The Biologic Syndrome of Frailty in Heart Failure

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ABSTRACT: As we continue to care for an older and sicker end-stage heart failure population, it has become challenging to evaluate patients based on current risk scores that mainly focus on subjective symptoms and patient disability. For generations, geriatricians have sought to identify the body's underlying vulnerabilities that characterize frailty. More recently, cardiologists have begun to recognize this entity in their own practice. Several studies have suggested rates of frailty as high as 50% in patients with cardiovascular disease. However, despite recognizing frailty, it remains difficult to define. Like heart failure, frailty is a biologic syndrome that affects multiple organ systems. Measures of frailty are shown to strongly correlate with adverse outcomes in the health care system.

KEYWORDS: frailty, heart failure, disability

Introduction

The United States population living with heart failure (HF) is aging. As of 2013, 80% of patients with HF were aged ≥65 years, and 25% were aged ≥80 years. Mortality is high, with 50% of Medicare beneficiaries surviving <3 years following hospitalization for HF. In the United States, costs associated with HF exceed $35 billion annually. Future costs estimated using an American Heart Association model predict that by 2030, 1 of 33 people will have HF, with direct costs of caring for these patients projected to rise to $53 billion. The high mortality and costs associated with caring for HF makes this one of the most clinically challenging chronic diseases to treat. As we continue to care for an older HF population, we are limited by our current assessment tools that primarily focus on subjective symptoms and patient disability. For generations, geriatricians have sought to identify the body's underlying vulnerabilities that characterize frailty. More recently, cardiologists have begun to recognize this entity in their own practice. Several studies have suggested rates of frailty as high as 50% in patients with cardiovascular disease. Like HF, frailty is a biologic syndrome that affects multiple organ systems. This review emphasizes the importance of measuring and assessing frailty in the evaluation of HF patients evaluated for cardiac resynchronization, mechanical circulatory support, aggressive medical regimens, and perhaps transplantation. In addition, some of the referrals we make to HF management programs and cardiac rehabilitation may be better served through more sensitive tools utilizing this concept. This review was compiled from a PubMed search including all items related to HF, cardiovascular disease, and frailty.

Definition of Frailty

The concept of frailty currently lacks a formally accepted definition; however, it is widely recognized in the health care literature. In essence, frailty is a biological syndrome of decreased homeostatic reserves, resulting in increased vulnerability to stressors. Frailty clinically manifests when a physical or psychological stressor causes a disproportionate change in health status. For example, an elderly subject with reduced ejection fraction undergoes elective same-day implantation of a defibrillator, which subsequently becomes complicated by a hematoma, resulting in an extended hospitalization and recovery period. An important principle is that frailty arises from an accumulation of subclinical deficits across multiple physiological systems, which, eventually, as an aggregate, surpass a threshold and become clinically apparent. The systems involved in the frailty pathobiology include the musculoskeletal (sarcopenia/osteopenia), endocrine (excessive catabolism), gastrointestinal (micronutrient deficiencies), and immune (a proinflammatory state) systems.

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Tools to Describe Frailty
Numerous tools have been developed to measure frailty (Table 1). These can be divided into two groups: the phenotype model vs. the accumulation of deficits model, as represented by the Fried Frailty Scale and the Frailty Index, respectively. In a secondary analysis of the Cardiovascular Health Study, Fried established a frailty phenotype based on five variables: unintentional weight loss, self-reported exhaustion, low physical activity, slow walking speed, and weakness. Patients with three or more variables were categorized as frail and those exhibiting one to two variables as prefrail. In this analysis, there was a graded association between adverse health outcomes, including mortality, and frailty status, a finding that has been subsequently validated in numerous other studies, including subsequent publications by Fried. There is debate as to whether the time-intensive nature of this scale is unrealistic for clinical practice and whether single-measure assessments such as 5 m gait speed or handgrip strength could suffice. Other examples of the phenotype approach include the Short Physical Performance Battery, the Gill Index, and the Barthel Index. Each of these scores incorporates measures of mobility and ability to complete activities of daily living. Using these scores, The Health, Aging, and Body Composition Study concluded that frailty is independently associated with risk of HF in older adults.

