

Frailty in Advanced Heart Failure: A Consequence of Aging or a Separate Entity?

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ABSTRACT: There are over 5 million Americans with heart failure (HF), the majority of whom are over age 65. Frailty is a systemic syndrome associated with aging that produces subclinical dysfunction across multiple organ systems and leads to an increased risk for morbidity and mortality. The prevalence of frailty is about 10% in community-dwelling elderly and 20% in those with advanced HF, and increases in both cohorts with age. Yet the relationship between the primary frailty of aging and frailty secondary to HF remains poorly defined. Whether the frailty of these two populations share similar etiologies or exist as separate entities is unknown. Teasing apart potential molecular, cellular, and functional differences between the frailty of aging and that of advanced HF has implications for risk stratification, quality of life, and pharmacological and therapeutic interventions for advanced HF patients.

KEYWORDS: frailty, heart failure, sarcopenia, geriatric cardiology

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Introduction

The phenotype of heart failure (HF) is changing. Likely due to improved management of chronic diseases such as hypertension and coronary artery disease, as well as interventions that impact survival, the HF population is aging. There are over 5 million Americans with HF, the majority of whom are over age 65. HF incidence doubles with each decade, starting at 5% between ages 65 and 74 years and rises to 20% for those over 80 years of age.¹ Common geriatric issues such as multimorbidity, polypharmacy, and frailty are encountered frequently in this population, creating a complex foundation upon which to build HF management plans.

The syndrome of frailty is prevalent both in community-dwelling elders and in individuals with chronic disease. Frailty is a systemic process affecting multiple organ systems, generating a phenotype of weakness, fatigue, lack of physiologic reserve, and decreased tolerance to stressors, and increases the risk of hospitalization, procedural complications, and mortality across all medical and surgical domains. The prevalence of frailty in community-dwelling elders is about 10% and the incidence increases with advancing age.² As a component of chronic disease, frailty prevalence is about 60%, 40%, and 20% in chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), and systolic HF populations, respectively.^{3–5} Similar to the aging data, frailty in chronic disease is associated with older age and the presence of additional

comorbidities, and predicts increased risk for falls, morbidity, and mortality.^{3–5} Whether there is an etiological distinction between the primary frailty of aging and frailty secondary to chronic disease is unknown.

At this time, it is not possible to clinically differentiate primary frailty from frailty secondary to chronic disease. With respect to the aging HF population, there is an urgent need to address the potential for this distinction. In addition to guideline-directed medical therapy (GDMT), patients of this demographic segment are increasingly considered for life-prolonging invasive procedures. Between 2008 and 2013, almost 30% of over 9000 left ventricular assist device (LVAD) placements occurred in patients over the age of 65.⁶ Generally, LVAD placement improves both survival and health-related quality of life (HRQoL), yet both older age and the presence of comorbidities increase the risk of poor outcomes.⁶ To determine whether the benefit of mechanically assisted hemodynamic support outweighs the risk of the procedure, it is crucial to understand the etiology of frailty in this elderly, advanced HF population. This review will examine the etiology and functional consequences of primary and secondary frailty, and distinguish these changes from those associated with normal aging. Ultimately, understanding the interaction between aging, HF, and frailty, as well as the potential for reversibility, will help guide clinicians and patients in the difficult decisions of advanced HF management.



Primary Frailty of Aging

Complicating the literature on frailty both with respect to primary frailty and frailty associated with chronic disease is the number of working definitions for seemingly similar processes. Sarcopenia is a condition of muscle mass loss and muscle weakness that results in poorer functional status, increased dependence, and increased morbidity and mortality.⁷ Although muscle mass loss is a normal component of aging,⁸ in sarcopenic states, not only is there less muscle quantity but the quality of the tissue is also inferior. In 2010, the European Workshop on Sarcopenia in Older People (EWSGOP) defined sarcopenia as meeting two of three criteria: muscle mass loss as determined by imaging; muscle weakness by grip strength; and slowness by gait speed.⁷ The phenotype of frailty is one that encompasses sarcopenia, and then furthers it with the addition of psychosocial dimensions. Multiple diagnostic tools exist for frailty, but they generally incorporate an assessment of five core elements: shrinking, weakness, slowness, fatigue, and low physical activity.⁴ As conceptualized by Fried and colleagues in 2001,⁹ frailty is a constellation of three or more of the following: unintentional weight loss, slow gait speed, weak grip strength, exhaustion, and decreased physical activity. Although the unintentional weight loss of frailty does not specify the tissue type, sarcopenia is a recognized component of this syndrome.⁹

