

1 Introduction

Heart failure (HF) is a major public health concern, especially in societies where a sizable proportion of the population is over 65 years of age. HF is often the last stage of cardiovascular disease, and its prognosis is grim—with high hospitalization and mortality rates. Interestingly, heart disease, including HF, is often accompanied by a psychological symptom complex, including low mood, hostility, anger, and poor quality of life [1].

In recent years, the study of depression in HF has garnered scientific interest due to its high prevalence in individuals with HF and its strong tendency to worsen medical prognosis [1–6]. Although the etiology of depression in HF remains unclear, the disorders appear to share a similar pathogenesis involving disturbance of the balance between sympathetic and parasympathetic tone and increased inflammation, as evidenced by elevated circulating levels of proinflammatory cytokines [2, 4]. Considering that depression has also been associated with incident HF [7, 8], most

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scholars favor a bidirectional pathophysiology, in which depression may precede or follow the development of HF.

The purpose of this chapter is to introduce the reader to the study of depression in HF, and how psychoneuroimmunologic principles have been applied to further elucidate the mechanisms linking these comorbid disorders. We begin the chapter with a brief discussion of the epidemiology and pathophysiology of HF, and then of the characteristics and consequences of depression in HF, and conclude with discussion and presentation of relevant psychoneuroimmunological findings concerning the shared pathophysiology of depression and HF.

2 Heart Failure

2.1 Epidemiology of Heart Failure

In the United States, among those aged 20 years and older, the prevalence of HF is 2.2% [9, 10]. At 40 years of age, the lifetime risk of developing HF is 1 in 5. HF incidence rates in men approximately double with each 10-year age increase from 65 to 85 years; however, the HF incidence rate triples for women between ages 65 and 84 years [11]. Researchers from the cohort study Multi-Ethnic Study of Atherosclerosis found that African-Americans had the highest risk of developing HF, followed by Hispanic, White, and Chinese-Americans (4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively). This higher risk may reflect racial and ethnic disparities as evidenced by the prevalence of hypertension, DM, and low socioeconomic status among various groups [12].

Despite significant advances in treatment, the prognosis for patients remains grim: 29.6% of HF patients die within 1 year of diagnosis and 50% die within 5 years [13]. Approximately three million patients get hospitalized each year with a primary or secondary diagnosis of HF making it one of the most common causes of hospitalization in the elderly population in the United States [14]. HF costs approximately $31 billion, and is projected to cost a total of $70 billion by 2030 [11].

2.2 Definition and Classification of Heart Failure

The American College of Cardiology (ACC) and American Heart Association (AHA) define HF as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood [15]. The upper chambers of the heart are composed of the right and left atria, and the lower chambers include the right and left ventricles. The ventricles are muscular chambers that contract to pump blood (*systole*). After systole, the ventricle muscles normally relax during *diastole*, allowing blood from the atria to fill the ventricles. The heart's ability to pump can be compromised via two mechanisms: (1) reduction in the volume of oxygenated blood ejected from the left ventricle as a result of diminished

myocardial contractility and (2) inadequate venous return to heart, resulting from impaired ventricle filling and relaxation.

Although HF varies in its etiologies and clinical features, it can be broadly classified into two categories: HF with systolic dysfunction (also known as "HF with reduced ejection fraction" (HFrEF)), characterized by a reduced left ventricle ejection fraction (LVEF), which is a measure of the percentage of blood that is ejected from the heart into the aorta with each systole, and HF with preserved ejection fraction (HFpEF) which is a complex disorder, where LVEF is normal or mildly abnormal. As far as treatment and outcome are concerned, patients with HFrEF respond favorably to the standard pharmacological treatment regimen and demonstrate better prognosis. In contrast, patients with HFpEF have not been shown to respond to standard pharmacological treatments, except for nitrates, and therefore have a poor prognosis, especially during the decompensated phase of HF [16]. Other left ventricle (LV) abnormalities include abnormal relaxation and filling, concentric remodeling, hypertrophy, increased extracellular matrix, abnormal relaxation and filling, decreased diastolic distensibility, and abnormal calcium handling.

There are two primary scales that are used to classify HF. The New York Heart Association (NYHA) functional scale, which is based on severity of symptoms and exercise intolerance, classifies HF in categories from I to IV (Table 1). However, symptom severity correlates poorly with many measures of LV functions. Although there is a clear relationship between severity of symptoms and survival, even patients with mild symptoms may still have an increased risk of hospitalization and death [17]. The other scale is the American College of Cardiology/American Heart Association (ACC/AHA) scale, a newer classification that stages patients as either A, B, C, or D based on structural changes and symptoms (Table 1) [15]. The ACC/AHA staging system classifies HF as a progressive disease, and once a particular stage is reached there is no opportunity to transition to a lower stage (e.g., a stage C HF patient cannot return to stage B). This system is often complemented by the NYHA functional classification system. In contrast, ACC/AHA Stage C patients can shift between functional classes I–IV at any given time. Movement up and down NYHA classes is common, depending on the clinical status of the patient during the time of assessment.

3 Pathophysiology of Heart Failure

HF is characterized by activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), as well as inflammatory pathways. Regardless of its etiology and classification, HF begins with injury to the myocardium (e.g., years of

Table 1
Functional classifications and disease progression stages of heart failure

New York Heart Association Functional (NYHA) classes		
	Definition	**Examples**
NYHA Class I	No limitation of physical activity	Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
NYHA Class II	Slight limitation of physical activity	Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
NYHA Class III	Marked limitation of physical activity	Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
NYHA Class IV	Unable to carry out any physical activity without discomfort	Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased
American College of Cardiology/American Heart Association stages of heart failure		
	Definition	*Examples*
Stage A	High risk for developing HF, but without structural heart disease or symptoms of HF	Hypertension, diabetes mellitus, CAD, family history of cardiomyopathy
Stage B	Structural heart disease, but asymptomatic	Previous myocardial infarction, left ventricular dysfunction, valvular heart disease
Stage C	Structural heart disease with previous or current symptoms, but managed with medical treatment	Structural heart disease, dyspnea and fatigue, impaired exercise tolerance
Stage D	Marked symptoms at rest despite maximal medical therapy	Advanced disease requiring hospital-based support, a heart transplant, or palliative care

sustained hypertension and/or myocardial infarction), which reduces cardiac output. In response, the body engages in a series of compensatory mechanisms, including (1) maintaining perfusion pressure by increasing the circulation of blood volume; (2) activating immune and inflammatory pathways; and (3) restructuring cardiac muscle cells and reshaping the ventricle chamber (called remodeling). This systematic response involves complex interactions between the RAAS and SNS, which are collectively referred to as neurohormonal responses.

