Frailty in Advanced Heart Failure

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KEYWORDS

• Frailty • Advanced heart failure • Sarcopenia • Cachexia • Fried phenotype
• Left ventricular assist device

KEY POINTS

- Frailty and associated conditions (cachexia, sarcopenia) are highly prevalent in patients with advanced heart failure (HF), and both syndromes share common underlying pathobiological processes.
- Frailty is associated with worse outcomes after interventional therapies (including mechanical circulatory support and heart transplantation), defines risk not yet captured by traditional risk scores, and represents a useful incremental prognostic tool to aid patient selection for advanced therapies.
- There is an unmet need for a single validated tool or scale capable of accurately defining frailty in the advanced HF population and is responsive to positive interventions.
- Left ventricular assist device implantation may be able to "de-frail" patients with predominantly HF-related (in contrast to age- or comorbidity-related) frailty by reversing myocardial failure and restoring cardiac output.

INTRODUCTION

Frailty is formally defined as a biologic syndrome reflecting a state of impaired physiologic and homeostatic reserve and heightened vulnerability to stressors, resulting from the accumulation of multiple morbidities, aging, and disability.[1,2] The evolving profile of cardiovascular disease, increased survival of aging patients with complex comorbidities, in parallel with an ever-expanding array of invasive therapeutic interventions, means that cardiologists (and, in particular, heart failure [HF] specialists) are becomingly increasingly aware of the burden of frailty and its downstream consequences on postintervention outcomes in their patients. Older patients with HF have consistently demonstrated the highest prevalence of frailty, up to 50% in some studies.[2,3] The strong association between HF and frailty is particularly evident in the setting of advanced HF, wherein the frail phenotype and associated cachexia and generalized muscle weakness frequently manifest in the later stages of disease. Although increasingly prevalent with advancing age, advanced age is not a prerequisite for frailty, with end-stage HF being a clinical prototype for "age-independent" frailty. In one study of 622 patients referred to an HF unit, one-third of patients less than the age of 70 years fulfilled one or more prespecified criteria for frailty.[4] This close overlap between both syndromes is particularly relevant in the setting of advanced HF patients being considered for high-risk invasive therapies, including left ventricular assist device implantation (LVAD) and/or cardiac transplantation.

Despite varying modes of assessment of frailty and variability in incorporated domains (biological, nutritional, functional, and cognitive), almost every

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proposed single- or multi-item definition has been associated with, or shown to be predictive of, adverse outcome in cardiovascular disease populations, including HF patients.[2] Frailty assessment therefore appears to contribute valuable and incremental prognostic insights in HF. The aim of this review is to focus on the role of frailty in advanced HF patients, including its prevalence, impact on morbidity and mortality, potential for refining candidate selection for advanced therapies, and in certain cases, possibility for regression following the restoration of cardiac output inherent with LVAD and/or cardiac transplantation.

PATHOBIOLOGY OF FRAILTY IN ADVANCED HEART FAILURE

The cycle of frailty, as hypothesized by Fried and colleagues,[1] is initiated by disease- and/or aging-related declines in lean muscle mass and strength, leading to reduced activity level and walking speed, and in turn, ultimately leading to and further compounded by weight loss and malnutrition. Considerable overlap exists in the constellation of weakness, wasting, exercise intolerance, and exhaustion that can manifest in both progressive HF and frailty (**Fig. 1**). Because of the fact that each syndrome may mimic the other, objective tools are needed to provide an independent assessment of the presence and severity of the frail phenotype in HF patients. The need for objective tools is even more important in advanced HF patients, where worsening fatigue, declining physical activity, and cachexia may reflect progressive myocardial failure and related downstream multiorgan system dysfunction requiring evaluation of candidacy for end-stage disease management options rather than a distinct frailty substrate predominantly driven by aging and other comorbidities.

The degree of clinical similarity between frailty and chronic HF reflects the many common pathobiological processes across multiple physiologic systems (including immunologic, metabolic, neurohormonal, and autonomic-based domains) shared by both syndromes. Each syndrome in turn increases risk for development of[5,6] and potentiates increasing morbidity[7–10] in the other, likely as a result of this common pathophysiologic pathway. Sarcopenia represents a key component of the frailty syndrome and is defined as a progressive loss of muscle mass and strength, beyond that expected from normal aging.[11] Intrinsic histologic and biochemical skeletal muscle changes, including fiber atrophy, increased type IIb fibers, and decreased oxidative capacity, are also characteristic of symptomatic HF.[12] Cachexia is a related condition that is incorporated as 1 of the 5 key domains in the traditional frail phenotype model.[1] It is also commonly used to describe the muscle wasting and tissue loss seen in advanced stages of HF and is formally defined as loss of greater than 5% of total body weight over the preceding 6 months.[13]

Inflammatory biomarkers (including interleukin-1, interleukin-6, tumor necrosis factor-α, and C-reactive protein) known to underpin disease development and progression in chronic HF by contributing to tissue wasting and cardiac cachexia[14] have also been demonstrated as biologic mediators of the frailty phenotype.[15,16] Dysregulated neurohormonal mechanisms, including those involving cortisol regulation and the growth hormone/insulin-like growth factor-1 (GH/IGF-1) signaling axis, leading to downstream anabolic-catabolic uncoupling and resultant

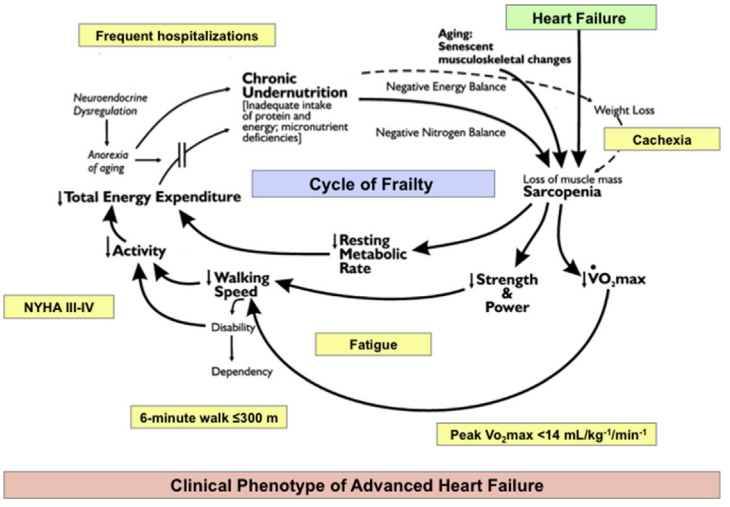

Fig. 1. Overlap between the clinical phenotypes of frailty and advanced HF. Elements of the classic cycle of frailty may also reflect key clinical markers in the progression of advanced HF. (*Adapted from* Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M147; with permission.)