Pathobiological Mechanisms and Physiological Consequences of Primary Frailty

On a molecular level, the pathobiology of this wasting and weakness process has been correlated with dysregulated immune, endocrine, and neurohormonal systems. Sarcopenic and frail patients have elevated levels of inflammatory markers such as interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF α).¹⁰⁻¹⁵ Frailty is also associated with dysregulated glucose management, as frail patients show elevated levels of growth hormone (GH), low levels of insulin-like growth factor-1 (IGF1) and evidence of insulin resistance.^{16,17} The list continues with a loss of the normal diurnal cortisol pattern,¹⁸ lower testosterone levels,¹⁹ and increased markers of oxidative stress.^{12,20} Together, these dysregulated systems create an anabolic-catabolic imbalance, leading to increased muscle catabolism, weight loss, and subclinical organ dysfunction. Upon exposure to additional stressors such as injuries, infections, or surgical procedures, patients with these signaling derangements are more prone to decompensation, hospitalization, and death.

Despite extensive work on altered muscle composition in normal aging, much less is known about this process with respect to frailty. In normal aging, the muscle mass loss has been attributed to the preferential muscle atrophy of fast-twitch glycolytic type II muscle fibers between the third and seventh decade of life,^{21,22} accounting for decreased muscle cross-sectional area.²³ The ultimate result is a fast-to-slow twitch fiber shift in muscle composition with an increased percentage

of slow-twitch oxidative type I fibers.²⁴ Data from aging primates demonstrate that these cellular changes are preceded by altered energy metabolism as a result of decreased mitochondrial activity,²⁵ suggesting that the process may represent an adaptation to decreased energy availability. Specific data on frailty-related muscle composition are not yet available. However, other disease states with substantial inflammatory and neurohormonal elements such as sepsis, diabetes, Cushing's disease, and malignancy-related cachexia show a pattern similar to that seen in aging, with atrophy of type II fibers.²⁴ A large body of evidence suggests a direct role for inflammation in mitochondrial function, and vice versa. Inflammation causes deficiencies of various mitochondrial subunits, ultimately resulting in decreased energy production, increased production of reactive oxygen species, and upregulation of nuclear factor kappa B (NF κ B). NF κ B is a downstream product of TNF α as well as a transcription factor responsible for the production of inflammatory cytokines.²⁶ As such, a dangerous cycle of inflammation and mitochondrial damage is set in motion, potentially laying the groundwork for the muscle loss, weakness, and exhaustion of the frailty phenotype.

As muscle composition changes, aerobic capacity declines, as well. In healthy individuals over age 60, peak oxygen uptake (VO₂) declines by 10%–15% per decade,²⁷ with a correlation between age-related muscle mass loss and aerobic capacity.²⁸ In sarcopenia, a similar relationship is seen between muscle loss and aerobic capacity. In community-dwelling older women without cardiovascular disease, those defined as sarcopenic based on a muscle-mass cutoff²⁹ showed evidence of decreased strength and diminished aerobic capacity as compared to women who did not meet sarcopenic criteria.³⁰ No studies to date have specifically addressed aerobic capacity in patients meeting frailty criteria.

In summary, primary frailty is a syndrome of inflammatory, metabolic, and hormonal derangements that shift homeostasis from an anabolic to a catabolic state. Wasting and weight loss are manifested by loss of muscle fibers, altering muscle composition, which in turn lays the foundation for the phenotypic weakness, slowness, and functional deterioration inherent to frailty syndrome. The potential for treatment and reversibility of the frail state is explored in the following section.