Neurohormonal activation and cytokine activation are designed for acute responses to injury, but prolonged activation of these compensatory mechanisms eventually leads to further declines in cardiac functioning. Currently, the most successful pharmacological therapies for HF block aspects of the body's

compensatory responses to myocardial injury [15]; thus, there is increasing scientific interest in understanding neurohormonal and cytokine activation in the context of HF.

3.1 Renin-Angiotensin-Aldosterone System

The RAAS system maintains renal blood flow after the myocardium has sustained injury via its effects on remodeling the vasculature and increasing plasma volume. Decreased renal perfusion pressure results in secretion of renin by juxtaglometer cells lining the afferent renal arterioles. Specifically, renin cleaves angiotensinogen to form decapeptide angiotensin I. The angiotensin-converting enzyme (ACE) cleaves two C terminal amino acids to form angiotensin II, the primary effector of the system. Receptors for angiotensin II are divided into subtypes, AT-1 and AT2. AT-1 is the predominate subtype in the vascular endothelium and a primary target for pharmacologic blockade. Binding of angiotensin II to AT-1 receptors results in increases in the release of intracellular calcium from the sarcoplasma reticulum via activation of protein kinase C. The binding of angiotensin II in the vasculature results in an increase in systematic vasculature resistance and restoration of blood pressure.

Prolonged compensatory actions of the RAAS in HF bring adverse consequences, however, including increased vascular resistance. Increases in resistance create undue myocardial burden and decreased cardiac output, resulting in left ventricular hypertrophy. Angiotensin II initiates apoptosis and interstitial fibrosis, which contribute to the remodeling of the extracellular matrix in the myocardium (e.g., myocyte hypertrophy). The effects of angiotensin II on the myocardium and peripheral vasculature result in decreased cardiac output and renal perfusion. Angiotensin II is also involved in the increase of plasma volume by initiating production of mineralocorticoid aldosterone by the adrenal cortex. Aldosterone acts on the distal tubules of the renal nephron and activates a sodium-potassium exchange, which results in the retention of sodium and water. The increased plasma volume exacerbates fluid overload and peripheral edema. Chronic excess of aldosterone leads to increased fibrosis in the atria, ventricles, kidneys, and perivasculature.

3.2 Sympathetic Nervous System

Vascular baroreceptors respond to declines in cardiac output and stroke volume by increasing sympathetic nerve activity and consequent release of the catecholamine norepinephrine. Sympathetic activation improves cardiac output by increasing heart rate, myocardial contractility, and stroke volume. Sympathetic activation also increases systematic resistance and blood pressure in the peripheral vasculature, and via catecholamines increases renin release and angiotensin II production, further increasing vascular resistance and afterload.

The direct effects of sympathetic activation on the myocardium itself are primarily mediated via two classes of β-adrenergic receptors, namely the β-1 and β-2 receptors. In a normal heart, β-1s comprise approximately 80% of the total β-adrenergic receptor pool [18]; however, chronic sympathetic activation significantly downregulates β-1 receptors leaving a greater proportional presence of β-2 receptors of approximately 40% [18]. While β-2 receptors are less downregulated, they are susceptible to inactivation from repetitive agonist stimulation, becoming less responsive to adrenergic agonists. Although the release of norepinephrine acutely increases myocardial contractility, chronic stimulation in HF worsens cardiac function (direct cytotoxic effects), resulting in progressive dysfunction of the left ventricle, worsening pulmonary edema, and potentially death. Higher levels of circulating norepinephrine have been associated with poorer survival, and greater functional decline in HF.

3.3 Systemic Inflammation

The "cytokine hypothesis" proposes that HF progression is an inflammatory process and that elevated levels of proinflammatory cytokines worsen LV dysfunction. There is a significant body of evidence to suggest that elevated levels of cytokines are associated with cardiac decline in HF. Particularly, the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interluekin-6 (IL-6) are among the most widely studied cytokines in HF.

TNF-α is a polypeptide that activates endothelial cells, recruits inflammatory cells, and enhances the production of other proinflammatory cytokines. TNF-α is secreted from immune cells during the early stages of HF; however in the final stages, the cardiac myocytes secrete TNF-α in high quantities. TNF-α appears to be particularly important in the transition from compensated to acute decompensated HF, the latter being a state of exacerbated HF requiring hospitalization. TNF-α has been extensively studied in animal models, and overexpression of TNF-α by the cardiac myocytes leads to inflammatory myocarditis and subsequent myocyte hypertrophy, LV dilatation, and progressive LV dysfunction. For example, exogenous administration of TNF-α at concentrations comparable to those observed in HF produces significant declines in myocardial contractility, worsening LV dysfunction and increasing pulmonary edema.

IL-6 is also elevated in HF, particularly in the end stages of the disease. Although IL-6 was initially thought to have only proinflammatory effects like those of TNF-α, research in murine models suggests that IL-6 also plays an immune-modulatory role in response to secretion of TNF-α. IL-6 has direct effects on the myocardium, including decreasing contractility, activating matrix metalloproteinases, and contributing to LV remodeling. Like TNF-α, IL-6 is secreted from the myocardial cells during the end stages of HF, but not during mild or moderate stages of the disease.

4 Depression in Heart Failure

4.1 Epidemiology of Depression in Heart Failure Patients

Depression in HF has been extensively studied because of its high prevalence in HF patients and its tendency to worsen medical prognosis [1–6]. Studies show that depression is one of the most important modifiable risk factors because it is responsible, in part, for the high readmission rates among HF patients. The estimated prevalence of depression in HF is 24–42%, which is 2–3 times higher than the general population. The prevalence rate of minor depression, as defined by the Beck Depression Inventory ≥ 10, is as high as 35.5%. Although the majority of studies demonstrate that depression worsens cardiac prognosis, the magnitude of the effects has varied greatly depending on how depression is measured [2].

Depression has also been associated with incident HF. In a community sample of 2501 patients (mean follow-up 14 years), Williams and colleagues found that depression was an independent predictor of developing HF in women (HR = 1.96, 95% CI = 1.11, 3.46, $p = 0.02$), but not in men [7]. In a study of 4538 older adult patients enrolled in the Systolic Hypertension in the Elderly Program (SHEP), depressed patients were 2.82 times (95% CI = 1.71, 4.67; $p < 0.001$) more likely to develop HF over a 4.5-year follow-up period [8]. The association between depression and HF did not significantly vary by sex. Although not all studies have found gender effects, Williams et al.'s findings follow trends seen in depressed, non-HF populations: the National Comorbidity Survey, for example, reported a 1.7 greater odds of women developing depression at some point in their lifetime compared to men [19].

