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Fatigue, Inflammation, and Projected Mortality in Heart Failure

Anne M. Fink, PhD, RN¹, Rosalia C. Gonzalez, DNP², Tadeusz Lisowski, BSN, RN³, Maria Pini, MS⁴, Giamila Fantuzzi, PhD⁴, Wayne C. Levy, MD⁵, and Mariann R. Piano, PhD, RN¹

¹Department of Biobehavioral Health Science, College of Nursing, University of Illinois at Chicago, Chicago, IL

²Department of Medicine, University of Illinois at Chicago, Chicago, IL

³Mercy Hospital and Medical Center, Chicago, IL

⁴Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL

⁵University of Washington Medical Center, Seattle, WA

Abstract

Background—Fatigue is a prominent and poorly understood symptom of heart failure with reduced ejection fraction (HFrEF). The purpose of this study was to determine whether fatigue correlated with immune biomarkers and prognosis.

Methods/Results—In patients with HFrEF (N = 59) and healthy controls (N = 25), we prospectively measured fatigue (Profile of Mood States), depressive symptoms (Patient Health Questionnaire-8), sleep quality (Pittsburgh Sleep Quality Index), and immune biomarkers (plasma C-reactive protein [CRP], tumor necrosis factor- α [TNF α], and interleukins [IL-6 and IL-10]). Seattle Heart Failure Model (SHFM) mortality risk scores were determined. Patients with HFrEF had significantly greater fatigue and depressive symptoms and poorer sleep quality compared to control subjects. When controlling for depressive symptoms, however, fatigue did not differ significantly between patients with HFrEF and controls. Patients with HFrEF had significantly lower levels of IL-10 compared to controls. Cytokines did not correlate significantly with fatigue, but fatigue was significantly associated with higher SHFM scores.

Conclusions—Depressive symptoms were an important covariate of fatigue in patients with HFrEF. Our study findings were the first to show a positive association between fatigue and the SHFM score, indicating that fatigue was associated with poorer prognosis.

Introduction

The purpose of this study was to determine relationships among fatigue, immune biomarkers, and prognosis in patients with reduced ejection fraction heart failure (HFrEF). Fatigue is a prominent and poorly understood heart failure (HF) symptom. In patients with

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Corresponding author: Anne M. Fink, PhD University of Illinois at Chicago Department of Biobehavioral Health Science College of Nursing (MC 802) 845 South Damen Avenue Chicago, IL 60612 Phone: 312-355-0689 Fax: 312-996-4979 afink2@uic.edu.

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HFrEF, fatigue portends worsening prognosis and increased mortality.^{1,2} Interestingly, fatigue is not necessarily attributable to aging, impaired ventricular function, or pharmacotherapies in this population. For example, in HF studies fatigue did not correlate with age^{3,4} or with ejection fraction (EF),³⁻⁵ and in a meta-analysis of randomized clinical trials, fatigue was not related to β -blocker therapy.⁶ Researchers of other chronic disease populations have implicated pro-inflammatory cytokines in the etiology of fatigue.⁷⁻¹¹ Increased plasma cytokine levels have been found in patients with HF.¹³⁻¹⁵ For example, increased levels of the pro-inflammatory cytokine—tumor necrosis factor- α (TNF α)—were associated with impaired left ventricular contractility, fetal gene expression, and myocyte hypertrophy and apoptosis.¹² Whereas, the anti-inflammatory cytokine—interleukin-10 (IL-10)—was correlated with improved left ventricular contractile performance in patients with HF.¹⁶ In addition, HF mortality was significantly higher in patients with elevated levels of TNF α ,¹³ interleukin-6 (IL-6),¹⁴ and C-reactive protein (CRP).¹⁵ Elevated levels of TNF α and IL-6 were associated with depressed mood in patients with HF,^{17,18} which may be mediated by the effects of cytokines on the hypothalamic pituitary adrenal axis. Meyer et al. investigated cytokines in patients with cardiovascular disease and found that those who had vital exhaustion (defined as unusual fatigue, irritability, and demoralization [Maastricht questionnaire score ≥ 21]) had significantly greater levels of circulating TNF α and IL-6 compared to patients with cardiovascular disease who did not have vital exhaustion.¹⁹ Collectively, these results suggest that immune factors may be an important mechanism in HF-related fatigue.

