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Identifying a Relationship Between Physical Frailty and Heart Failure Symptoms

Quin E. Denfeld, PhD, RN; Kerri Winters-Stone, PhD, FACSM; James O. Mudd, MD; Shirin O. Hiatt, MS, MPH, RN; Christopher S. Lee, PhD, RN, FAHA, FAAN, FHFSA

Background: Heart failure (HF) is a complex clinical syndrome associated with significant symptom burden; however, our understanding of the relationship between symptoms and physical frailty in HF is limited. **Objective:** The aim of this study was to quantify associations between symptoms and physical frailty in adults with HF. **Methods:** A sample of adults with symptomatic HF were enrolled in a cross-sectional study. Physical symptoms were measured with the HF Somatic Perception Scale–Dyspnea subscale, the Epworth Sleepiness Scale, and the Brief Pain Inventory short form. Affective symptoms were measured with the Patient Health Questionnaire-9 and the Brief Symptom Inventory–Anxiety scale. Physical frailty was assessed according to the Frailty Phenotype Criteria: shrinking, weakness, slowness, physical exhaustion, and low physical activity. Comparative statistics and generalized linear modeling were used to quantify associations between symptoms and physical frailty, controlling for Seattle HF Model projected 1-year survival. **Results:** The mean age of the sample (n = 49) was 57.4 ± 9.7 years, 67% were male, 92% had New York Heart Association class III/IV HF, and 67% had nonischemic HF. Physically frail participants had more than twice the level of dyspnea ($P < .001$), 75% worse wake disturbances ($P < .001$), and 76% worse depressive symptoms ($P = .003$) compared with those who were not physically frail. There were no differences in pain or anxiety. **Conclusions:** Physically frail adults with HF have considerably worse dyspnea, wake disturbances, and depression. Targeting physical frailty may help identify and improve physical and affective symptoms in HF.

KEY WORDS: heart failure, physical frailty, symptoms

As a common end-point of many cardiovascular conditions such as hypertension and coronary artery disease,[1,2] heart failure (HF) is a highly prevalent and complex clinical syndrome. For the millions living with HF, this syndrome is highly burdensome symptomatically[3,4] and difficult to manage clinically.[5] Given the little to no association between HF symptoms and traditional objective markers of heart function,[6–8] we are severely hampered in our ability to reduce symptom burden. As a new frontier in HF symptom biology, the relationship between HF and common geriatric syndromes may help us better understand symptoms in HF.

Physical frailty, a common geriatric syndrome, is considered an indicator of biological aging[9] and has become a high priority in cardiovascular disease research.[10,11] Among adults living with HF, physical frailty is highly prevalent and associated with worse clinical- and patient-oriented outcomes.[12–20] Furthermore, it is thought that both physical frailty and HF share common pathophysiological mechanisms,[21] and

Quin E. Denfeld, PhD, RN
Post-Doctoral Fellow, Knight Cardiovascular Institute, Oregon Health & Science University, Portland.
Kerri Winters-Stone, PhD, FACSM
Elnora E. Thompson Distinguished Professor, Research Professor, School of Nursing and Knight Cancer Institute, Oregon Health & Science University, Portland.
James O. Mudd, MD
Associate Professor, Knight Cardiovascular Institute, Oregon Health & Science University, Portland.
Shirin O. Hiatt, MS, MPH, RN
Research Associate, School of Nursing, Oregon Health & Science University, Portland.
Christopher S. Lee, PhD, RN, FAHA, FAAN, FHFSA
Carol A. Lindeman Distinguished Professor, Associate Professor, Knight Cardiovascular Institute and School of Nursing, Oregon Health & Science University, Portland.

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Correspondence
Quin E. Denfeld, PhD, RN, Oregon Health & Science University Knight Cardiovascular Institute, L334, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239-2941(denfeldq@ohsu.edu).

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therefore, the symptoms of HF would mirror physical frailty. A few studies have found that frail adults with HF have worse depression,[16,19,22] and 1 study[22] showed worse anxiety among adults with HF who are frail. No studies, however, have examined the relationship between physical frailty—as assessed by the Frailty Phenotype[9]—and both physical and affective symptoms in HF. The purpose of this article was to quantify the associations between symptoms and physical frailty in adults with HF. We hypothesized that physically frail adults with HF would report worse physical and affective HF symptoms compared with those who are not considered physically frail.