4.2 Patient Characteristics and Depression

The prevalence of depression in HF appears to significantly differ by health status, demographics, and social factors. In their meta-analysis of depression in HF, Rutledge et al. found that 11–25% of outpatients and 35–70% of inpatients were depressed [20]. Rutledge and colleagues also found that depressive symptomatology increased with severity of HF diagnosis, ranging from 11% of patients with New York Heart Association (NYHA) functional class I to 42% of NYHA class IV patients [20]. Several studies have found higher depression in younger as well as female HF patients [2, 21]. Social factors may contribute to incident depression in HF. In a study of 245 HF patients without depression at baseline, living alone, alcohol abuse, perception of medical care as being a substantial economic burden, and poor health status were independent predictors of developing depressive symptoms [22]. The effects appear to be multiplicative in nature: 15.5% of patients developed depression when only one of the factors were present, 36.2% developed depression when two factors were present, and 69.2% developed depression when three or more were present.

4.3 Clinical Outcomes in Heart Failure Patients with Depression

Of great clinical significance, studies find that depression has adverse effects on the course and prognosis of HF. Increased psychological surveillance of HF patients over the past 15 years has highlighted the pivotal role of depression in HF [23]. Development of depressive symptoms after the diagnosis of HF is associated with a 1.5- to 2.2-fold increase in all-cause and cardiovascular mortality [24]. Depression is an independent risk factor for hospital readmission in patients with HF [25–27]. In the Telemonitoring to Improve Heart Failure Outcomes Trial, the 30-day readmission rate was 17.1% [28]. Kato et al. found that depression was associated with more cardiac mortality or HF hospitalization in both HFrEF (55% vs. 12%, $p < 0.01$) and HFpEF (35% vs. 11%, $p < 0.05$; [29]). Sherwood et al. [30] reported that depressive symptomatology was associated with a 1.56 (95% CI; 1.07, 2.29; $p < 0.001$) increased risk of death or hospitalization during a median 3-year follow-up period. In a sample of 374 patients hospitalized for HF, Jiang and colleagues [31] found that HF patients with major depression had 2.23 greater odds (95% CI 0.04, 4.77; $p = 0.04$) of mortality and 3.07 (95% CI 1.41, 6.66; $p = 0.005$) greater odds of readmission at 1 year compared to HF patients with no depression. In a sample of 1006 hospitalized HF patients, Jiang et al. [32] found that patients whose Beck Depression Inventory (BDI) scores were 5 to 9, 10 to 18, and ≥19 were 21%, 53%, and 83%, respectively, more likely to die than patients whose BDI score was ≤5 ($p < 0.001$). Vaccarino et al. [33] also found that there was a grade associated between the number of depressive symptoms and increased risk of death or decline of daily living at 6 months. In this prospective study of 391 patients with decompensated HF on admission to the hospital, patients with ≥11 depressive symptoms, compared with those with <6 depressive symptoms, had an 82% higher risk of either functional decline or death. In a study of longitudinal outcomes (mean follow-up 39 months) in HF patients with comorbid atrial fibrillation, Frasure-Smith and colleagues [34] found that elevated depressive symptoms significantly predicted cardiovascular mortality (HR: 1.57; 95% CI 1.20, 2.07; $p < 0.001$). The authors also commented that the increased risk of death was similar to risks associated with not taking standard medications to manage HF, such as anticoagulants and aldosterone antagonists. Worsening depressive symptomatology over time is also associated with increased risk of adverse outcomes. A study of 147 HF outpatients found that a 1 point change in BDI scores was associated with 1.07 increased risk of death or cardiovascular hospitalization (95% CI 1.02, 1.12, $p = 0.007$) [24]. The results from these studies indicate that depression is an independent predictor of worse clinical outcomes in HF patients [23].

4.4 Quality of Life in Heart Failure Patients with Depression

In addition to its cardiotoxic effects, depressed HF patients suffer from reduced physical functioning and of course worse quality of life: depressed patients report poorer quality of life and greater functional impairment than nondepressed patients, even when compared with patients of a higher (i.e., worse) NYHA functional class, which may suggest that patient perceptions of physical functioning, rather than the clinical status itself, predict quality-of-life outcomes [35, 36]. In a small study ($n = 58$) of associations between disease severity, functional status, depression, and daily quality of life, greater depression severity was positively associated with worse self-reported physical and emotional quality of life in HF patients. A recent study by Hallas et al. [37] conducted in 146 HF patients found that patients with more negative beliefs about the consequences of HF, and less perceived control, were more anxious and depressed compared to patients with more positive beliefs. Greater depression ratings also predicted poorer quality of life. Patients with more negative beliefs also had more maladaptive behaviors and less coping resources, which may also have downstream effects on quality of life. In a study of 155 HF patients, Gottlieb et al. [21] found that depressed patients scored significantly worse than nondepressed patients on all components of the quality-of-life questionnaires. In a more recent study, Gottlieb and colleagues [38] demonstrated that depression is minimally related to objective assessments of HF severity, such as peak O_2 consumption, B-type natriuretic peptide (BNP) levels, or ejection fraction. However, depression significantly affects subjective measurements of HF severity, such as NYHA classification or 6-min walk test [10]. Undoubtedly, depression negatively affects quality of life, but there is building evidence to also suggest that depression alters patient perceptions of physical functioning and disease severity, which may result in poorer ratings on subjective measures.

4.5 Screening for Depression in Heart Failure Populations

Given that depressive symptoms are a strong predictor of HF outcomes, screening has become an important part of patient assessment [20]. The American Heart Association (AHA) advocates a two-step screening process using two versions of the Patient Health Questionnaire (PHQ): the PHQ-2, which includes two items from the PHQ-9 is administered as a first-line screening for depression. Positive results on the PHQ-2, the PHQ-9 is subsequently administered for further evaluation [39]. The usefulness of the PHQ-2 or the PHQ-9 results as a predictor of prognosis in patients with HF has been examined in many studies [40–42]. However, it is unclear if there is any advantage in using a two-step screening process as opposed to using the PHQ-2 alone or the PHQ-9 alone [43].

4.6 Treatment of Depression on Heart Failure Outcomes

It is difficult to diagnosis depression in HF due to the overlapping symptoms of the two conditions. Considering the prevalence of depression in HF, as well as the magnitude of its negative effects on the clinical outcomes, it is surprising that as few as 7% of patients receive antidepressant therapies [16]. Depressive symptoms continue to be persistent in HF patients even in the face of antidepressant therapy. In the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study, a randomized trial of aerobic exercise in patients with systolic HF, Gottlieb et al. reported that 29% of patients taking antidepressantshad at least mild depression (BDI $\geq$ 10; [38]). However, even under the most ideal conditions, such as the Sertraline against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) where patients in the intervention group receive 12 weeks of antidepressant therapy as well as a nurse facilitated support intervention, 46% of the treatment group did not remit during the trial [44]. Although there is no strong evidence to indicate that treating depression improves cardiovascular outcomes in HF [6], the SADHART-CHF study found that remission from depression, regardless of treatment assignment, was associated with fewer cardiovascular events [45].