To our knowledge, the study presented herein was the first to determine the relationships among fatigue, cytokines, and projected mortality in HFrEF. To elucidate the biological and clinical correlates of HFrEF-related fatigue, we prospectively measured immune biomarkers (cytokines and CRP) and calculated Seattle Heart Failure Model (SHFM) scores²⁰ to determine whether fatigue was related to inflammation and to HF prognosis, respectively. Potentially confounding demographic and clinical variables were examined (e.g., age, New York Heart Association [NYHA] functional classification, body mass index [BMI], and EF). We controlled for depressive symptoms and poor sleep quality in analyses because these factors may affect fatigue.

Methods

Subjects

The sample included 59 patients with HFrEF and 25 age/gender/race-matched control subjects who were recruited between September 2009 and January 2011. Patients with HF were attending outpatient clinics at two Midwestern medical centers and were eligible to participate if they were diagnosed with HFrEF for at least one year (based on physical exam and EF $\leq 40\%$ determined by echocardiography) and under the care of a board-certified cardiologist. Patients were excluded if they had hospital admissions for decompensated HF ≥ 30 days, implantable cardioverter-defibrillator (ICD) placement ≥ 30 days, or myocardial infarction or coronary artery bypass ≥ 6 months. We also excluded any patients who had comorbid inflammatory conditions (e.g., infections, autoimmune diseases, chronic obstructive pulmonary disease), cancer within the past five years, or A1C $> 8\%$, and those who used immunomodulatory medications or tobacco within the past six months.

Control subjects responded to advertisements inviting healthy participants and were screened for eligibility by phone. Control subjects were defined as those who did not have asthma, cancer, chronic obstructive pulmonary disease, HF, diabetes mellitus, myocardial infarction, chronic infections, autoimmune diseases, and use of immunomodulatory medications. Those who were receiving antihypertensive medications were eligible if their

blood pressure was within normal limits.²¹ All subjects gave informed consent, and the study procedures were approved by the institutional review board.

Questionnaires

All subjects (controls and patients with HFrEF) completed the 65-item Profile of Mood States; herein, we report scores for the 7-item fatigue subscale (POMS-F; score range 0–28).²² Subjects also completed the Patient Health Questionnaire-8 (PHQ-8; range 0–24)²³ to measure depressive symptoms and the Pittsburgh Sleep Quality Index (PSQI; global score range 0–21)²⁴ to measure sleep quality.

Biological Markers

Venous samples were collected via venipuncture and centrifuged (1,000 rpm x 15 min, 4°C). Plasma was aliquoted and frozen (–20°C) until time of analysis.^{25,26} As previously described by our laboratory,²⁷ TNF α , IL-6, and IL-10 in plasma were quantified using a high-sensitivity colorimetric enzyme-linked immunoassay (R&D Systems® Quantikine™). High-sensitivity CRP (plasma) was quantified by nephelometry²⁸ (Quest Diagnostics Incorporated). Also measured were laboratory variables required for the SHFM (i.e., hemoglobin, % lymphocyte, uric acid, sodium, cholesterol; Quest Diagnostics Incorporated).

Clinical Variables and Mortality Prediction

Subjects provided information about their medical and medication history. Height and weight were measured to calculate BMI. For patients with HFrEF, additional demographic and clinical data were obtained from the medical record (e.g., ischemic etiology, NYHA classification, EF, and use of β -receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone blockers, diuretics, statins, and allopurinol, as well as other medications). As previously described,^{20,29} these variables were used to calculate SHFM scores. Patients were assigned SHFM scores of –1, 0, or 1, and a higher score indicated greater projected mortality.

Statistical Analysis

Demographic characteristics of patients with HFrEF and control subjects were compared using *t* tests for continuous variables and χ^2 for categorical variables. Fatigue, depressive symptoms, sleep quality, and cytokines were all analyzed as continuous variables. Similar to others,³⁰ we examined plasma cytokine levels (picograms/ml [pg/mL]) and also calculated ratios of pro-inflammatory to anti-inflammatory cytokines (TNF α /IL-10 and IL-6/IL-10) because *in vivo* inflammatory responses are influenced by the balance between pro- and anti-inflammatory molecule levels;³¹ these ratios may reflect the degree of systemic inflammation better than concentrations of individual cytokines. Pearson's correlations were determined, to analyze the relationships between fatigue and other variables. When necessary, we controlled for significant covariates (e.g., BMI, depressive symptoms, sleep quality) using analysis of covariance (ANCOVA). We also compared fatigue and immune biomarkers among the mortality-risk groups determined by the SHFM using analysis of variance (ANOVA; least significant difference [LSD] post-hoc tests). All data are presented as mean $\pm$ standard error of the mean (SEM).