Methods

This article addresses a primary aim of a US National Institutes of Health–funded cross-sectional study on physical frailty in HF conducted by a single group of HF investigators from July 2015 to March 2016. Key aspects of the study included assessing physical frailty and symptoms in patients scheduled for a right heart catheterization procedure. Participants were recruited from an HF practice (both outpatient and inpatient facilities) at an academic medical center in the Pacific Northwest. Formal inclusion criteria included 21 years or older, ability to read and comprehend fifth grade English, New York Heart Association (NYHA) functional classification II to IV (as determined by the HF cardiologist), and scheduled for a right heart catheterization *for clinical purposes only*. Potential participants were excluded if they had had a previous heart transplant or ventricular assist device, had major uncorrected hearing dysfunction, or were otherwise unable to complete the requirements of the study (eg, life-threatening illness). Study staff not directly involved in patient care obtained written informed consent from each participant, and this study was approved by our institutional review board.

Measurement

Data on age, gender, marital status, race, and education were obtained using a sociodemographic questionnaire. Functional status (ie, NYHA) was assessed by an attending HF cardiologist. Data on history, duration, etiology, and treatment of HF along with clinical characteristics were collected through an in-depth review of the electronic medical record. Comorbid conditions were summarized using the Charlson Comorbidity Index.[23] Objective markers of heart function included reports and waveform tracings derived from the right heart catheterization procedure and recent echocardiographic and cardiopulmonary exercise test reports. The Seattle HF Model (SHFM) projected survival was calculated based on the model developed by Levy and colleagues (2006)[24] and available online (https://depts.washington.edu/shfm/); this model uses objective clinical variables and HF treatments to generate estimated projected survival.

Mild Cognitive Dysfunction

Cognitive function was assessed in-person using the Montreal Cognitive Assessment.[25] The Montreal Cognitive Assessment is a cognitive screening instrument designed for use by first-line clinicians, with a cutoff score of 26 (ie, <26/30) and a sensitivity of 90% and a specificity of 87% to detect mild cognitive dysfunction in adults.[25] The Montreal Cognitive Assessment has an adjusted algorithm for persons with chronic cardiovascular disease (<24/30) that is 100% sensitive to detect amnestic mild cognitive dysfunction.[26] Thus, a Montreal Cognitive Assessment score of 24 was used as the cutoff for subclinical mild cognitive dysfunction in this study.

Physical Frailty

Using the Frailty Phenotype,[9] a well-validated measure in older adults, we assessed the 5 criteria of physical frailty: shrinking, weakness, slowness, physical exhaustion, and low physical activity. For practicality and feasibility in a patient population, we selected our measures based on their ability to be assessed in clinical practice.

Shrinking was measured by a self-report of unintentional weight loss of more than 10 lb over the last year. *Weakness* was measured using 5-repeat chair stands. Participants were assessed and timed on their ability to rise out of a chair 5 times without using their arms. A cutoff of greater than 12 seconds or inability to rise 5 times was used to define weakness.[27] *Slowness* was measured by clocking the time it took a participant to walk 4 m (ie, gait speed in meters per second). We defined slowness as less than 0.9 m/s based on a review of previous studies.[17,28,29] *Physical exhaustion* was assessed using the 13-item Functional Assessment of Chronic Illness Therapy Fatigue Scale (v. 4).[30,31] On the basis of the application of the Functional Assessment of Chronic Illness Therapy Fatigue Scale in the general population,[32] we used a cut point of 17 on the Functional Assessment of Chronic Illness Therapy Fatigue Scale, which corresponds to 2 standard deviations below the mean of the general population, to identify those with severe physical exhaustion. *Level of physical activity* was measured by the participants' response to a single question "During the past week, how much total time did you spend exercising?" Those who reported less than 1 hour per week were classified as having low physical activity.