Treatment and Reversal of the Primary Frailty Phenotype

Although significant evidence demonstrates that physical activity reverses or slows the muscle wasting process of aging,³¹⁻³⁴ less is known with respect to physical activity and the frailty syndrome. In normal aging, data indicate that directed physical therapy with progressive resistance training increases muscle mass and strength.³¹⁻³⁴ However, these mostly small, nonrandomized trials generally do not address outcomes such as mortality, HRQoL, or functional disability.³⁴ Analysis of the literature with respect to sarcopenia and frailty is limited



by the lack of consistent definitions and heterogeneity of inclusion criteria. Yet, in patients with specific health problems or existing functional limitations (ie, those who would most likely meet criteria for sarcopenia and frailty), the benefit of resistance training demonstrated a much smaller effect, if any at all.^{32,35} In larger studies that used validated definitions of frailty, patients identified as “pre-frail” or “transitionally frail” showed a positive response to exercise and balance interventions, resulting in improvements in physical performance and decreased fall risk.^{36,37} However, those meeting criteria for full frailty actually fared worse, with the intervention group experiencing more injuries requiring medical attention, usually related to increased incidence of falls.^{37,38} No studies to date have addressed the potential for an exercise-related mortality benefit in sarcopenic or frail patients.

Pharmacological interventions for the treatment and prevention of primary frailty remain in the early stages. Attempts to target the molecular pathways discussed above have been met with mostly disappointing results. Hormone replacement therapy with estrogen, testosterone, or GH have occasionally been shown to increase muscle mass and strength, but the results are mixed.³⁹ There may be a role for the renin–angiotensin–aldosterone system in muscle wasting. Exogenous administration of angiotensin II in animal models precipitates skeletal muscle atrophy with increased proteolysis and elevated levels of reactive oxygen species.⁴⁰ An observational study found that use of angiotensin-converting enzyme (ACE) inhibitors slowed the progression of muscle-loss-related weakness in elderly women with hypertension,^{41,42} which may be due to the effects of ACE inhibition on insulin sensitivity and inflammation rather than preservation of cardiac function.⁴³ However, subsequent prospective randomized trials administering angiotensin-receptor or aldosterone antagonists to patients with functional impairments have failed to demonstrate benefit.^{44,45} Moreover, no studies have addressed pharmacological interventions with respect to mortality benefit in frailty.

In summary, both therapeutic and pharmacologic treatments for frailty have been attempted. Although physical activity improves muscle mass and function in older individuals who are not frail, there appears to be limited benefit in the frail population. Pharmacologic treatments targeting hormonal derangements have been similarly ineffective. Hopefully, future work delineating the etiology of primary frailty will improve upon current capabilities of counteracting and reversing this systemic process.

Frailty Secondary to Heart Failure

The constellation of muscle loss, weakness, and exhaustion has been a long recognized component of HF. In addition to sarcopenia and frailty, cardiac cachexia, defined as loss of >5% of one’s body weight over 6 months,⁴⁶ is a third term referring to the wasting process of this population. Depending on the definition used, studies in HF find about a 20%

prevalence of sarcopenia, a 20%–50% prevalence of frailty, and 15% prevalence of cardiac cachexia.^{47–49} All predict increased risk of hospitalization and mortality, along with decreased HRQoL.⁴⁹ Notably, the risk for HF-related frailty rises dramatically with age, as a 30% prevalence has been identified in patients younger than age 70, versus a 52% prevalence in those 70 years or older.⁵⁰

Pathobiological Mechanisms of HF-Related Frailty and Physiological Consequences

Similar to that seen in community-dwelling elders, the wasting process of HF is likely related to an anabolic–catabolic imbalance in which initially adaptive neurohormonal mechanisms and autonomic nervous system activation yield detrimental systemic effects over time. Consistent evidence exists for TNF α , IL-1, and IL-6 upregulation,^{51–54} along with abnormalities in the GH/IGF-1 axis, cortisol regulation,⁵¹ and uric acid production⁵⁵ in HF-related frailty. In addition to HF precipitating frailty, the reverse is also true. Frail community-dwelling elders are more likely to develop *de novo* HF than their non-frail counterparts.⁵⁶ In animal models, exogenous administration of TNF α as well as transgenic overexpression of inflammatory cytokines results in left ventricular remodeling and increased mortality,^{57,58} implicating a significant contribution of systemic inflammation to HF development. Therefore, similar inflammatory and neurohormonal components contribute to the etiology of both primary frailty and frailty secondary to HF.