Results

Demographics

The majority of patients with HFrEF (EF 23.6% $\pm$ 1.0) were NYHA class II (46%), and 36% were NYHA class III. Only small percentages were NYHA classes I (15%) or IV (3%). The etiologies of HFrEF were ischemic (33%) and non-ischemic (67%), and the majority of

patients with HFrEF (69%) had an ICD. No differences were found between controls and patients with HFrEF in terms of age, gender, race/ethnicity, or marital status (Table 1). Compared to controls, patients with HFrEF had significantly greater BMI values, as well as greater B-type natriuretic peptide (BNP) and uric acid levels. Total cholesterol was significantly lower in patients with HFrEF compared to controls (Table 1).

Levels of Fatigue, Depressive Symptoms, and Poor Sleep Quality

In univariate analyses, patients with HFrEF had significantly greater fatigue and depressive symptoms and poorer sleep quality compared to control subjects (Table 1). Age, EF, and BMI were not correlated with fatigue in patients with HFrEF, but fatigue was associated with NYHA class ($r = .44$, $p < .001$). In addition, fatigue in patients with HFrEF was significantly correlated with both depressive symptoms and poorer sleep quality (Table 2). Fatigue remained significantly greater in patients with HFrEF compared to control subjects when controlling for sleep quality ($F = 10.9$, $p = .001$). When controlling for depressive symptoms, however, fatigue no longer differed significantly between patients with HFrEF and control subjects ($F = 2.6$, $p = .11$).

Fatigue and Biomarkers

Compared to controls, patients with HFrEF had significantly greater TNF α , IL-6, and CRP values, and IL-10 levels were significantly lower; the ratios of TNF α /IL-10 and IL-6/IL-10 were also significantly greater in patients with HFrEF (Table 1). When controlling for depressive symptoms, however, only IL-10 ($F = 7.5$, $p = .01$) differed significantly between these groups. In patients with HFrEF, plasma cytokine levels were not correlated with greater fatigue; however, IL-6 levels were significantly correlated with poor sleep quality (Table 2).

Fatigue and Projected Mortality

The mean SHFM score for patients with HFrEF was 0.2 ± 0.09 (range of -1 to 1), and the estimated 1-year mortality was approximately 5%. Higher SHFM scores were correlated with greater fatigue ($r = .37$, $p = .01$) and with higher IL-6 levels ($r = .42$, $p = .01$). Fatigue was significantly and incrementally increased with each increase in the SHFM score; however, depression and sleep quality were not associated with mortality risk (Table 3). IL-6 levels differed among the mortality-risk groups; the *SHFM score = 1* group had significantly increased IL-6 compared to the other two groups (Table 3), and fatigue remained significantly associated with SHFM scores after controlling for IL-6 ($F = 4.2$, $p = .02$).

Discussion

To our knowledge, this was the first study about fatigue, immune biomarkers, and projected mortality in patients with HFrEF. In the present study, more than half of patients with HFrEF reported significant fatigue. Fatigue was positively associated with moderate to severe depressive symptoms that were present in 40% of HFrEF patients. Findings extend the growing literature on the association between fatigue and depression in HF; however, relationships must be tempered because fatigue was no longer more likely in patients with HFrEF than control subjects after adjusting for depressive symptoms. CRP, IL-6, and TNF α levels were significantly increased in patients with HFrEF compared to control subjects, and IL-10 levels were lower in HFrEF patients compared to controls. There were no significant associations between immune biomarkers and fatigue. Finally, independent of depressive symptoms, fatigue scores were significantly and incrementally increased with each increase in the SHFM score, suggesting that the presence of fatigue portends a poor prognosis.

The presence of fatigue in patients with HFrEF was consistent with our previous findings,³ as well as reports from other investigators.^{1,4,5,32} In the present study, fatigue was correlated with higher NYHA class, depressive symptoms, and poorer sleep quality. Consistent with others,⁴ age and EF did not correlate significantly with HFrEF-related fatigue, but fatigue and depressive symptoms were related, such that once the analysis was adjusted for depressive symptoms, control subjects had similar prevalence of fatigue. To examine the relationship between fatigue and depression, Skapinakis et al.³³ conducted a secondary analysis of data from the World Health Organization longitudinal collaborative study of psychological problems in general health care. After adjusting for confounding variables (e.g., comorbid conditions), individuals with depression at baseline were 4 times more likely to develop new unexplained fatigue at the 12-month follow-up; similarly, unexplained fatigue at baseline was independently associated with the development of a new episode of depression at the 12-month follow-up. Similar to others, we considered the confounding issue of overlapping criteria or questions between the POMS-F and PHQ-8 with respect to fatigue.³⁴ The PHQ-8 contains one question related to fatigue or tiredness. Interestingly, when we re-analyzed data eliminating this question, the association between fatigue and depression remained unaltered (data not shown). Future research is needed to better understand the complex association between fatigue and depression and predictors of fatigue in HF. Other important predictors of HFrEF-related fatigue may include polypharmacy, fluid overload, poor diet, physical deconditioning, arrhythmias, or recurrent/progressive ischemic disease.