Serotonergic agents are the first line of antidepressant treatment even though placebo-controlled, randomized trials of sertraline and escitalopram have not demonstrated improved HF outcomes [1]. There is evidence to suggest that more complex interventions that incorporate cognitive-behavioral therapy may reduce depressive symptomatology, anxiety, and fatigue, but there is no evidence to suggest that these interventions significantly improve cardiovascular outcomes or self-care practices related to HF management, such as low-sodium diet, exercising, taking prescribed medications, and monitoring edema [46]. Given that HF patients are disproportionately affected by depression, and those suffering with it experience worsened health outcomes, understanding relationships between HF and depression and its treatment is of growing importance among many clinicians.

5 Psychoneuroimmunology: Understanding Pathophysiological Links Between Heart Failure and Depression

Given the adverse effects of depression on cardiac prognosis, understanding the biological pathways that link HF and depression may provide routes for pharmacological and behavioral interventions. The comorbid nature of HF and depression suggests that they share a similar pathophysiology: inflammation.

After more than a decade of research on this topic, although the mechanistic relationships between depression and inflammation are

not fully understood, much progress has been made. Depressed patients without HF have significantly higher levels of IL-1β, IL-6, TNF-α, and interferon-gamma (IFN-γ) [47]. Potential sources of inflammatory activation in HF include SNS activation and hyperactivity of the hypothalamic-pituitary-adrenal axis [48, 49].

5.1 Lessons Learned on Inflammatory and Other Immune Responses in Depression in HF

One of the main lines of investigation in our laboratory has been the application of the cytokine model and other theoretical models of broader immune activation in the context of depression in HF. We have conducted several studies that lend support to the theory that systematic inflammation, as well as broader dysregulation of immune system, may underlie the relationship between depressive symptoms and progression of HF. Our approach to the study of these topics is the use of both cross-sectional and prospective studies. For the former, we have assessed a broad range of inflammatory and cell adhesion biomarkers in patients with established HF and with a range of depressive symptomatology. For the latter, we are studying ACC/AHA Stage B patients, individuals who were at risk for developing symptomatic HF but who were not symptomatic. In these individuals, we are assessing a broad range of inflammatory and cell adhesion biomarkers as well as depression, but this time repeatedly over the course of several years. The intention is to temporally model inflammation as it relates to the onset and offset of depression and to the onset and progression from non-symptomatic to symptomatic HF.

5.2 Assessing Depressive Symptoms

A potential explanation for the link between depression and HF may be inherent due to the diagnosis of depression, and measure of its severity. The diagnostic criteria for major depressive disorder as well as screening for depressive symptoms include both cognitive and somatic symptoms. Thus, depressive symptomatology, such as fatigue, loss of energy, problems concentrating, weight loss or gain, and sleep disturbance, may be the result of underlying cardiac dysfunction [5]. More recent studies have recognized this overlap, and now it is favored to report somatic and cognitive symptomatology separately as we have done in our studies.

In our studies we have primarily measured depression via the Beck Depression Inventory (version–IA; BDI-IA), which is a 21-item self-administered assessment of extent to which patients experience depressive symptoms [50]. Scores of 0–9 indicate minimal or no depression, 10–18 mild-moderate depression, 19–29 moderate-severe depression, and 30–63 severe depression. The reliability of this measure in our samples has been $\alpha > 0.90$. A BDI score of less than 10 is usually not considered to be clinically significant depression, but yet studies have shown scores of 4–9 to be associated with increased mortality in post-myocardial infarction patients [2]. Since there has been some evidence to suggest that cognitive/affective and somatic aspects of depression differentially

relate to clinical course in HF [51], we also independently examine these BDI subscales of depression in our studies: (1) the cognitive/affective subscale assesses symptoms such as sadness and dissatisfaction (13 items, score range 0–39) and (2) the somatic subscale assesses features such as changes in appetite and feelings of fatigue (7 items, score range 0–21).

5.3 Assessing Cytokines and Cellular Adhesion Molecules

Circulating TNF-α, IL-6, and IL-1β levels are determined in plasma by commercial ELISA. For IL-6, the intra-assay CV (%) is 2.2, the inter-assay CV (%) is 3.9, and the assay sensitivity is <0.71 pg/mL; for TNF-α, the intra-assay CV (%) is 8.0, the inter-assay CV (%) is 16.3, and the assay sensitivity is <0.18 pg/mL; for IL-1β, the intra-assay CV (%) is 6.8, the inter-assay CV (%) is 8.3, and the assay sensitivity is <0.1 pg/mL.

Circulating CRP levels are determined in plasma using commercial ELISA. Intra- and inter-assay coefficients of variation are <5%. Precision and sensitivity performance values are excellent: intra-assay CV (%) < 1.0, inter-assay CV (%) = 1.6, and sensitivity <0.05 mg/L.

Soluble intercellular adhesion molecule-1 (sICAM-1, sCD54) and sP-selectin (sCD62P) are too determined by commercial ELISA. The precision and sensitivity performance values are as follows: sICAM-1 (intra-assay CV (%) = 4.6, inter-assay CV (%) = 6.6, sensitivity <0.35 ng/mL) and sCD62P (intra-assay CV (%) = 5.1, inter-assay CV (%) = 8.8, sensitivity <0.5 ng/mL).

