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The Relationship Between Pain, Fatigue, Depression and Functional Performance in Stable Heart Failure

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Introduction

Heart failure (HF) is an incapacitating chronic condition. It currently affects 5.7 million Americans, and is a significant cause of morbidity and mortality.[1] Adults with HF suffer from a myriad of symptoms including dyspnea, edema, pain, depression, fatigue, nausea, constipation, sleep disturbance and anxiety.[2-5] Symptom burden increases as cardiac function declines, interfering with an individual's ability to function and perform daily activities.[2-6]

Symptomatology in HF is complex and multifactorial in etiology.[4,7] Pain is common in HF populations, with prevalence ranging from 51-84%, present across the spectrum from mild to advanced disease. [7-10] Yet despite pain's pervasiveness in HF, it often goes unrecognized by healthcare providers and is underreported by patients.[4,8,9] Previous research suggests that patients with HF experience pain during acute exacerbations and stable periods.[8-10] Among HF patients, pain is associated with interference with general activity, and measures of function.[8,9]

However, impairments in activity and function are likely associated with multiple, rather than single symptoms, in stable HF. For example, fatigue and depression are also commonly reported, distressing symptoms in HF, that have been show to negatively impact function[11-13] Indeed, a growing body of research has found interactions among these three symptoms. For example, findings that pain is related to both fatigue and depression suggest that the pain in HF increases the likelihood of these other symptoms as well.[10-13] Although the associations among pain, fatigue, depression have been described,[10-13] the interaction and impact of these symptoms together on specific components of functional status, have yet to be described in the literature.

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Leidy[14] defines functional status as a multidimensional concept that includes four main aspects: functional performance, functional reserve, functional capacity and capacity utilization. Thus, functional status is characterized by one's ability to fulfill usual roles in daily life to meet basic needs. Functional performance, as defined by Leidy,[14] is the multidimensional activities that an individual performs on a daily basis and that are necessary for the preservation of health, wellness, roles within society, and basic needs. In contrast, functional capacity is defined as an individual's maximum ability to accomplish these daily activities.[14] Leidy defines functional reserve as the degree of exertion available to an individual in times of extreme functional need. Thus functional reserve is the difference between functional performance and maximum capacity. Finally, capacity utilization represents the individual's ability to recognize and utilize their functional potential.[14]

When considering the evaluation symptoms, Leidy[14] argues that illness symptomatology, such as pain, fatigue, and depression, represents predictors of functional performance and functional capacity, rather than elements or direct measures of these functional variables. Thus, evaluation of the relationship between symptoms and functional performance and capacity is important, and can help to describe the relationship between disease manifestations and functional status. Previous research has evaluated the relationship between HF and measures of function, more commonly functional performance or functional capacity.[15-18] However, the contribution of specific, commonly occurring HF symptoms, together to both functional performance and capacity remains to be described.

Evaluating the relationship between the symptoms of pain, fatigue, and depression and their interactions with functional measures may expand current understanding of HF symptoms and the relationship between symptoms and function. Impairments in function can lead to life disruption potentially impacting overall patient well-being.[19,20] Therefore, the purpose of this study was to (1) explore the relationships between clinical and demographic variables and symptoms (pain, fatigue, depression) and function (functional performance and functional capacity) and (2) examine the contributions of symptoms (pain, fatigue and depression) to functional performance and functional capacity in patients with stable HF.

Methods

Study Design—This study was a secondary data analysis of data obtained from a cross sectional study originally designed to explore the relationships among sleep, sleep disordered breathing, daytime symptoms and functional performance. The full details of the original study design and methods have been reported elsewhere.[6,18] Summarized here are the aspects that are relevant to the current study.

Sample—The sample included stable HF patients recruited from five HF clinics in the Northeastern United States. Stability was defined as the absence of hospital admission, emergency department visits, or titration of vasoactive medication, during the month prior to sleep evaluation. Study inclusion criteria were stable heart failure, New York Heart Association (NYHA) functional class I-IV, 18 years of age or older and cognitively intact as reported by the referring health care provider, based on clinical observation. Participants

were excluded who were currently pregnant, had previously identified sleep disordered breathing, who had unstable medical or psychological disorders, end stage renal disease, cognitive impairment, or neurological or musculoskeletal conditions affecting the non-dominant arm (due to actigraphy use in the original study). Human subjects approval was obtained and all participants provided informed consent.