Fatigue may not be mediated by immune factors, such as CRP, IL-6, or TNF α . Other unidentified biologic factors should be studied for involvement with fatigue. We may have found significant relationships between cytokines and fatigue if we measured other cytokines (e.g., IL-1 β) and soluble cytokine receptors, which have longer half-lives than their cognate cytokine. For example, others found that increased plasma levels of the soluble TNF receptors were associated with depression¹⁷ and independently predicted mortality in patients with HFrEF.¹³ In this study, the sample size and effect sizes for CRP and cytokine values were small. In addition, cytokine measurements may have been influenced by short half-lives, circadian variation, and other circulating factors that affect the plasma levels of immune molecules.³⁵ Considering this, it may be more appropriate to measure cytokine levels in response to an immune challenge (e.g., *ex vivo* stimulation with endotoxin).²⁷ The latter method may more reliably reflect the *in vivo* innate immune response, which is modulated by complex interactions among circulating cytokines and other molecules. In the present study, cytokine levels were reported in patients with stable HFrEF. Although they were increased compared to control subjects, levels were low compared to levels found in other inflammatory conditions.³⁶

Simone de Beauvoir noted, “death seems far less terrible when you are tired.”^{37,38} This statement is interesting to reflect upon in light of our data and those of others who found that fatigue predicted worsening prognosis and mortality.^{1,2,39} Although other researchers reported a significant relationship between fatigue and mortality,^{1,2} the pathophysiologic underpinnings of this association remain unknown. In the present study, IL-6 was significantly increased in patients with HFrEF that had the greatest projected mortality. Previously, IL-6 was a predictor of 1-year mortality in older (mean age 80) patients with HFrEF ($N = 54$, EF < 40%, NYHA class III–IV).¹⁴ In the Vesnarinone Trial (VEST, $N = 1169$), increased levels of both IL-6 and TNF α predicted all-cause mortality ($N = 1169$, EF 20%, NYHA class III–IV).¹³ The larger sample size in VEST may account for the ability to detect the relationship between significantly increased TNF α and mortality. Study findings were the first to show a positive association between fatigue and SHFM scores. Although patients were categorized into relatively low SHFM mortality risk groups, Mozaffarian et al. found that the *SHFM score = 1* indicated a 50% greater risk of sudden cardiac death and a 4-

fold greater risk of pump failure death in comparison to patients with HFrEF with lower SHFM scores (i.e., -1 and 0).²⁹

Study Limitations and Strengths

This was a cross-sectional study with a small number of controls and patients with HFrEF. With a larger sample size, significant relationships between cytokines and fatigue may have been found. Patients with HFrEF were predominantly NYHA class II; therefore, findings cannot be generalized to patients with HFrEF with more advanced disease or to patients who have HF with a preserved ejection fraction. In addition, the SHFM score may have underestimated mortality risk in African Americans.⁴⁰ Our study included a number of strengths, such as the inclusion of a control group, the measurement of comorbid depressive symptoms and sleep quality, and the quantification of both pro- and anti-inflammatory molecules.

Conclusion

There is a high prevalence of fatigue in a contemporary cohort of patients with stable HFrEF and a complex interplay between fatigue and depressive symptoms. Although fatigue was unrelated to immune biomarkers, fatigue was significantly increased with each incremental category for the SHFM score. Further research is required to understand the relationship between depression and fatigue and potential biologic mechanisms.

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Table 1

Characteristics of control subjects and patients with HFrEF.