Proinflammatory cytokines, such as TNF, IL-6, and CRP, are associated with cardiac dysfunction in both human and animal models. However, in 2009 Wirtz et al. [52] in our group provided the first study investigating whether depressive symptoms were associated with exercise-induced increases in circulating levels of adhesion molecules expressed on endothelial cells (sP-selectin and soluble sICAM-1), leukocytes (sICAM-1), and platelets (sP-selectin). Using data from 39 middle-aged male HF patients and 19 male control subjects, the authors found that higher depression symptomatology moderated greater increases in sP-selectin levels in response to an acute exercise challenge over time in HF patients as compared with control subjects ($F = 3.25$, $p = 0.05$). Post hoc testing revealed that in HF patients, higher depression scores (BDI) were significantly associated with greater increases in sP-selectin levels over time in response to the exercise (Fig. 1). Also, in the HF patients, higher BDI scores were associated with higher sP-selectin levels at pre-exercise and post-exercise time points (main effect of BDI: $F = 4.86$, $p = 0.035$). These effects were not found for the control subjects. These findings suggested that levels of sP-selectin are higher before and after exercise and have greater increases in response to exercise in male HF patients with increasing depressive symptom severity. These findings could have

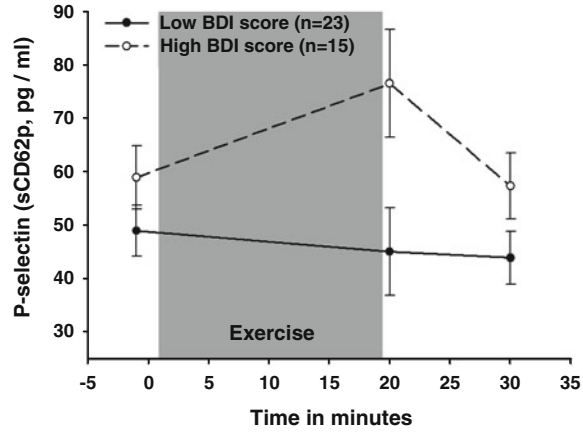

Fig. 1 Changes in sP-selectin in response to acute exercise in HF patients with high (>10, $n = 15$) and low (≤10, $n = 23$) BDI scores

implications for acute coronary syndromes associated with exercise and thereby may impact mortality.

While it is widely acknowledged that indictors of inflammation are cross-sectionally associated with both depression and HF severity, our laboratory was among the first to explore whether different types of inflammatory markers prospectively predict depressive symptom in HF patients. Wirtz et al. [53] assessed the relationship of proinflammatory cytokines and cellular adhesion molecules on depressive symptoms at 12 months following initial study of 30 HF patients. The authors found that sICAM-1—but not IL-6 or C-reactive protein (CRP)—was associated with depression scores 12 months later ($r = 0.38$, $p = 0.045$). Hierarchical linear regression models revealed that sICAM-1 significantly predicted depression scores at the 12-month follow-up, with sICAM-1 independently explaining between 7% ($\beta = 0.26$, $p = 0.040$) and 10% ($\beta = 0.35$, $p = 0.045$) of the total variance in depression scores. These findings suggest that the adhesion molecule sICAM-1 is an independent, prospective predictor of depressive symptoms in HF. The prospective nature of these findings supports the suggested role for inflammation in increasing the severity of future depressive symptomatology.

5.4 Assessing Chemotaxis and Cellular Immunity

Until recently, immune cell migration, particularly chemotaxis, has been largely ignored in respect to depression symptoms and HF. Chemokines are essential for providing signaling to leukocytes for extravasation from the blood and directing locomotion [54, 55]. When overexpressed, recruitment and migration factors are injurious to the cardiovascular system [56] and can generate angiogenesis and fibrous tissue deposition, which can lead to myocardial dysfunction in HF [57, 58]. Particularly, studying acute physiologic responses to controlled challenges serves as a window

into the complex physiologic processes involved in cardiac diseases [59].

One of the members of our group therefore developed an in vitro chemotaxis assay to assess functional capacity of peripheral blood mononuclear cells (PBMCs). PBMCs are separated from whole blood using Ficoll-Hypaque, washed, and then resuspended in RPMI 1640 with 20 mmol/L HEPES (serum-free media). In a modified Boyden chamber, the patient's PBMCs are then incubated with either the bacterial peptide f-met leu phe (fMLP), the physiologic chemokine stromal cell-derived factor-1 (SDF-1), or the adrenergic agonist isoproterenol, or chemotaxis buffer. Chemotaxis responsiveness of PBMCs to the bacterial peptide fMLP is commonly used to measure nonspecific natural immune activity. The chemokine SDF-1 binds to its specific receptor CXCR4, and subsequently stimulates lymphocyte adhesion and transendothelial migration, playing a role in adaptive cellular immunity. Levels of SDF-1 and CXCR4 are elevated in patients with HF and have been found to attenuate cardiac myocyte contractility [37]. PBMCs are incubated with these agents for 2 h at 37 °C, then the top of the membrane is then gently rinsed with phosphate-buffered saline, and the non-migrated cells are removed. The membrane is then removed from the plate and briefly submerged in phosphate-buffered saline. Once dry, the membrane is read by a fluorescence plate reader (CytoFluor) at an excitation of 485 nm and emission of 530 nm.

Redwine and colleagues [60] studied the relationship between depressive symptoms and PBMC chemotaxis both at rest and in response to a moderate acute exercise challenge in 65 middle-aged HF patients and 45 non-HF control subjects. Chemotaxis of PBMCs was examined in vitro to either fMLP or SDF-1 immediately before and after the exercise. The author found that HF patients had reduced chemotaxis to SDF-1 compared with non-CHF subjects ($p < 05$). The authors also found that higher BDI scores were significantly associated with reduced baseline chemotaxis to SDF-1 in both CHF and non-CHF subjects ($p = 0.025$). In contrast, higher BDI scores were associated with increased chemotaxis to fMLP and SDF-1 in response to exercise in the HF patients ($p = 0.027$; Fig. 2). The authors also found that cognitive depressive symptoms, but not somatic depressive symptoms, were inversely associated with baseline chemotaxis to fMLP and SDF-1 in HF and controls. When stratified by HF diagnosis, these associations persisted when controlling for covariates. However, neither cognitive nor somatic symptoms were associated with changes in chemotaxis from pre- to post-exercise task.

The results from the study suggested a shift in immune cell mobility in HF patients with greater depressive symptom severity, with reduced chemotaxis to a physiologically specific chemokine at rest but increased chemotaxis to both nonspecific and specific