Variables and Measures

Demographic and Clinical Variables—Demographic characteristics of the study sample included age, gender and race obtained by self-report. Clinical variables included NYHA class, body mass index (BMI), Left Ventricular Ejection Fraction (EF), and the Charlson Comorbidity Index, obtained by patient interview and medical record review.[21] The Charlson predicts 10-year mortality in patients with a range of comorbid conditions and has been previously validated in community-based populations.[22,23]

Measures of Function—Functional performance was measured using the Short Form 36 Health Survey (SF-36) role limitations due to physical functioning subscale (role limits-physical). The scale measures limitations in the type and amount of role performance due to physical problems where roles are the things people actually do to meet basic needs. This scale is applicable to people with one or more usual role and to those who are retired.[24] The role limits-physical subscale is an essential element in the comprehensive assessment of health, provides information on the limitations in engaging in normative roles as a result of health problems, and also captures disability.[25] This subscale is also conceptually congruent with Leidy's definition of functional performance, defined as one's ability to fulfill normative roles. Low scores are associated with decreased role functioning due to physical health.[24, p. 3.5] The SF-36 has well established validity and reliability in the chronically ill and healthy populations.[25-29]

Functional capacity was measured using the 6-Minute Walk Test (6-MWT). The 6-MWT is a valid and reliable objective measure of the distance that one can walk under controlled conditions.[30-32] The 6MWT has been found to have good reliability, moderate validity, and a significant ability to predict functional capacity in HF populations.[33] The 6-MWT measures submaximal functional exercise capacity and reflects exercise levels used for activities of daily living.[31,34,35] The 6-MWT was obtained using standard methods in a hallway in the outpatient clinical setting and was measured in feet.[31]

Symptoms—Three common symptoms experienced by HF patients[3,8,36-38] were included in this analysis, including pain, fatigue, and depression. Pain was measured using the Bodily Pain (BP) scale from the SF-36. The BP scale is a well-validated instrument for the measurement of pain in the chronically ill.[25,27-29,39,40] The BP score elicits the intensity or discomfort level of pain and the extent of interference pain has on normal work.[24] Scores range from 0 to 100. Lower scores indicated more severe and limiting pain. The total BP score was used as a continuous variable. We also used a dichotomized BP score (defined as less than the normalized 50th percentile for HF) to determine the prevalence of pain.[24]

Fatigue was measured with the Global Fatigue Index from the Multi-Dimensional Assessment of Fatigue Scale (MAF).[41,42] This is a valid and reliable instrument in the

chronically ill[42-44] and is reliable in HF.[18] Scores range from 1 to 50, with higher scores indicating a higher level of fatigue. We also looked at how many people reported pain on all or most days on the MAF.

Depression was measured with the Centers for Epidemiological Studies Depression Scale (CESD).[45,46] The CESD is a valid, sensitive and reliable measure in multiple populations including the chronically ill and those with HF.[6,47-49] The total score (0-60) was used with higher scores indicating more depression. The dichotomized score of ≥16, indicating the likelihood of a clinically relevant mood disorder, was used to determine the prevalence of depression in the sample.[50,51]

Data Analysis—Data were double entered into SPSS, corrected for errors and examined for skewness. Continuous variables were analyzed using means and standard deviations and compared with t-tests. Categorical variables were analyzed using proportions and compared with Chi-square tests and with Fisher's exact test (for cell counts were less than five). The associations between pain, fatigue and depression and demographic and clinical covariates were explored. A two-step hierarchical regression was used to examine the unique contribution of pain to the variance in functional performance. The SF-36 role limits-physical subscale score was entered as the dependent variable. Demographic (age, gender) and clinical (EF, Charlson Comorbidity Index, BMI) were entered in step 1, in order to control for their effects on the dependent variable. NYHA class was not included in the model because it is a measure of function and would be redundant with the dependent variable.[52] In step 2, the independent variables of fatigue, depression and pain were added for the purpose of evaluating their unique contributions to the variance in the dependent variables. A second regression was performed with the same independent variables, entered in identical order and with the 6MWT as the dependent variable. Significance level was set at $p \leq .05$.

Results

Sample

Demographic, clinical and patient characteristics, self-reported symptoms, and functional measures for the total sample are presented in Table 1. The sample consisted of 173 participants with stable HF. Of the sample 65% (n = 113) were male and 64% (n = 110) were white. The mean age was 60.4 years (SD 16.1). Sixty percent (n = 103) had a history of hypertension (HTN), and 40% (n = 69) had a previous myocardial infarction. The mean EF was 33% (SD =15.2) with 89% (n = 154) of the sample having systolic dysfunction. Forty-one percent of the sample (n = 70) had an ischemic HF etiology. Fifty-five percent of the sample (n = 95) had NYHA class II, and 35% of the sample (n = 61) had NYHA class III. Of the sample, 57% (n =100) had pain, 54% (n = 94) had fatigue on all or most days, and 46% (n = 79) had depression.

