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## Coexisting Frailty, Cognitive Impairment, and Heart Failure: Implications for Clinical Care

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### Abstract

**Objective**—To review some of the proposed pathways that increase frailty risk in older persons with heart failure and to discuss tools that may be used to assess for changes in physical and cognitive functioning in this population in order to assist with appropriate and timely intervention.

**Methods**—Review of the literature.

**Results**—Heart failure is the only cardiovascular disease that is increasing by epidemic proportions, largely due to an aging society and therapeutic advances in disease management. Because heart failure is largely a cardiogeriatric syndrome, age-related syndromes such as frailty and cognitive impairment are common in heart failure patients. Compared with age-matched counterparts, older adults with heart failure 4 to 6 times more likely to be frail or cognitively impaired. The reason for the high prevalence of frailty and cognitive impairment in this population is not well known but may likely reflect the synergistic effects of heart failure and aging, which may heighten vulnerability to stressors and accelerate loss of physiologic reserve. Despite the high prevalence of frailty and cognitive impairment in the heart failure population, these conditions are not routinely screened for in clinical practice settings and guidelines on optimal assessment strategies are lacking.

**Conclusion**—Persons with heart failure are at an increased risk for frailty, which may worsen symptoms, impair self-management, and lead to worse heart failure outcomes. Early detection of frailty and cognitive impairment may be an opportunity for intervention and a key strategy for improving clinical outcomes in older adults with heart failure.

Approximately 5.7 million persons in the United States are diagnosed with heart failure, and the number of reported new cases is expected to increase to over 700,000 cases annually by the year 2040 [1]. This rising incidence is fueled by an aging population; by the year 2030, 1 in 5 Americans will be over 65 years of age [2]. Heart failure is prevalent among those 65 years of age and older and is the most common reason for hospitalization in this age-group. High readmission rates, approaching 50% over 6 months, are a major contributor to the the escalating economic burden associated with heart failure [3].

Persons with heart failure are more likely to be frail and experience cognitive impairment than their age-matched counterparts without heart failure. The reasons for this are not well

known but may be related to hemodynamic, vascular, and inflammatory changes occurring as heart failure progresses. In this paper, we review the link between frailty and cognitive impairment in heart failure, instruments that may be useful for early detection, and interventions such as exercise that may be beneficial for attenuating both conditions.

## Frailty in Heart Failure

### Epidemiology

Frailty is a heightened vulnerability to stressors in the presence of low physiological reserve [4]. When exposed to stressors, persons who are frail have a much higher probability for disproportionate decompensation, negative events, functional decline, disability, and mortality [5]. Among persons with heart failure, frailty may predispose them to decompensate at a lower threshold, requiring more frequent hospitalizations. Persons with heart failure are more likely to be frail than their age-matched counterparts without heart failure [6,7].

Frailty is a powerful predictor of poor clinical outcomes and mortality in cardiovascular disease [8,9]. Compared with the non-frail, frail persons with heart failure have increased rates of mortality (16.9% vs 4.8%) and increased rates of heart failure hospitalization (20.5% vs 13.3%) [10]. Frailty has also been shown to predict falls, disability, and hospitalization in heart failure patients [6,9,11] and was found to have a negative linear relationship with health-related quality of life [12]. Frail heart failure patients are also more likely to have comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, depression, anemia, and chronic kidney disease [9,13].

### Pathophysiology

There is significant overlap in the underlying pathological mechanisms of heart failure and frailty. Symptoms of heart failure, such as dyspnea, fatigue, and muscle loss, mirror components that occur with frailty. Further, cardiac cachexia, a metabolic syndrome in advanced heart failure characterized by a loss of muscle mass, is very similar to the sarcopenia that occurs in frailty.

Frailty, characterized by an increased physiologic vulnerability to stressors, may predispose frail persons with heart failure to exacerbation and worsening of heart failure due to greater susceptibility to the harmful pathophysiologic processes in heart failure, such as inflammation and autonomic dysfunction. Proposed pathophysiologic pathways in frailty include free radicals and oxidative stress, cumulative DNA damage, decreased telomere length, and nuclear fragmentation [14,15]. Frailty has been associated with low-grade chronic inflammation and increased inflammatory cytokines, such as C-reactive protein, tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin-6 (IL-6) and fibrinogen [16–18]. Heart failure also is associated with a low-grade and chronic cardiac inflammatory response that is correlated with disease progression [19].