	Controls (N = 25)	HFrEF (N = 59)	P
Age	57.0 ± 1.7	61.0 ± 1.9	0.14
Female Gender	60% (n = 15)	42% (n = 25)	0.14
Race/Ethnicity			0.21
African American	64% (n = 16)	69% (n = 41)	
Hispanic/Latino	8% (n = 2)	17% (n = 10)	
White, Non-Hispanic	28% (n = 7)	14% (n = 8)	
Marital Status			0.48
Married	36% (n = 9)	32% (n = 19)	
Single	40% (n = 10)	27% (n = 16)	
Widowed	8% (n = 2)	17% (n = 10)	
Divorced/Separated	16% (n = 4)	24% (n = 14)	
Medications			
Angiotensin-converting enzyme (ACE) inhibitors	4% (n = 1)	63% (n = 37)	< .001
Angiotensin receptor antagonists	8% (n = 2)	31% (n = 18)	.02
Aldosterone antagonists	0% (n = 0)	1% (n = 1)	.52
β blockers	8% (n = 2)	97% (n = 57)	< .001
Hydralazine	0% (n = 0)	20% (n = 12)	.75
Digitalis	0% (n = 0)	37% (n = 22)	.01
Loop diuretic (Furosemide)	0% (n = 0)	76% (n = 45)	< .001
Statins	8% (n = 2)	66% (n = 39)	< .001
Selective serotonin reuptake inhibitors	0% (n = 0)	14% (n = 8)	.05
Tetracyclic antidepressants	0% (n = 0)	2% (n = 1)	.50
Physiologic Variables			
TNF-α (pg/mL)	0.2 ± 0.1	1.3 ± 0.3	< .001
IL-6 (pg/mL)	4.4 ± 0.7	6.6 ± 0.6	.04
IL-10 (pg/mL)	10.1 ± 2.2	5.1 ± 0.5	.002
C-reactive protein (mg/L)	1.7 ± 0.5	6.0 ± 1.1	< .001
TNF-α/IL-10 (pg/mL)	0.1 ± 0.03	0.5 ± 0.1	< .001
IL-6/IL-10 (pg/mL)	0.5 ± 0.1	2.5 ± 0.6	< .001
Body mass index (BMI; kg/m ²)	28.6 ± 1.5	34.5 ± 1.4	.02
Leukocytes (k/ml)	6.0 ± 0.3	6.8 ± 0.3	.07
Hemoglobin (mg/dL)	13.5 ± 0.3	12.8 ± 0.2	.07
Total cholesterol (mg/dl)	206.3 ± 7.3	161.4 ± 5.0	< .001
B-type natriuretic peptide (pg/ml)	12.8 ± 3.2	306.7 ± 73.9	< .001
Sodium (mg/dL)	139.7 ± 0.8	139.6 ± 0.4	.98
Blood urea nitrogen (mg/dL)	15.8 ± 3.2	27.6 ± 2.4	.12
Creatinine (mg/dL)	1.1 ± 0.1	1.3 ± 0.1	.18
Uric acid (mg/dL)	6.5 ± 0.6	8.7 ± 0.3	.01
Questionnaire scores			

	Controls (N = 25)	HFrEF (N = 59)	p
Fatigue (POMS-F)	4.3 ± 0.6	7.3 ± 0.9	< .001
Depressive Symptom (PHQ-8)	1.6 ± 0.9	8.4 ± 1.2	< .001
Sleep Quality (PSQI)	5.3 ± 0.7	7.6 ± 0.5	.02

Values are mean ± SEM or % of the group.

Table 2

Relationships among fatigue, depressive symptoms, poor sleep quality, and immune biomarkers in patients with HFrEF (N = 59).

	Fatigue	Depressive Symptoms	Poor sleep quality	TNF α	IL-6	CRP
Depressive Symptoms	.79 *					
Poor sleep quality	.40 *	.56 *				
TNF α	.21	.30	.13			
IL-6	.14	.09	.27 *	.13		
CRP	.16	.29	-.13	-.02	.54 *	
IL-10	-.04	-.10	.26	.07	.05	.07

* Indicates $p < .05$.

Table 3

Comparisons of fatigue and immune biomarkers among SHFM mortality groups.

	SHFM = -1 (n = 8)	SHFM = 0 (n = 29)	SHFM = 1 (n = 22)	P
Symptoms				
Fatigue (POMS-F score)	6.0 ± 1.0	9.5 ± 1.2 *	13.7 ± 1.7 *	.02
Depressive symptoms (PHQ-8)	4.5 ± 2.5	8.2 ± 1.9	9.2 ± 1.9	.67
Sleep quality (PSQI)	4.9 ± 1.3	9.2 ± 1.9	7.7 ± 0.9	.14
Physiologic Variables				
Body mass index (m ² /kg)	31.1 ± 1.6	33.8 ± 1.8	36.7 ± 2.8	.41
TNFα (pg/ml)	1.1 ± 0.8	1.0 ± 0.3	1.9 ± 0.5	.21
IL-6 (pg/ml)	4.3 ± 1.3	5.2 ± 0.6	9.1 ± 1.2 *	.003
CRP (mg/L)	3.7 ± 1.6	4.8 ± 1.0	8.9 ± 2.7	.16
IL-10 (pg/ml)	4.5 ± 1.4	5.0 ± 0.7	5.3 ± 0.8	.85

Values are mean ± SEM.

* Indicates group(s) that differ from the reference group (SHFM = -1 group).