Associations Between Demographic, Clinical, Symptom and Functional Variables

Having a history of myocardial infarction, HTN, diabetes or osteoarthritis was not associated with pain, depression or fatigue. A history of angina was associated with pain (p

= .018), but not fatigue or depression. In addition, a psychiatric disorder history was associated with all three symptom variables (p = .001, p = 0.32, p =.001). Neither HF dysfunction nor etiology was associated with the symptom variables. See Table 2.

There were significant correlations among the symptom variables: pain and fatigue (r = -.375, P < .0001; pain and depression (r = -.360, p < .0001), and fatigue and depression respectively (r = .552; p <.0001). In addition, pain was associated with comorbidity (r = -.180, p = .018), NYHA class (r = -.214, p = .005), and both functional performance (r = .358, p <.0001) and functional capacity (r =.221, p = .005). Fatigue was not associated with any demographic or clinical variables, but was associated with both functional performance (r = -.527, p = <.0001) and functional capacity (r = -.260, p = .002). Depression was associated with age (r = -.207, p =.007), NYHA class (r = .154, p = .043) and functional performance (r = -.470, p <.0001), but not functional capacity. The clinical variables of BMI and EF were not correlated with any of the symptom variables. See Table 3.

Hierarchical Modeling of Functional Performance and Functional Capacity— The contributions of clinical and demographic variables to functional performance, as measured by the role-limits physical subscale, were measured using a hierarchical multiple regression. See Table 4. Only gender explained a statistically significant proportion of the variance in the dependent variable (*B* = -.196, p =.023). This step of the model explained 6% of the variance in functional performance (adjusted r^2 .021, p = .158).

After controlling for the influence of the clinical and demographic variables of age, gender, BMI, LVEF, and comorbidity, fatigue made the largest contributions to the variance in functional performance (*B* = -.346, p = <.0001), followed by depression (*B* = -.247, p = .005) and pain (*B* = .185, p = .016). Each of the symptom variables contributed to the change in variance in functional performance. This step accounted for an additional 32% of the variance in the dependent variable (adjusted $r^{2\ =}$ .338, p <.0001).

A hierarchical multiple regression analyses was also conducted to evaluate the contributions of the demographic and clinical variables, and symptom variables of depression, fatigue, and pain, to functional capacity as measured by the 6-MWT distance. In the first step, age (*B* -.267, p = .005), gender (*B* -.354, p = <.0001), and comorbidity (*B* -0.240, p = .004) were negatively associated with functional capacity, with gender making the largest contribution. The first step accounted for 25% of the variance in the 6-MWT (adjusted r^2=.223, p<.0001). In the second step, after controlling for age, gender, BMI, LVEF and comorbidity, none of the symptoms explained a statistically significant proportion of the variance in functional capacity (p = .175, p = .324, p = .239). See Table 5.

Discussion

Our findings document the unique contributions of depression, fatigue, and pain to functional performance, defined as the ability to perform daily work such as activities of daily living. We found that pain, fatigue and depression all contributed to changes in functional performance. However, pain, fatigue and depression were not associated with functional capacity as measured by the 6-MWT, age, gender and comorbidity were

associated with this functional measure. This finding was unexpected but is consistent with Leidy[14] who suggests that functional capacity is more closely related to age and comorbidities, rather than a single condition or disease process. These results are also consistent with previous finding that symptoms and hemodynamic parameters are poorly correlated[53]

Our findings extend the literature on the nature of the relationships between symptoms and function among HF patients by suggesting that symptoms such as pain, fatigue, and depression may limit daily activity (functional performance), but do not limit the actual potential to perform normal activities (functional capacity). These findings suggest that interventions targeted at pain, fatigue and depression may potentially increase functional performance so that people are able to reach their functional capacity in stable HF. These results are consistent with Leidy's[14] argument that factors that contribute to functional performance are modifiable. Therefore, symptom management interventions that specifically target functional performance may have a greater impact on preventing and reducing disability than those that target functional capacity. The differences in the contributions of symptoms to functional performance and functional capacity also underscore the conceptual differences between these two often-used functional measures. They are clearly not interchangeable.

Fatigue made the largest contribution to reduced functional performance and was a commonly reported symptom for the participants in this study. Fatigue can be a difficult symptom to manage, but active fatigue management must be a priority for this population due to its debilitating effects.[12] A potentially effective strategy to manage fatigue could be to manage the influencing symptoms, such as depression and pain, as a reduction in these symptoms may indirectly reduce the burden of fatigue.[12] However, additional research is needed to develop and test effective fatigue management interventions in this population.