**Inflammation**—IL-6 is detectable in a higher proportion of persons who are frail compared to non-frail [16] and is the most highly correlated biomarker with frailty. In addition, among those with detectable IL-6 levels, those categorized as frail have higher IL-6 levels

compared to those who are non-frail [16,20]. Individuals categorized as frail were found to have significantly higher levels of TNF $\alpha$  than those who were non-frail [16,20]. Increased IL-6 levels are associated with decreased muscle strength, while increased TNF $\alpha$  levels are associated with decreased skeletal muscle protein synthesis [21,22], thus contributing to frailty.

**Oxidative stress**—Protein carbonyls result from protein oxidation promoted by reactive oxygen species and are markers of oxidative stress. Protein carbonylation is implicated in the pathogenesis of the loss of skeletal muscle mass; high serum protein carbonyls are associated with poor grip strength [23]. 8-OHdG is an oxidized nucleoside indicative of oxidative damage to DNA and a measure of oxidative stress. Accumulation of 8-OHdG in skeletal muscle leads to loss of muscle mass and is associated with decreased hand grip strength in the elderly [24]. Higher serum levels of 8-OHdG are present in older adults who are frail as compared to those who are non-frail [25].

### Measurement of Frailty in the Clinical Setting

Frailty has been conceptualized in a number of studies using different models and measures; however, there continues to be a lack of consensus on the definition and operationalization of frailty. Prior research has led to the development of several validated models of frailty that have demonstrated good prediction of adverse outcomes in older adults. Some models, such as the Fried phenotype [6], focus solely on the physical dimension, while other models take a multidimensional approach. Single-item measures (eg, gait speed, 6-minute walk test, handgrip strength) are also commonly used to screen for frailty, but a frailty measure that incorporates more than 1 physical dimension may be more sensitive and reliable. In our opinion, the ideal measure of frailty would consist of a brief assessment that can be serially performed in most clinical practice settings that can identify change in function over time. The incorporation of sensitive physical function measures that can detect frailty early has the potential to slow physical function decline by preserving physiological thresholds.

## Cognitive Impairment in Heart Failure

### Epidemiology

Cognitive impairment occurs frequently in patients with heart failure, and the presence of cognitive impairment in persons with heart failure has been shown to heighten risk for adverse clinical outcomes, disability, poor quality of life, and mortality [26,27]. Heart failure negatively influences cognitive functioning in most domains [28–32]. The most common domains adversely affected by heart failure and aging are memory and executive function. Deficits in these domains can substantially diminish patient ability to carry out essential self-care behaviors [30,32].

The most common form of cognitive impairment seen in patients with heart failure is mild cognitive impairment (MCI), which is a measurable deficit with memory or another core cognitive domain. Up to 60% of persons with heart failure have been reported to have MCI. Patients with MCI have cognitive deficits that are more pronounced than those seen in normal aging, but lack other symptoms of dementia, such as impaired judgment or

reasoning. MCI often will not impede patients' ability to carry out the activities of daily living (ADLs) independently, but patients may have difficulty in performing some instrumental activities of daily living (IADLs), such as remembering medications, scheduling provider appointments. Dementia, a decline in cognitive ability severe enough to hinder an individual's ability to perform ADLs or IADLs or engage in social activities or occupational responsibilities, occurs in approximately 25% of persons with heart failure [33].

Persons with heart failure have a fourfold greater likelihood of developing CI than persons without heart failure. Several cohort studies have shown that persons with heart failure had lower performance on cognitive tests than individuals without heart failure [34,35] and were 50% more likely to progress to dementia.

### Assessment Tools

Although a comprehensive neurocognitive battery would aid in detecting cognitive impairment in heart failure, few clinical practice settings have the resources to perform such a detailed and time-consuming measurement. Most studies in heart failure have relied on global screening questionnaires such as the Mini-Mental State Examination (MMSE) [36] to assess cognitive functioning in persons with heart failure and in other cardiovascular disorders. Global cognitive measures, however, often lack sensitivity for detecting subtle cognitive deficits such as seen in MCI [28–30]. Screening that measures executive function may be the most beneficial for busy clinical settings, since declines in this domain are well established as contributing to poor outcomes in persons with heart failure.

The Montreal Cognitive Assessment (MoCA) is a rapid screening test designed to detect MCI. It assesses different cognitive domains, including attention, memory, language, and executive function [37]. The MoCA lends itself to use in clinical setting because it is brief, requires little training to administer, and is easy to score. This instrument has been used successfully to assess MCI in persons with heart failure and may be more sensitive than the MMSE in identifying clinically relevant cognitive dysfunction. In 2013 study, Cameron et al [38] administered the MMSE and MoCA to 93 hospitalized heart failure patients and found that the MoCA classified 41% of patients as cognitively impaired that were not classified using the MMSE. For persons with a vascular cognitive deficit, the MMSE has been portrayed as an inadequate screening test due to lack of sensitivity for visuospatial and executive function deficits. Because the MoCA was designed to be more sensitive to such deficits, it may be a superior screening method for persons with heart failure. Although previous studies support the use of the MoCA in persons with heart failure, more research is needed in larger, more diverse heart failure samples with a wide range of cognitive deficits.