Frailty can also be assessed as a multidimensional accumulation of deficits as opposed to a single clinical phenotype.

| PHENOTYPE MODEL | Description |
|-----------------|-------------|
| **Fried frailty index** | The Fried Criteria is based on the assessment of five dimensions that reflect the frail biologic phenotype. These five dimensions are: weight loss, exhaustion, weakness, slowness, and low levels of activity. Each dimension corresponds to five specific criteria indicating adverse function which can be implemented using a combination of self-reported and performance-based based measures. Those who meet at least three of the criteria are defined as “frail”, while those not matching any of the five criteria are defined as “robust”. |
| **Short physical performance battery** | A short physical performance battery is a group of measures that combines gait speed, chair stand, and balance tests. It can be used as a predictive tool for disability and aids in the monitoring of function in older people. Score ranges from 0–12. |
| **Gill index** | The Gill index is based on a composite of chair-stand and walking speed tests. Severe frailty is defined when the subject is unable to stand-up from the chair without the use of the arms and showed a walking speed lower than 0.6 m/s; moderate frailty was defined as only one of the two tests being abnormal; and non-frailty if neither were present. |
| **Barthel index/Activities of daily living** | Measure of Functional Independence and need for assistance in mobility and self care. Items are rated in terms of whether individuals can perform activities independently, with some assistance, or are independent. The scale ranges from 0–100. |
| **Gait speed** | Patient is positioned behind a start line and asked to walk at a comfortable pace past a 5 meter finish line. Time starts with first footfall past start line and ends with first footfall past finish line. The test is repeated three times and averaged. |
| **Grip strength** | Patient is asked to squeeze a handgrip dynamometer as hard as possible and this test is repeated three times and the maximum value is recorded. |

| ACCUMULATION OF DEFICITS MODEL | Description |
|---------------------|-------------|
| **Frailty index** | The Index is based on an accumulation of deficits with signs, symptoms, diseases, and disabilities that accumulate with age. It is a continuous variable with a direct relationship to chronological age and includes a 70 item scale. The ratio of the number of items present to the total number of items assessed equals the Frailty Index. |
| **Modified frailty score** | The Modified Score utilizes sixteen variables within the National Surgical Quality Improvement database corresponding to eleven items in the Canadian Study of Health and Aging. These domains include current illnesses, ability to manage activities of daily living (ADL) and physical signs. This model allows for the calculation of a frailty index. |
| **Rai 2.0 scale** | Developed by a collaborative network of researchers in over 30 countries to assess and improve the care of complex and frail seniors with a comprehensive assessment. The coding is based on independence in performing activities of daily living. Score is from 0–3 with 0 scores being tasks completed fully independently. |
| **CHESS scale** | The CHESS scale was originally developed to detect frailty and instability in health in persons residing in residential or complex continuing care settings. It has since been adapted for use in home care and inpatient psychiatry settings. The CHESS is based on 9 items with six items (vomiting, dehydration, decrease in food or fluid, weight loss, shortness of breath, edema) summed to a maximum of two, then three additional items are added: decline in cognition, decline in ADL, and end-stage disease. Higher CHESS scores are predictive of adverse outcomes such as mortality and hospitalization. |
| **MSSA** | The MacArthur Study of Successful Aging (MSSA) scale consists five items: cognitive impairment, self-reported weakness, anorexia, high IL-6, and high CRP; four or more positive items are required to classify the patient as frail. An analysis of the MSSA scale sub-dimensions revealed that the combination of weakness and cognitive impairment was most predictive of frailty. |
Frailty in heart failure

This approach is best represented by the Frailty Index, which was developed as a part of the Canadian Study of Health and Aging, wherein 92 baseline variables consisting of signs, symptoms, disabilities, and laboratory values were used to define frailty. The index is calculated as the proportion of variables present to the total assessed and is strongly linked to risk of death and institutionalization. Subsequent work has demonstrated that the Frailty Index can be simplified to a 30-item bedside assessment tool without the loss of predictive validity.

The field of geriatrics leads clinical medicine in the ability to evaluate and manage patients with complex chronic diseases by acknowledging the interrelated but distinct concepts of disability, frailty, and comorbidity. While an understanding of the concept of comorbidities (the co-occurrence of multiple diseases) is self-evident to most, the distinction between disability and frailty is not well appreciated in the health care field. Disability is commonly defined as difficulty with either activities of daily living or mobility, whereas frailty represents a state of heightened vulnerability that places an individual at risk for adverse outcomes. Although frailty and disability often overlap, they should be considered distinct as they carry independent prognostic implications. Frailty is not assessed the entire phenotypic picture that defines frailty. Disability, as considered for invasive therapies is beginning to gain recognition in the non-HF literature. It is generally agreed upon that the population with HF, in particular, is vulnerable to poor outcomes if not carefully selected. It is therefore logical to assume that frailty may be an important tool in risk stratification for device therapy in the older HF patient.