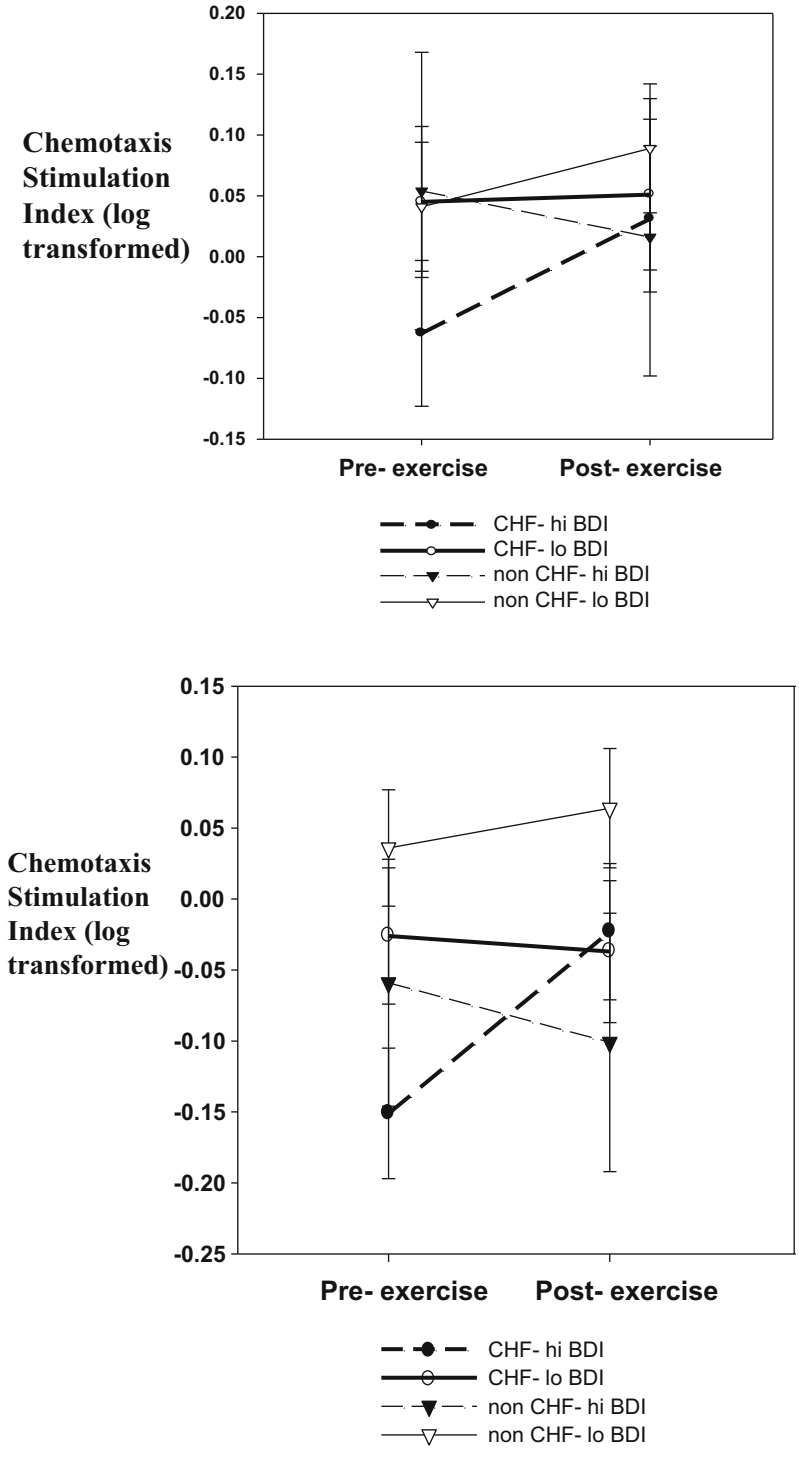

Fig. 2 Changes in a logarithmic transformed stimulation index (SI) of chemotaxis to fMLP (TOP PANEL) and the chemokine SDF-1 (BOTTOM PANEL) in HF patients and non-HF controls with high (hi) and low (lo) Beck Depression Inventory (BDI) scores in response to exercise. Data are expressed as means ±SEM

chemical attractants in response to physical activity. Findings could have implications for cardiac repair and remodeling in HF patients and therefore disease progression.

A second chemotaxis study conducted by Redwine and colleagues [61] investigated if depressive symptoms were related to alterations in the sensitivity of PBMCs to the β-adrenergic agonist isoproterenol in patients at rest and after acute exercise in 77 patients with HF and 44 controls. As mentioned previously, sympathetically modulated immune dysregulation is a part of the pathophysiology of HF; however, this process may be exacerbated in the presence of depression. The study results indicated that depressive symptom severity ($p = 0.001$) and higher resting levels of plasma norepinephrine ($p = 0.003$) were associated with greater chemotaxis after exercise in patients with HF (Fig. 3). The authors concluded that patients with HF with higher depressive symptoms and plasma norepinephrine exhibit increased circulating immune cell chemotaxis to isoproterenol, suggesting greater adrenergic sensitivity. Increased immune cell migration in patients with HF

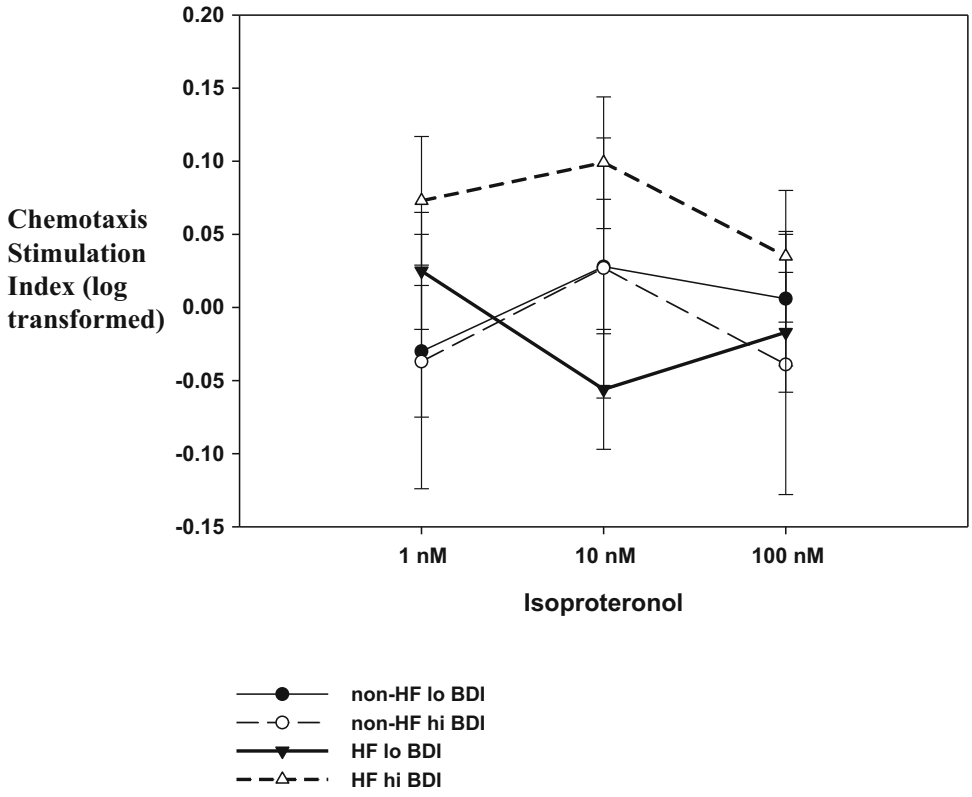

Fig. 3 Change scores (pre- minus post-exercise) and chemotaxis to three concentrations of isoproterenol (1 nM, 10 nM, and 100 nM/l) in HF patients and non-HF controls. High (hi) versus low (lo) depression are determined by scores $\geq$10 and $<$10 on the Beck Depression Inventory (BDI). Data expressed as means $\pm$ SEM

who have elevated depressive symptoms could be associated with cardiac remodeling and HF disease progression.