### A Reasonable Clinical Assessment Approach

Considering the link between heart failure, frailty, and MCI, incorporating simple physical performance measures with cognitive screening may be an effective strategy to identify persons at risk for frailty. Two clinically relevant physical performance-based measures of frailty are proposed: the Fried phenotype (mentioned earlier) and the Short Physical Performance Battery (SBBP). In addition, cognitive screening using the MoCA is

recommended as part of the routine examination for determining possible MCI or more severe cognitive deficits. The predictive validity of measuring physical frailty is enhanced when cognitive impairment is included in the assessment [36,39].

The performance-based measures included in this review have previously demonstrated excellent psychometric properties as well as sensitivity for change that is clinically meaningful. Minimal detectable change (MDC), a threshold score that refers to the minimal amount of change outside of error that reflects true change by a patient between 2 time points (rather than variation in measurement), is important for interpreting level of risk for frailty and is included for each instrument [40,41]. If a more brief frailty examination is needed, cut-points for gait speed and handgrip have been used effectively in a number of studies as a threshold for determining frailty, including in older patients with cardiovascular disease and in heart failure [8,42,43].

### **Fried Frailty Phenotype**

The Fried phenotype is an appropriate method of measuring frailty in a clinical setting due to its wide application across diverse populations and consistent identification of adverse outcomes [44]. This model is derived from a frailty model proposed by Fried et al [6] in which a phenotypic cycle exists that includes disease, sarcopenia, decreased walking speed, chronic undernutrition, decreased total energy expenditure, senescent musculoskeletal changes, decreased resting metabolic rate, weight loss and decreased maximal oxygen consumption. Frailty exists when a critical mass of these cycle components are identified in an individual [6].

To validate the model, Fried et al used data from the Cardiovascular Health Study and used the model to show association with a 3-year and 7-year incidence of mobility and ADL disability among 4317 community-dwelling men and women aged 65 years and older, independent of comorbidities. Several studies have directly tested the frailty phenotype model alone and in comparison to other models of frailty in large prospective studies across different populations, such as the Survey of Health, Aging and Retirement in Europe (SHARE) [45], the European Male Aging Study [46], and the Canadian Health Study of Aging [47]. While these studies found the prevalence of frailty to vary across the populations, they all validated the Fried model and found no significant differences in the predictive ability of the Fried model and other models of frailty. The Frailty Consensus conference evaluated the different models of frailty and determined that the Fried model is a validated construct of frailty and is acceptable for use in the identification of individuals who are frail or likely to become frail [48]. Thus, the Fried et al frailty phenotype model is considered to be a standard measure of frailty in older individuals.

The Fried phenotype assesses 5 criteria: shrinking, weakness, exhaustion, gait speed and physical activity (Table 1) [6]. A score of 0 or 1 is assigned to each of the 5 criteria and summed to get a total frailty score. Scores of 3 or greater are assigned as frail, while scores of less than 3 are considered non-frail. Scores of 1 or 2 can also be assigned as intermediate or at-risk for frailty (pre-frail). The focus of the Fried phenotype on physical domains makes it a particular appropriate measure to consider in the heart failure population since physical function declines occur as disease severity worsens.

## Short Physical Performance Battery

The SPPB has been used to evaluate frailty risk in older adults with heart failure [49,50]. The SPPB assesses lower extremity physical performance by testing balance, walking, and muscle strength (Table 2). Scores on the SPPB are easy to interpret for clinicians, with a change of 5 clinically meaningful. Three studies have evaluated outcomes using the SPPB as a risk assessment of frailty in older adults with heart failure. Di Bari et al compared SPPB scores and the 6-minute walk test distance (6MWD) in older adults with and without heart failure [51]. SPPB scores and 6MWD were lower and predicted poor clinical outcomes in patients with heart failure compared with those without heart failure. The SPPB was used by Chiarantini et al to assess whether the SPPB predicted the long-term survival of 157 older adults (mean age, 80 yr) discharged following a heart failure exacerbation [52]. The mean SPPB score was 4.5 but varied considerably by NYHA class (class I:  $7.4 \pm 1.1$ ; class II:  $5.0 \pm 0.5$ ; class III:  $4.8 \pm 0.5$ ; class IV:  $2.3 \pm 0.7$ ;  $P < 0.001$ ). Poorer SPPB scores were associated with higher mortality rates; compared with a SPPB score of 9 to 12, scores of 0, 1 to 4, and 5 to 8 were associated with mortality risks of 6.06, 4.78, and 1.95, respectively. Importantly, of approximately 30% ( $n = 47$ ) of participants who scored 0 on the SPPB, 47% were NYHA class IV and 74% were unable to perform any of the 3 tests on the SPPB. An average of 10 to 15 minutes were required to administer the SPPB in these frail, elderly hospitalized heart failure patients and no adverse events were reported.