In 2011, Matlock et al. described an interesting practice pattern. His group surveyed 1124 cardiologists in regard to their current attitudes and recommendations for implantable device therapy in the older HF patient. His group surveyed 1124 cardiologists in regard to their current attitudes and recommendations for implantable device therapy in the older HF patient.

Frailty, Disability, and Heart Failure

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Figure 1. Overlap of disability, comorbidity and frailty. Reproduced with permission from Fried LP et al. J Gerontol A Biol Sci Med Sci. 2001;56:M146–57.
## Table 2. Summary of trials in heart failure and frailty.

| STUDY (REF #) | PATIENTS (N) | STUDY DESIGN | FRAILTY TOOL | AGE (YEARS) MEAN | LVEF (%) MEAN | MAIN OUTCOMES |
|---------------|--------------|--------------|--------------|-----------------|---------------|---------------|
| Chiarantini, 2010 (23) | 157 | Prospective cohort from Italy of elderly patients with decompensated HF assessed for frailty prior to hospital discharge. | Short Physical Performance Battery | 80 | 43.4% | 30 month mortality inversely correlated to SPPB score. Compared with a score of 9–12: Score 0 = HR: 6.06 (95% CI: 2.19–16.76) Score 1–4 = HR: 4.78 (1.63–14.02) Score 5–8 = HR: 1.95 (0.67–5.70) |
| Chaudhry, 2013 (24) | 758 | Longitudinal study of community-living older persons with a new diagnosis of HF to determine if geriatric conditions are independent risk factors for hospitalization. From the Cardiovascular Health Study. | Gait Speed and Hand Grip Strength | 79.7 | Not specified in all patients. 43% noted to have LVEF <45% | Risk factors for hospital admission: Slow Gait = HR: 1.28 (95% CI: 1.06–1.55) Weak Grip = HR: 1.19 (95% CI: 1.00–1.42) |
| Rozzini, 2003 (25) | 995 | Prospective cohort from Italy of acute patients admitted to the cardiac care unit with NYHA Class 3 or 4 HF. | Frailty divided into 3 groups based on presence of dementia and disability (neither, either or both) | 80.2 | Not specified. | 6 month mortality for frail vs not frail: 28% vs 12% (P < 0.05) |
| Lupon, 2008 (15) | 622 | Prospective cohort of patients in Spain with chronic heart failure referred to a HF clinic to determine the impact of frailty and depressive symptoms on 1 year mortality and rate of hospitalization for heart failure. | Altimir scale | 68 (median) | 30 (median) | Frail vs not frail at one year: Hospitalization for HF: 21% vs 13% (P = 0.01) Mortality: 17% vs 5% (P < 0.001) |
| Dunlay, 2014 (22) | 99 | Retrospective review of patients undergoing LVAD as destination therapy to determine if pre-operative frailty is associated with worse outcomes after implantation. | Deficit Index | 65 | 18.5 | Mortality compared to those who were not frail: Intermediately frail—adjusted HR: 1.70 (95% CI 0.71 to 4.31) Frail—HR: 3.08 (95% CI 1.40 to 7.48) (P = 0.004 for trend) |
| Cacciatore, 2005 (12) | 120 | Secondary analysis of a cohort study of elderly patients in Italy with chronic HF to examine the predictive role of frailty on long-term mortality. | Lachs Fragility Staging System | 76 | Not specified | Mortality at 12 years increased by frailty scale from 69% to 94%; HR: 1.62 (95% CI 1.08–2.45) |
| Altimir, 2005 (26) | 360 | Cross sectional study of elderly patients referred to a HF Unit in Spain to determine the prevalence of frailty. | Altimir Scale | 65.2 | 31.7 | Overall prevalence of frailty = 42%. Highest in women and ≥70 years. |
| Tjam, 2012 (10) | 149 | Secondary analysis of cohort study of elderly patients living with chronic HF in long term care to determine if the RAI 2.0 is superior to NYHA for heart failure prognosis. | RAI 2.0 Scale | 68% ≥85 years | Not specified | 6 month mortality suggests data from the RAI 2.0 can better predict mortality than the NYHA classification |
| McNallan, 2013 (27) | 233 | Prospective analysis of Minnesota residents with HF to compare frailty as defined by accumulation of deficits versus the biologic phenotype (frailty index). | Deficit Index and Frailty Scale | 71 | 44.1 | Mortality at mean follow up of 2.4 years: Frailty Score: HR: 2.04 (95% CI 0.99–4.18) for frail vs not frail Deficit Index: 0.1 unit increase in deficit index associated with a 44% increased risk of death Both measures predicted mortality equally: C statistic: 0.687 vs 0.700 |
Frailty in heart failure

Mean follow up of 2 years. Frailty was associated with a 93% increased risk for increase in hospitalizations. Frailty scale was used to determine the prevalence of frailty and whether frailty is associated with emergency department visits and 65% increase in hospitalizations.