Following the results of the previous study, which suggested increased β-AR sensitivity, Redwine and colleagues explored the sensitivity of the leukocyte beta-adrenergic receptor and depression sensitivity [62]. Depression was measured using the self-report (BDI) and the Structured Clinical Interview for the DSM-IV (SCID). Patients with major depression determined by SCID had significantly higher β-AR sensitivity than nondepressed. However, the BDI revealed a more complex relationship. Minimal, mild, and moderate-to-severe depression symptom groups had significant differences in β-AR sensitivity ($F(7, 73) = 7.03$, $p = 0.002$, $\eta_2 = 0.18$), with mild symptoms corresponded with reduced β-AR sensitivity and moderate-to-severe symptoms with higher β-AR sensitivity.

5.5 Th1/Th2 Ratio

Although, as we have discussed, inflammatory cytokines have been implicated as a possible mediator of psychological symptoms of depression and HF, it has been unclear if systematic inflammation represents a broader dysregulation of the immune system. Particularly, cellular immunity is important for protection against infection. Th1 cells promote cellular immunity by rapidly producing a range of cytokines such as IFN-γ that activate other Th1 cells to fight infectious agents. Th1 cells also exert a negative regulatory role on Th2 cells that produce cytokines such as IL-4 and IL-10. Th2 cytokines, on the other hand, attenuate immune defenses if they are locally over-expressed, by decreasing activities of major effectors such as Th1 cells [63, 64]. A Th2 shift may have a profound effect on the susceptibility of the organism to infection [65], increase inflammation, and lead to dilated cardiomyopathy and HF [66]. Maintaining Th1/Th2 homeostasis is important for preserving health. Thus, examining Th1/Th2 ratios can provide information on the balance of cellular immune activation versus negative regulation of cellular immunity.

Redwine et al. [67] examined the relationship of depressive symptoms with cellular immune activity measured by the Th1/Th2 ratio and cardiac rehospitalization and/or death in 18 HF patients (mean age = 62, NYHA classes II–IV). The authors reported that higher baseline depression scores were associated with a prospective increase in incidence of cardiac-related hospitalizations and/or death ($p = 0.037$). Lesser IFN-γ/IL-10-expressing CD4+ T cell ratios were related to higher depressive symptom scores at baseline ($p = 0.005$, Fig. 4) and a prospective increased incidence of cardiac-related hospitalization or death over a 2-year period ($p = 0.05$). The results suggest that a shift in the Th1/Th2 ratio may play a role in the association between depressive symptoms and morbidity and mortality in HF patients, suggesting broader immune dysregulation.

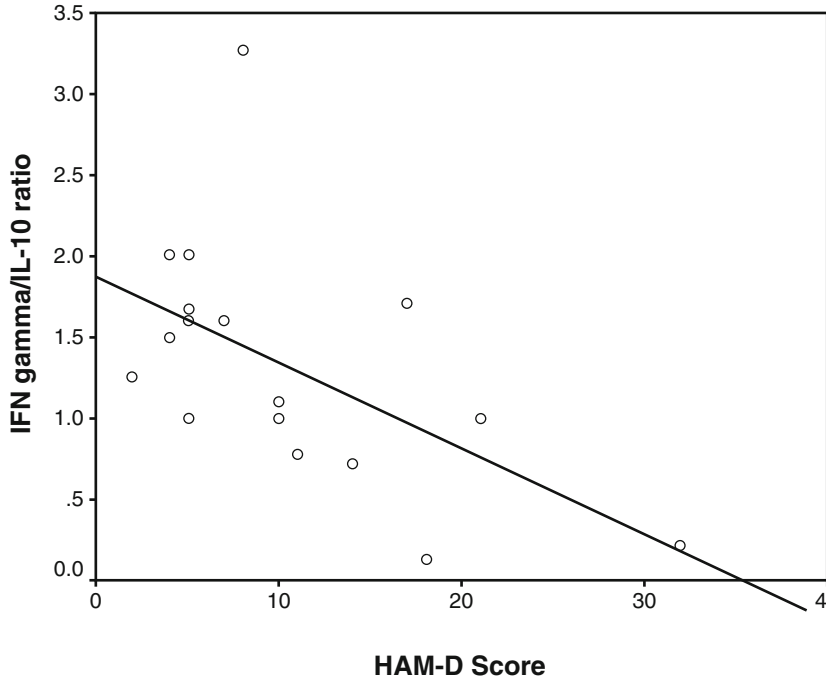

Fig. 4 Relationship between IFN-γ/IL-10 ratios and Hamilton Depression Scores in HF patients

5.6 Alterations of the Gut, Gut Microbiota, and Metabolites in Heart Failure

A burgeoning new area of interest in our laboratory is the role of the "heart-gut axis" and the "gut hypothesis" of HF, which are recently emerging concepts that attempt to address the complex pathophysiology of HF. HF is associated with altered gastrointestinal function due at least in part to ischemic conditions and congestion within the gut. The host may then be affected by impaired gut barrier function, resulting in systemic inflammatory responses and oxidative stress. In the context of the microbiota, altered composition and/or function may influence metabolic processes in HF. For example, the gut microbiota metabolizes dietary choline and L-carnitine into trimethylamine which is then oxidized to trimethylamine *N*-oxide (TMAO) in the liver [68]. Circulating TMAO is an important predictive risk factor for cardiovascular disease and has been observed as elevated in HF patients compared to age- and sex-matched controls [69, 70]. Increased TMAO levels are also associated with a greater-than-threefold increase in mortality risk [70]. In addition, plasma concentrations of TMAO, choline, and betaine have been observed as elevated in patients with chronic HF compared to control subjects, and patients with New York Heart Association classes III and IV have the highest levels [71]. Moreover, elevated TMAO has been observed as anticorrelated to long-term survival in HF patients even after controlling for cardiorenal parameters. As TMAO is detoxified through the kidneys, renal functional status may affect TMAO levels. In HF patients, TMAO

concentration has been positively correlated with renal impairment severity [72]. Gut dysbiosis can lead to increased TMAO and uremic toxin levels and subsequently the progression of chronic HF and kidney disease. The biological mechanisms by which the gut microbiota or TMAO directly influences the development of HF have not been fully elucidated. Further studies are needed to clarify the mechanisms of impact of TMAO on cardiorenal function and disease.