After completing the measures for each of the 5 criteria, the scores were totaled (range, 0–5). Each participant was then classified as either "nonfrail" (0/5 criteria met), "prefrail" (1–2 criteria met), or "frail"

(≥3 criteria met) as determined by the original Frailty Phenotype.[9]

Physical Symptoms

Physical HF symptoms were measured with the 18-item HF Somatic Perception Scale.[33] In total, the HF Somatic Perception Scale measures perceived severity of both nonspecific symptoms (eg, fatigue and weight gain) and acute symptoms (eg, orthopnea and dyspnea) in HF. However, for the purposes of this study and to avoid measurement overlap with the physical frailty measures, the 6-item subscale for dyspnea (HF Somatic Perception Scale–Dyspnea) was used. Scores on the HF Somatic Perception Scale–Dyspnea range from 0 to 30, with higher scores indicating worse perceived dyspnea. Reliability and predictive validity of the HF Somatic Perception Scale–Dyspnea have recently been demonstrated.[33] The reliability of the HF Somatic Perception Scale–Dyspnea in our sample was .94.

Wake disturbances were measured with the Epworth Sleepiness Scale.[34] The Epworth Sleepiness Scale asks respondents to rate how likely they would be to doze off in 8 different situations by choosing response options that range from 0 (would never doze) to 3 (high chance). Scores on the Epworth Sleepiness Scale range from 0 to 24, with higher scores indicating worse wake disturbances; a cutoff score greater than 10 indicates excessive wake disturbances. The reliability of the Epworth Sleepiness Scale in our sample was .86.

The Brief Pain Inventory Short Form[35] was used for the assessment of both pain severity and interference. The Brief Pain Inventory consists of 4 questions about pain severity (Brief Pain Inventory Severity) and 7 questions about pain interference (Brief Pain Inventory Interference). Respondents rate their worst, least, average, and current pain intensity and also rate the degree to which pain interferes with domains of functioning on a scale of 0 (no pain or does not interfere) to 10 (as bad as you could imagine or interferes completely). Scores for each scale are summed and averaged; scores for both scales range from 0 to 10. The reliability of both the Brief Pain Inventory Severity and Interference scales in our sample was .92.

Affective Symptoms

The 9-item Patient Health Questionnaire[36] was used to assess depression. The Patient Health Questionnaire scores each of the 9 related *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, criteria for depression. Scores on the Patient Health Questionnaire range from 0 to 27, with higher scores indicating worse depression; a cutoff score of 10 or higher indicates moderate or greater depression. The Patient Health Questionnaire is a valid and reliable measure of depression in HF.[37] The reliability of the Patient Health Questionnaire in our sample was .85.

Anxiety was measured using the 6-item Brief Symptom Inventory anxiety scale.[38] Scores on the Brief Symptom Inventory anxiety scale (calculated by adding the ratings and dividing the total by the number of items in the subscale) range from 0 to 4, with higher scores indicating worse anxiety. The Brief Symptom Inventory anxiety scale is a valid and reliable measure of anxiety in HF.[39] The reliability of the Brief Symptom Inventory anxiety scale in our sample was .84.

Statistical Analysis

This study was powered to detect a statistically significant difference in 1 primary measure (dyspnea) between groups. With a minimum sample size of 47 and an α of .05, we determined we would preserve a power of 0.80 using a Student t test, with approximately equal group sizes, to detect a Cohen's d of greater than 0.85 (large effect size). Internal consistency of each measure was quantified using Cronbach's α. Standard descriptive statistics of frequency, central tendency, and dispersion were used to describe the sample. Because only 1 participant was considered nonfrail, we combined nonfrail and prefrail into 1 category: "not physically frail." Comparative statistics, including Student t, Mann-Whitney U, or Fisher exact tests or Pearson χ^2, were used to compare demographic and clinical characteristics and symptoms between those considered physically frail and those not physically frail. We used generalized linear modeling to generate relative differences in symptoms comparing physically frail participants with those who were not physically frail, adjusting for SHFM projected 1-year survival. All analyses were performed using Stata/MP version 13MP (StataCorp, College Station, Texas).