Depression was also common among participants, with 46% scoring a 16 or greater on the CESD. In addition, depression had the next largest contribution after fatigue on reduced functional performance. This is consistent with other depression findings in HF.[36,51,54-56] Depression is of particular concern in HF because, in addition to its association with reduced functional capacity, there is a strong association between depressive symptoms and adverse outcomes in HF.[57,58]. Due to the associations of depression with decreased functional performance and adverse outcomes, in HF vigilant assessment and treatment of depression in HF is warranted.

The high prevalence of pain (57% of the sample) was consistent with the rates reported in past studies conducted in patients with primarily advanced HF (51%-84%).[7-10] In the current study pain was present across all stages of HF, but was more common as NYHA class increased. These findings suggest that pain management should be a priority for patients in all stages of HF, but specifically those with advanced disease.

We found that pain, fatigue and depression were all highly correlated with each other. The relationships between pain, fatigue and depression are complex and probably synergistic. Although the study did not focus on the full array of symptoms experienced by HF patients,

the correlations among pain, fatigue, and depression provide further evidence that symptoms do not occur in isolation; rather, they occur in clusters.[59-61] It is possible that interventions designed to address the symptom cluster or interventions designed to address individual symptoms, such as pain, may influence the cluster of symptoms.[60] For example, interventions to improve pain may also improve depression or vice versa. Further research is needed to examine these ideas.

In addition, research is needed to identify safe and effective symptom management interventions for people with stable HF, as some this population has unique needs. For example, common pain treatment modalities, such as NSAIDS are not recommended for use in this population.[62] Due to concerns with use of traditional pharmacological pain management strategies in HF, behavioral interventions for pain such as cognitive behavioral therapy and self-hypnosis are of particular interest and should be explored for their potential use in this population.[63,64]

Our study findings highlight several clinical and research implications. Clinicians should carefully evaluate for the presence of fatigue, depression and severity of cardiac and non-cardiac pain at every clinical encounter as these symptoms are common in HF and in particular in those with advanced HF.[7,8] Proactive treatment of all of these symptoms in patients with stable HF may have a beneficial impact functional performance.

There are several limitations to this study. First, our study sample only included stable HF patients with NYHA class I –IV HF. Caution must be used to generalize these findings beyond this population. In addition, this was a cross-sectional study and therefore the temporality of the relationships among the primary variables cannot be fully explained. Also we were not able to capture the additional components of function, as defined by Leidy,[14] including functional reserve and which is the difference between functional performance and maximum capacity, and functional capacity utilization which is an individual's ability to recognize and use their functional potential. The effects of symptoms on these functional attributes should be explored further. Also the measurement of depression was self-reported in this study and does not therefore indicate a clinical diagnosis of depression. Finally, as this study was a secondary data analysis, we were unable to determine the source of patient reported pain. However, the most common sites of pain reported in other studies include pain below the knees, back pain, joint pain and pain at multiple sites.[7,8] Other sources of pain that have been suggested in HF include musculoskeletal conditions, poor tissue perfusion, cardiac pain and psychological pain.[8,10]

Conclusion

Pain, fatigue and depression are common in stable HF and are present throughout all stages of the disease. Our study found that while pain, fatigue and depression were associated with decreased functional performance after controlling for demographic and clinical variables, these symptom variables were not associated with functional capacity. Thus, treatment of these symptoms, through appropriate pharmacological or behavioral interventions and symptom management programs, may improve aspects of functional status in this population who are at high risk for poor function and excessive symptom burden.

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Table 1
Sample Demographic, Clinical, Symptom & Functional Variables (n = 173)

Demographic Variables	
Age, years M (SD)	60.4 (16.1)*
Gender n (%)	
Male	113 (65.3)*
Female	60 (34.7)*
Race n (%)	
White	110 (64.3)
Minority	61 (35.7)
Marital Status n (%)	
Married	95 (54.9)
Single	33 (19.1)
Divorced/Separated	29 (16.8)
Widowed	16 (9.2)
Clinical Variables	
Charlson Comorbidity Index M (SD)	2.4 (1.5)*
BMI M (SD)	30.7 (8.3)*
Medical History n (%)	
Angina	35 (20.2)
Myocardial Infarction	69 (39.9)
Hypertension	103 (59.5)
Stroke	12 (6.9)
Diabetes	50 (28.9)
PVD	27 (15.6)
Osteoarthritis	28 (16.2)
Cancer	21 (12.1)
COPD	20 (11.6)
Psychiatric Disorder	13 (7.5)
Left Ventricular Ejection Fraction M (SD)	32.6 (15.2)*
Type of Dysfunction n (%)	
Systolic	154 (89.0)
Diastolic	13 (7.5)
HF Etiology n (%)	
Ischemic	70 (40.5)
Dilated	48 (27.7)
Idiopathic	22 (12.7)
Unspecified	25 (14.5)
NYHA n (%)	
I	5 (2.9)
II	95 (54.9)