HF is associated with increases in various gut pathogens, intestinal permeability, and inflammation [73]. Increased populations of adherent gut bacteria have been identified in the mucosa of HF patients compared to controls [74]. Altered gut microbiota composition can lead to increased systemic inflammation and uremic toxins [75], originating from microbial metabolism, which have both been associated with HF and cardiorenal compromise. In addition, patients with chronic HF have increases in gut bacterial pathogens such as Campylobacter, Salmonella, Shigella, and Yersinia compared to controls. Candida yeast are also elevated in HF compared to controls [76]. The intestinal microbial overgrowth and increased intestinal permeability are associated with disease severity, venous congestion, and inflammation. Numerous studies suggest that decreased gut mucosal barrier function allows gut-derived lipopolysaccharide (LPS) to enter the systemic circulation. This systemic LPS exposure leads to generation of cytokines such as IL-6 and TNF-α and subsequent inflammation and may contribute to the development of cardiometabolic disease [77–79]. Moreover, circulating LPS has been observed in patients with diabetes and HF and may increase systemic inflammation in these populations [80, 81]. In addition to endotoxin translocation, hypoxia may also lead to increased intestinal permeability. The reduced cardiac output, edema, and systemic congestion in HF further increase the risk of intestinal ischemia [82]. In HF, intestinal ischemia and congestion may lead to altered intestinal morphology, function, and permeability [74, 83]. Since the gut maintains a high oxygen demand, the small intestinal villi are susceptible to ischemia from conditions that cause reduced blood flow. Intestinal ischemia in turn leads to dysfunction such as reduced nutrient absorption and pH of the gut mucosa [82].

Intestinal function and permeability are significantly impaired in chronic HF [74]. In these patients, the wall of the colon is often significantly thickened [84]. Edema localized to the intestinal wall in HF patients due to systemic congestion and reduced abdominal blood flow may increase LPS leakage into the circulation and cytokine production. Cytokine production not only promotes inflammation but also fibrosis and microvascular and myocardial disease. HF patients with edema have higher plasma concentrations of LPS compared to patients presenting without edema [85]. In addition, patients with HF and low rate of intestinal blood flow

have higher serum levels of LPS antibody [86]. Numerous proinflammatory cytokines, such as IL-1, IL-2, IL-6, TNF-α, and C-reactive protein, are observed as elevated in HF patients due in part to circulating endotoxin [87, 88]. However, clinical trials targeting the removal of these cytokines have largely failed; thus endotoxins have been suggested as the trigger for increased cytokine production in HF. The intestinal hypoperfusion and congestion due to reduced cardiac output may further increase intestinal permeability and bacterial translocation to create a vicious cycle of additional inflammation, HF exacerbation, and potential renal damage. Additional mechanistic studies as well as novel therapies targeting the gut microbiota and metabolic dysfunction in HF are warranted.

5.7 Altered Plasma Metabolites in Patients with Heart Failure and Depression

HF is associated with depression, and key differences have been identified in the metabolome of depressed compared to nondepressed HF patients [89]. The amino acids aspartate and serine are significantly elevated in depressed HF patients compared to controls. Aspartate, the main excitatory amino acid in the central nervous system (CNS), can activate, while serine functions as co-agonist, N-methyl D-aspartate (NMDA) receptors, which are cation channels that mediate fast synaptic transmission in the brain and are important in memory and behavioral functioning. Elevated concentrations of these amino acids in the synaptic space may promote selective neuronal loss and various chronic neurological disorders [90]. The amino acids leucine and isoleucine are also elevated in depressed compared to nondepressed HF patients. These branch-chain amino acids have stress response and protein regulatory functions. Leucine is also relevant to key brain metabolic functions.

In addition, numerous dicarboxylic acid (DCA) species, which are produced in the context of fatty acid oxidation dysfunction or saturation of mitochondrial β-oxidation, are elevated in depressed compared to control HF patients. Decreased concentrations of the ketone body 3-hydroxybutyrate, which are used as energy for the CNS and generated through β-oxidation of fatty acids, are found in the depressed subjects. During β-oxidation of lipids, the acetyl-CoA generated may then enter the tricarboxylic acid cycle (TCA); however excess concentrations of acetyl-CoA will saturate the TCA cycle and contribute to the formation of ketone bodies such as 3-hydroxybutyrate. Thus, concentrations of 3-hydroxybutyrate are decreased while DCA species are increased in depressed compared to nondepressed HF patients, which suggests a metabolic shift away from the primary route of fatty acid metabolism via β-oxidation toward ω-oxidation of fatty acids in which the ω-carbon is oxidized to carboxylic acid to form DCA. These results are consistent with previous associations between altered amino

acid neurotransmitters, fatty acid metabolism, and depression; however, additional studies are needed to identify the role of HF pathophysiology on the alterations of these plasma concentrations.

5.8 Behavioral Pathways

The management of HF relies on a complex regimen of self-care practices, and patients who do not adhere may suffer from worse cardiac prognosis [52]. Self-care maintenance refers to the decision-making process underlying the performance of healthy practices and self-care management refers to the behaviors used to manage signs and symptoms of illness [91]. Self-care maintenance practices in HF may include adherence to medications and low-salt diets as prescribed, as well as limiting alcohol consumption and avoiding tobacco use [91]. The most widely discussed behavioral pathway in the literature is medication adherence [52]. Cardiac patients, including those with HF, who have comorbid depression have three times higher risk of cardiac medication nonadherence compared to nondepressed patients [53]. Self-care management behaviors include the recognition of early signs and symptoms of worsening physical or mental condition, and a subsequent response to address them [91]. A large multisite trial found that patients with HF and depression were 45% more likely to delay hospital admission for more than 72 h as opposed to those HF patients without depression [92]. Patients with depression tend to wait longer to consult a health-care provider in response to worsening HF symptoms as opposed to HF patients who are not depressed.

6 Conclusions

HF is a major and costly public health concern, and its prognosis is grim—with high hospitalization and mortality rates. It is well documented that HF patients experience disproportionately high rates of depression and that depressed HF patients have worse clinical outcomes than their nondepressed counterparts. Thus, understanding mechanisms that link HF and depression has become a major area of scientific interest. A psychoneuroimmunological approach to examining these relationships is proving fruitful and merits increasing attention. The work conducted thus far in our laboratory group, as well as other groups, suggests that HF and depression may be linked by increased neuroimmune activation and possibly gut dysbiosis.

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