Results

Sample characteristics are described in Table 1. The average age of the total sample enrolled (n = 49) was about 57 years, and most were male and non-Hispanic white. Most had NYHA class III or IV and nonischemic HF, and most were on evidence-based therapies, including β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. At the time of enrollment and assessment of physical frailty, 69% of participants were outpatient status. Half of the participants were physically frail (n = 24), and nearly the rest of the sample were considered prefrail (n = 24). Physically frail participants had significantly worse 1-year projected survival and peak oxygen consumption and significantly higher proportions of NYHA class IV functional classification and mild cognitive dysfunction compared with those not physically frail.

Physically frail participants had significantly worse dyspnea and had higher rates of excessive wake disturbances

TABLE 1 Characteristics of the Sample and by Level of Physical Frailty

	Total (n = 49)	Not Physically Frail (n = 25)[a]	Physically Frail (n = 24)	*P*[b]
Patient characteristics				
Age, y	57.4 ± 9.7	54.8 ± 11.7	60.1 ± 6.4	.056
Male	33 (67.4)	19 (76.0)	14 (58.3)	.187
Non-Hispanic white	40 (81.6)	22 (88.0)	18 (75.0)	.289
Charlson Comorbidity Index (weighted)	2.3 ± 1.2	2.2 ± 1.2	2.4 ± 1.2	.532
Outpatient (vs inpatient) at enrollment	34 (69.4)	20 (80.0)	14 (58.3)	.128
General heart failure characteristics				
Time with heart failure, y	8.4 [2.4–14.8]	8.4 [4.8–15.0]	8.0 [1.0–13.5]	.207
NYHA functional class				.008
Class II	4 (8.2)	4 (16.0)	0 (0.0)	
Class III	34 (69.4)	19 (76.0)	15 (62.5)	
Class IV	11 (22.5)	2 (8.0)	9 (37.5)	
Nonischemic etiology	33 (67.4)	19 (76.0)	14 (58.3)	.187
Prescribed a β-blocker	35 (71.4)	20 (80.0)	15 (62.5)	.217
Prescribed an ACE-I or ARB	39 (79.6)	21 (84.0)	18 (75.0)	.496
Left ventricular ejection fraction, %	24.3 ± 8.9	25.2 ± 6.8	23.3 ± 10.7	.473
Peak VO_2 (mL/kg/min)	15.4 ± 3.6	16.2 ± 3.7	13.6 ± 2.8	.049
SHFM projected 1-y survival, %	93.0 [81.0–96.0]	95.0 [92.0–97.0]	89.0 [70.0–95.0]	.007
Mild cognitive dysfunction (MoCA < 24)	16 (32.7)	2 (8.0)	14 (58.3)	<.001
Physical frailty measures				
Unintentional weight loss	17 (34.7)	6 (24.0)	11 (45.8)	.108
Weakness by chair stands, s[c]	17.6 ± 8.0	14.4 ± 7.1	21.3 ± 7.6	.004
Slowness, m/s[c]	0.9 ± 0.2	1.1 ± 0.2	0.7 ± 0.2	.001
Physical exhaustion (FACIT-F; 0–52)	24.0 ± 10.6	28.4 ± 9.6	19.5 ± 9.8	.002
Low physical activity	33 (67.4)	12 (48.0)	21 (87.5)	.005

Data are presented as mean ± SD, n (%), or median [IQR].
Abbreviations: ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; NYHA, New York Heart Association; SHFM, Seattle Heart Failure Model; VO_2, peak oxygen consumption.
[a] Not physically frail includes both nonfrail (n = 1) and prefrail (n = 24).
[b] *P* values comparing physically frail versus not physically frail.
[c] Data include only those who could successfully complete these assessments (ie, several could not complete 5-repeat chair stands or gait speed).

compared with those who were not physically frail (Table 2). There was no significant difference in reported pain severity or interference. After adjusting for SHFM projected 1-year survival, physically frail participants were more than 2 times as dyspneic and had 75% worse wake disturbance symptoms than did those who were not physically frail (Table 3).

Physically frail participants had significantly higher rates of moderate or greater depression compared with those who were not physically frail (Table 2). There was no significant difference in reported anxiety. After adjusting for SHFM projected 1-year survival, physically frail participants had 76% more depressive symptoms than those who were not physically frail (Table 3).