Prospective study of patients with heart failure and whether frailty is associated with emergency department visits and 65% increase in hospitalizations.

According to Gill index, those classified as frail were at greater risk of incident HF:

- Moderate frailty – hr 1.36 (95% CI 1.08–1.71)
- Severe frailty – hr 1.88 (95% CI 1.02–3.47)

Median follow up of 11.4 yrs: 466 (15.9%) and whether frailty is associated with health care utilization.

According to Modified Short Physical Performance Battery, those classified as frail were at greater risk of incident HF:

- Low frailty score – 70.3
- Moderate frailty – 77.5
- High frailty score – 81.3

Frailty in heart failure offers precedents for frailty assessment as a risk stratification tool. The short-distance 5-m gait speed is a simple-to-perform tool that has been adopted by many preoperative research protocols. Afilalo et al. prospectively demonstrated that a slow 5-m gait speed before cardiac surgery was associated with a three-fold increase in postoperative morbidity and mortality. Similarly, hand grip strength has been shown to predict outcomes after left ventricular assist device (LVAD) placement. In addition, in a retrospective analysis, categorization of frailty via the deficit index was associated with mortality after LVAD implantation. These data in cardiac surgery demonstrate the potential of frailty assessment in patient selection for invasive therapies.

**Future Directions**

While the addition of frailty tools to the management of the HF patient holds promise, multiple topics must be clarified and validated before mainstream clinical application. These include identifying which of the many tools provides the best combination of performance and facility. Furthermore, cohort studies to define standardized cutoff values of frailty within these tools, based on age and sex, are necessary. This is particularly relevant for the younger population with HF because frailty may coexist, but identifying it based on values validated in an older population may underestimate its prevalence. In this regard, integration of biomarkers of frailty may increase the sensitivity of current tools. The next step would be to design intervention trials based on frailty assessment in HF. These could include the following: (1) selection for invasive therapies, whereby the outcomes would include not simply procedural success but also quality of life and cost-effectiveness; (2) larger prospective validation of referral to an intensive cardiac defibrillators (ICD). The investigators found that physicians in high-utilization areas were more likely to recommend an ICD to frail patients or patients with life expectancies <1 year – a group less likely to garner benefit and more likely to have complications. Unfortunately, the criteria used to describe frailty in their paper relied upon age. The investigators are to be commended for raising the issue of frailty as a prognostic tool before ICD use; however, their study is limited by their misconception that aging is an equivalent to frailty.

The evidence for cardiac resynchronization therapy stems from studies of patients in their 60s. In order to assess the effectiveness of cardiac resynchronization therapy (CRT) in an octogenarian population, Foley et al. evaluated patients before and after CRT implantation with a 6-minute walk test and the Minnesota Living with Heart Failure Questionnaire. There was an improvement in both scores for patients older or younger than 80 years, a finding that emphasizes that age alone is an inadequate prognostication tool. The two aforementioned studies are important investigations that allude to our current gap in risk stratification of elderly HF patients undergoing ICD placement and/or CRT – further studies examining whether frailty can fill this gap are necessary.

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disease management program, wherein geriatric interventions are combined with those of the HF field; and (3) referral to cardiac rehabilitation and nutritional supplementation based on frailty status.

Conclusion
It is intriguing to speculate that integration of frailty assessment into the clinical evaluation of HF may refine our understanding of this disease. Ultimately, incorporation of frailty into HF algorithms may be the next advancement in the management of this complex disease by allowing providers to make more informed decisions and make more responsible and efficient use of health care resources.

Author Contributions
Conceived the concepts: SP. Analyzed the data: RJ. Wrote the first draft of the manuscript: RJ. Contributed to the writing of the manuscript: RJ. Agree with manuscript results and conclusions: SP. Developed the structure and arguments for the paper: RJ. Made critical revisions and approved final version: SP. Both authors reviewed and approved of the final manuscript.

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