In other chronic illness populations, the SPPB has also been used as a predictor of outcomes before, during, or after hospitalization. Valpato et al [53], for example, used the SPPB to assess older adults (mean age, 78 yr) admitted to the hospital with a diagnosis of heart failure (64%), pneumonia (13%), chronic obstructive pulmonary disease (16%), or minor stroke (6.6%) at admission (baseline) and discharge. Patients with the lowest SPPB quartile scores at hospital discharge had a fivefold greater risk of rehospitalization or mortality compared to the highest quartile. In addition, those who had an early decline in SPPB scores 1 month after hospital discharge had greater limitations in performing activities of daily living and a significantly greater probability of being rehospitalized or death during the 1-year follow-up period. These studies suggest that the SPPB at the first follow-up outpatient visit following hospital discharge may be beneficial for identifying need for further intervention or the need for more frequent follow-up care. Although the SPPB is not part of the Fried et al phenotype, it may provide additional information concerning risk for falls and lower extremity strength that may be beneficial in the evaluation of some persons with heart failure [54]. The SPPB along with instructions and normative data are available for clinical use at no charge at [www.grc.nia.nih.gov/branches/ledb/sppb/index.htm](http://www.grc.nia.nih.gov/branches/ledb/sppb/index.htm).

## Interventions for Frailty in Heart Failure

Interventions to address frailty have included exercise training, comprehensive geriatric assessment and management services, social support systems, nutrition, and drugs; however, few intervention studies have examined frailty in heart failure [8]. Restoration of physical function through aerobic exercise and resistance training has shown benefit in frail older adults [55–57] and in persons with heart failure [58]. Maintaining and/or restoring physical

function through aerobic and resistance exercise training may be the key to preventing further decline or potentially reversing frailty in older adults with heart failure.

Aerobic exercise has been shown to be beneficial for both frail older adults and frail persons with heart failure [18]. In a study of community-dwelling frail older adults aged 65 and older, a combined aerobic and resistance exercise intervention, performed over 16 weeks, demonstrated significant improvement in frailty scores during the 1-year follow-up in contrast to worsening frailty measures in the control group [57].

Older adults with heart failure experience a much lower exercise tolerance largely due to a 50% to 75% decrease in aerobic capacity in addition to the well-known alterations in peripheral musculoskeletal performance that contribute to fatigue and greater symptom severity. Aerobic exercise has been shown to be beneficial for most heart failure patients by altering the peripheral and central mechanisms, such as inflammatory cytokines, that contribute to heart failure exacerbations, worsened symptom severity, and poor clinical outcomes [59–62]. Lower rates of hospitalization, improved physical function, and enhanced health-related quality of life are reported in heart failure patients who routinely exercise [59]. Resistance training has been shown to improve physical function in frail older adults [55]. Further, the use of TheraBand exercise bands in resistance training demonstrated improvement in physical function among frail older adults [56].

Exercise also appears to exert a positive effect on cognition, particularly executive functioning, and may also have a protective effect against cognitive decline with aging and among those with heart failure. The underlying mechanism for improvement in cognition remains poorly understood but is likely related to improved cardiac function, cerebral perfusion, and oxygenation, although this has not been clearly established. Larson et al (2006) evaluated the frequency of participation in a variety of physical activities (eg, walking, bicycling and swimming) over 6 years in 1740 older adults [63]. Older adults who exercised more than 3 times per week during initial assessment were 34% less likely to be diagnosed with dementia than those who exercised fewer than 3 times per week. Several meta-analyses in recent years have shown a consistent and positive relationship between aerobic exercise and cognition [64,65]. Importantly, findings from meta-analyses have shown a moderate effect size ( $> 0.5$ ) from aerobic training, which was similar for normal and cognitively impaired adults [64].