Discussion

The purpose of this study is to quantify associations between symptoms and physical frailty among adults with HF. The main finding from this study is that

TABLE 2 Symptom Characteristics of the Sample and by Level of Physical Frailty

Symptomatology	Total (n = 49)	Not Physically Frail (n = 25)[a]	Physically Frail (n = 24)	*P*[b]
Dyspnea (HFSPS-D; 0–30)	12.0 ± 9.1	7.4 ± 5.9	16.7 ± 9.5	<.001
Pain severity (BPI; 0–10)	3.0 ± 2.3	2.7 ± 1.9	3.4 ± 2.6	.270
Pain interference (BPI; 0–10)	3.6 ± 2.7	3.2 ± 2.5	4.0 ± 2.8	.262
Excessive wake disturbances (ESS score > 10)	20 (40.8)	4 (16.0)	16 (66.7)	<.001
Moderate depression (PHQ9 score ≥ 10)	26 (53.1)	8 (32.0)	18 (75.0)	.003
Anxiety (BSI; 0–4)	0.76 ± 0.74	0.62 ± 0.63	0.91 ± 0.83	.169

Data are presented as mean ± SD or n (%).
Abbreviations: BPI, Brief Pain Inventory; BSI, Brief Symptom Inventory; ESS, Epworth Sleepiness Scale; HFSPS-D, Heart Failure Somatic Perception Scale–Dyspnea subscale; PHQ9, Patient Health Questionnaire.
[a]Not physically frail includes both nonfrail (n = 1) and prefrail (n = 24).
[b]*P* values comparing physically frail versus not physically frail.

TABLE 3 Adjusted Relative Differences in Physical and Affective Symptoms Among Physically Frail Adults With Heart Failure

	% Difference (% ± SE)	*P*
HFSPS-D scores[a]	136.9 ± 58.3	<.001
ESS scores[a]	74.7 ± 25.2	<.001
PHQ9 scores[a]	75.9 ± 33.3	.003

Abbreviations: ESS, Epworth Sleepiness Scale; HFSPS-D, Heart Failure Somatic Perception Scale–Dyspnea subscale; PHQ9, Patient Health Questionnaire.
[a] Adjusting for Seattle Heart Failure Model projected 1-year survival.

physically frail adults with HF have significantly worse dyspnea, wake disturbances, and depression compared with those who are not physically frail. These results demonstrate that (1) an assessment of physical frailty may help explain the underlying pathophysiological mechanisms of symptoms in HF and (2) a phenotype of physical frailty mirrors some of the burdensome symptoms experienced by adults with HF, providing an additional instrument with which to assess symptoms in HF.

Because our understanding of the biological underpinnings of symptoms in HF is limited, our finding of a significant association between physical frailty and both physical and affective symptoms may help elucidate the pathophysiological mechanisms giving rise to symptoms in HF. The general disconnect between symptoms and objective markers of heart function[40] indicates that symptoms are not necessarily a function of traditional invasive hemodynamic or echocardiographic assessments. Even though the biological mechanisms of physical frailty continue to be unraveled,[41] the most common areas of dysregulation involve the endocrine, immune, and neurohormonal symptoms.[42] In HF specifically, the inability of the heart to adequately perfuse the tissues may lead to downstream impairments at multiple levels, including skeletal muscle structure and metabolism, and manifesting in physical frailty, which may in turn give rise to burdensome HF symptoms. However, the direct relationship between HF pathophysiology, physical frailty, and symptoms in HF is not well understood and should be a focus of future research.

The results from this study confirm physical frailty and symptoms mirror each other in HF. In essence, those adults with HF who have some combination of shrinking, weakness, slowness, physical exhaustion, and/or low physical activity have significantly worse dyspnea, wake disturbances, and depression. Even though others have provided evidence that frail adults with HF have worse depression and anxiety,[16,19,22] this is the first study to examine both physical and affective symptoms in HF. Furthermore, toward a strength of this study, we chose measures that would minimize overlap between symptoms and physical frailty as opposed to studies that have used depression questionnaires to assess physical exhaustion. Our intent was to capture *physical frailty* that is distinct from, but also complementary to, common symptoms in HF. Notably, our approach also identified significant differences in mild cognitive dysfunction between groups; cognitive function has been shown to improve the predictive value of a physical frailty assessment in HF,[43] and further study of the relationship between physical frailty and cognitive function in HF is warranted.