Demographic Variables	
III	61 (35.3)
IV	12 (6.9)
Symptom Variables	
Pain n (%), M (SD)	100 (57), 60.2 (27.2)
Fatigue n (%), M (SD)	94 (54.3), 29.8 (14.2)
Depression n (%), M (SD)	79 (45.7), 17.1 (11)
Functional Variables	
SF-36 Role Limits-Physical M (SD)	41.9 (27.2)
6-MWT (Feet) M (SD)	989.4 (435.5)

*(Redeker et al., 2010)

Table 2

Differences Between Means for Categorical Demographic Variables and Pain, Fatigue & Depression (n = 173)

	Pain	Fatigue	Depression
Medical History M (SD)			
Angina			
Yes	50.4 (24.1)*	29.0 (14.7)	17.3 (11.5)
No	62.4 (27.4)	30.1 (14.7)	16.9 (11)
Myocardial Infarction			
Yes	55.6 (25)	29.4 (14.8)	17.2 (10.3)
No	62.9 (28.1)	30.1 (14.7)	16.9 (11.6)
HTN			
Yes	59.2 (27)	30 (14.9)	16.8 (10.9)
No	61.8 (27.6)	29.5 (14.3)	17.3 (11.3)
Diabetes			
Yes	54.9 (25.8)	30.4 (13.8)	18.9 (11)
No	62.4 (27.5)	29.6 (15.0)	16.2 (11)
Osteoarthritis			
Yes	51.1 (29.1)	29.2 (13)	17.4 (14)
No	61.7 (26.5)	30 (15)	16.9 (10.4)
Psychiatric Disorder			
Yes	44.5 (31.3)*	44.7 (10.4)*	26.4 (13.3)*
No	61.2 (26.6)	28.9 (14.4)	16.3 (10.6)
Type of Dysfunction			
Systolic	59 (27.4)	29.8 (14.6)	17.3 (11.3)
Diastolic	71.1 (26.5)	29.4 (18.3)	14.5 (9.2)

* $p < 0.05$ significance for t-test equality of means

Table 3

Correlations Among Demographic, Clinical, Symptom & Functional Variables (n = 173)

	Pain	Fatigue	Depression
Demographic/Clinical Variables			
Age	-.032 (.678)	-.104 (.198)	-.204 (.007)
Comorbidity	-.180 (.018)	.092 (.256)	.119 (.120)
BMI	.016 (.837)	-.015 (.858)	.010 (.901)
LVEF	.009 (.904)	.018 (.832)	-.136 (.080)
NYHA Class	-.214 (.005)	.131 (.106)	.154 (.043)
Symptom Variables			
Fatigue	-.375 (<.0001)		
Depression	-.360 (<.0001)	.552 (<.0001)	
Functional Variables			
Role Limits-Physical	.358 (<.0001)	-.527 (<.0001)	-.470 (<.0001)
6-MWT	.221 (.005)	-.260 (.002)	-.128 (.111)

Table 4

Hierarchical Multiple Regression for Demographic, Clinical and Symptom Variables Explaining Functional Performance (SF-36 Role Limits-Physical)

Step	Variable	r	r^2	F (change)	P (change)	Coefficient	Overall F (df), p
1		**.236**	**.056**	**1.62**	**.158**		**1.623 (5), p = .158**
	Age					.062	.548
	Gender					-.196	.023
	BMI					.056	.554
	LVEF					.088	.326
	Comorbidity					-.133	.134
2		**.613**	**.375**	**22.84**	**<.0001**		**10.1 (8), p <.0001**
	Fatigue					-.346	<.0001
	Depression					-.247	.005
	Pain					.185	.016

Table 5

Hierarchical Multiple Regression for Demographic, Clinical and Symptom Variables Explaining Functional Capacity (6-MWT)

Step	Variable	r	r^2	F (change)	P (change)	Coefficient	Overall F (df), P
1		**.502**	**.252**	**8.5**	**<.0001**		**8.5 (5), p <.0001**
	Age					-.267	.005
	Gender					-.354	<.0001
	BMI					-.043	.626
	LVEF					-.026	.749
	Comorbidity					-.240	.004
2		**.555**	**.308**	**3.287**	**.023**		**6.8 (8), p <.0001**
	Fatigue					-.130	.175
	Depression					-.093	.324
	Pain					.098	.239