## Implications for Clinical Care

A systematic assessment performed periodically using physical and cognitive measures that may identify prefrailty may be the best strategy for preventing further functional loss, limitations, and disability in persons with heart failure. Persons with heart failure ideally should be evaluated annually for physical function, since a decline has been consistently shown to be a strong predictor of adverse health outcomes, disability, and death [6,66]. Cognitive function should also be assessed routinely in persons with heart failure, particularly when first diagnosed, when changes in treatment regimen occur, and with worsening disease severity, since these events have been shown to occur before changes in cognition [31]. Incorporating geriatric performance-based measures in heart failure

management would allow for more treatment strategies aimed at improving physical function, cognitive outcomes, and quality of life. Further, identifying frailty in heart failure is an important component of clinical decision-making when determining if a patient can tolerate therapies such as implantable defibrillators, cardiac resynchronization therapy, or left ventricular assist device placement.

In older adults, performance measures are well established and commonly used as part of geriatric assessment to evaluate physical and cognitive functioning. Performance-based measures may be particularly beneficial in older adults with heart failure to monitor serial changes in physical function. Performance measures in clinical settings require staff time but little training, space, equipment, or risk. As performance measures become more common in practice settings, MDC thresholds may need to be re-evaluated based on the characteristics of the population [67].

For persons with heart failure whose screening outcomes suggest MCI, more comprehensive neuropsychological testing should be available as well as provision of resources to optimize functional independence. Early identification of impaired cognition may lower risk of poor self-management through simplification of medication regimens or providing resources to help manage other regimens essential for optimal heart failure care. It is also important to recognize that depressive symptoms are common in persons with heart failure and are highly correlated with cognitive impairment in this population. Screening for depressive symptoms therefore, may also enhance identification of persons with heart failure at risk for frailty [4,28].

## Conclusion

Effective appraisal and development of effective interventions are essential in older adults with heart failure who are at high risk for frailty and cognitive impairment. This will become increasingly important as the population ages and the incidence of heart failure rises proportionately. Although curative treatments for frailty and cognitive impairment are not available, interdisciplinary interventions such as exercise and comprehensive geriatric assessment may improve outcomes in older persons with heart failure [68]. Information gained from objective, simple, inexpensive physical performance measures, when used in combination with cognitive screening, may enhance the ability to evaluate change that signal onset of frailty or cognitive impairment [54,69,70]. The high morbidity and mortality associated with frailty and cognitive impairment indicate that it should be a priority for future research as a strategy to improve clinical outcomes, enhance quality of life, and lower health care costs in this growing population.

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**Table 1**

## Phenotype of Frailty Criteria

Characteristic	Measure	Score 1 for each of the following:
Shrinking	Self-reported unintentional weight loss > 10 pounds in the last year	Yes
Weakness	Hand grip strength measured using handheld dynamometer	
	Men	
	BMI < 24	29
	BMI 24.1–28	30
	BMI > 28	32
	Women	
	BMI < 23	17
	BMI 23.1–26	17.3
Exhaustion	BMI 26.1–29	18
	BMI > 29	21
	Self-report using 2 statements from the CES–D Depression Scale:	
	a. I felt that everything I did was an effort	
	b. I could not get going	
	The question is asked: How often in the last week did you feel this way?"	Answer 2 or 3
	0 = rarely or none of the time (<1 day)	
	1 = some or a little of the time (1–2 days)	
2 = a moderate amount of the time (3–4 days)		
3 = most of the time		
Slowness	Time to walk 15 feet	
	Men	
	Height < 173 cm	7 seconds
	Height > 173 cm	6 seconds
	Women	
	Height < 159 cm	7 seconds
Height > 159 cm	6 seconds	
Low physical activity	Self-reported sedentary behavior based on the short version of the Minnesota Leisure Time Activity questionnaire.	
	Kcal per week:	Men < 383 Women < 270

Note: A score of 3 or greater is assigned as frail. (Adapted from reference 6.)

**Table 2**

## Scoring for Short Physical Performance Battery

Task	Score
Balance	
Side-by-Side Stance 0–9 seconds	0
Side-by-Side Stance 10 seconds but Semi-Tandem Stand 0–9 seconds	1
Semi-Tandem Stand 10 seconds but Full Tandem Stand 0–2 seconds	2
Full Tandem Stand 3–9 seconds	3
Full Tandem Stand 10 seconds	4
Walk 8 feet	
Unable to walk	0
> 8.70 seconds	1
6.21–8.70 seconds	2
4.82–6.20 seconds	3
< 4.82 seconds	4
Chair stands (5)	
Unable to complete 5 chair stands	0
> 16.7 seconds	1
13.7–16.6 seconds	2
11.2–13.6 seconds	3
< 11.1 seconds	4
Total score	