Clinically speaking, these findings indicate that a simple physical frailty assessment, which takes about 5 to 7 minutes to complete, could provide much needed insight into both physical and affective symptoms experienced by patients with HF. And vice versa, worse physical and affective symptoms could be a signal that patients are concurrently physically frail. Moreover, the presence of physical frailty may alert clinicians in identifying patients with more advanced HF, particularly in relation to worse symptoms coupled with worse cognition, exercise capacity, and 1-year projected survival. Hence, an assessment of physical frailty may help pinpoint those HF patients at risk for worse clinical- and patient-oriented outcomes. Furthermore, what this article highlights is that not only are physically frail patients suffering from functional decline related to loss of muscle mass, exercise capacity, and ability to perform normal, daily activities, but also they are suffering from burdensome physical and affective symptoms. As such, even though the directional relationship between physical frailty and symptoms has not been elucidated, it behooves clinicians to consider both physical frailty and symptoms concurrently as improvements in one may lead to improvements in the other. In addition, assessing and targeting physical frailty could potentially be an effective strategy to improve symptoms particularly in advanced, medically refractory HF patients seeking palliative care treatment. Finally, it is also important to note that physical frailty in HF is often independent of advanced age; indeed, our sample of younger HF patients had higher rates of physical frailty compared with studies of community-dwelling older adults.[9]

This study has a few noted limitations. This was a cross-sectional study, and we were only able to report associations and not causal mechanisms. In addition, this was a small, young, racially homogenous, and predominantly nonischemic sample, and these participants were referred to an advanced HF clinic; hence, the results may not be generalizable to the entire HF population at large. Furthermore, given our small sample size, we may have been underpowered to detect small effect sizes, and further research with larger samples is needed in this area. Finally, all but 1 of the participants were physically frail or prefrail, most likely because of the more advanced stage of HF in these patients, and we did not fully capture the spectrum of frailty as originally outlined by Fried and colleagues.[9] The lack

What's New and Important

- Physical frailty is associated with worse physical and affective HF symptoms.
- Assessing physical frailty in HF is clinically helpful.
- Targeting physical frailty may improve HF symptoms.

of a nonfrail group as a comparison group limits the generalizability of our findings but also highlights that many adults with HF are physically frail or prefrail.[21]

Given the significance of our findings, there is a large potential for important physical frailty-related study in future HF research. First, longitudinal research is needed to study the directional relationship between physical frailty and HF symptoms to understand how physical frailty changes over time across the HF spectrum (eg, from NYHA class I to IV) and how this change tracks with symptoms. This type of study would also permit a better understanding of the pathophysiological mechanisms underlying the parallel relationship between physical frailty and symptoms in relation to changing HF severity. Importantly, more research is also needed to understand how this relationship changes after advanced HF interventions such as ventricular assist device placement, which would yield information about the reversibility of physical frailty and the etiology of physical frailty in HF (HF related vs non–HF related, such as comorbidities or age).[44] Second, there is a need to study targeted exercise, nutritional, or specialized HF disease management interventions[45,46] guided by the cycle of frailty proposed by Fried and colleagues,[9] which may improve both physical frailty and HF symptoms. Finally, the strong relationship between mild cognitive dysfunction and physical frailty in HF warrants further investigation, including understanding the shared pathophysiology, the combined effect of mild cognitive function and physical frailty on HF self-care, and potential treatments to address both conditions.

Conclusions

In summary, physically frail adults with HF have significantly and clinically worse dyspnea, wake disturbances, and depression than nonphysically frail adults with HF. Using measures based on the Frailty Phenotype, these findings demonstrate that an assessment of physical frailty may tell us more about symptoms experienced by adults with HF than other traditional objective markers of heart function. Therefore, incorporating an assessment of physical frailty may help clinicians in interpreting and targeting the burdensome symptoms in HF.

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