Cellular and molecular alterations to muscle cell composition are frequently noted in patients with symptomatic HF, but are slightly different than those of normal aging and strict inflammatory processes. Similar to aging, fast-twitch glycolytic type II fibers are atrophic.⁵⁹ Unlike normal aging, however, the total percentage of fast-twitch type II fibers actually increases as compared to slow-twitch oxidative type I fibers, resulting in an overall slow-to-fast twitch fiber shift.⁵⁹ Interestingly, this slow-to-fast twitch fiber shift is also seen in deconditioning due to extended bed rest⁶⁰ and microgravity,⁶¹ and is hypothesized to be related to the easy muscle fatigability seen in HF patients.⁶² In contrast to peripheral skeletal muscles, diaphragmatic muscle biopsies taken during LVAD placement or heart transplant show a fast-to-slow twitch fiber shift with an increase in type I fibers at the expense of type II.⁶³ It is unknown whether this fast-to-slow twitch fiber shift is related to the higher diaphragmatic workload of HF patients, the underlying chronic inflammatory state, or a combination of the two. Skeletal muscle changes in HF are therefore complex and site-specific, and most likely represent a mixed picture of chronic deconditioning and inflammation. However, the specific relationship between these muscle changes and HF-related frailty has yet to be fully explored.

Although decreased functional capacity is a component of frailty, the correlation between functional capacity and HF-related frailty is infrequently addressed. Reduced exercise



tolerance due to fatigue and dyspnea is an independent predictor of mortality and rehospitalization.⁶⁴ In HF patients, both diminished strength and decreased aerobic capacity correlate with decreased muscle mass.^{47,65} In one study of 200 HF patients, New York Heart Association (NYHA) class II–III, 19% had evidence of muscle wasting by dual energy X-ray absorptiometry scan. Handgrip strength, gait speed, and absolute peak VO₂ were all significantly reduced in the group with muscle wasting as compared to those without.⁴⁷ In addition, the amount of skeletal muscle apoptosis seen on peripheral skeletal muscle biopsy corresponded with decreased aerobic capacity, while the percentage of fast-twitch type II muscle fibers was inversely related.⁶⁶ Interestingly, the relationship between aerobic capacity and muscle composition remains similar whether or not HF patients meet criteria for cardiac cachexia,⁶⁷ implying that the functional consequences of altered muscle composition manifest before full cachexia is evident.⁵¹ This phenomenon may be explained by the hypothesis that, similar to frailty, exercise intolerance in this population relates to impaired oxygen utilization by skeletal muscles due to inflammation, oxidative stress, and mitochondrial dysfunction.^{68–70} Therefore, although an important component in HF prognosis, much about the cellular, molecular, and functional consequences specific to frailty in HF have yet to be elucidated. Information extrapolated from HF-related muscle wasting suggests that there are striking similarities between the molecular fingerprints of primary frailty and HF-related frailty, although notable differences exist with respect to muscle cell composition. Further work to understand the molecular and cellular etiology of HF-related frailty as distinct from primary frailty may have implications for prevention, treatment, and reversibility, which will be further discussed below.

Treatment and Reversal of HF-Related Frailty

Exercise may impart an overall benefit to HF patients with respect to mortality,⁷¹ improvements in HRQoL, and decreased risk of HF-related hospitalizations,^{72,73} but the relationship between exercise and HF-related frailty is incompletely understood. Data from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) showed that after adjustment for known predictors of mortality, exercise training was associated with a reduced risk for mortality and hospitalization.⁷⁴ HF-ACTION further demonstrated safety of exercise in a population of patients NYHA class II–IV, improvements in six-minute walk tests, exercise time, peak oxygen consumption, HRQoL, and depressive symptoms.^{74–76} Exercise also affects intrinsic HF-related muscle changes. In a prospective, randomized, age-matched control trial, Gielen and colleagues (2012) showed increased force endurance and peak VO₂ of HF patients via a 4-week endurance training program.⁷⁷ These improvements correlated with a post-training increase in IGF-1 as well as decreased markers of muscle apoptosis. Others have shown that physical training increases peak VO₂ and decreases circulating

levels of TNF α and IL-6,⁷⁸ although these findings are not consistently replicated.⁷⁹ Therefore, there are signals that physical activity may positively alter the hormonal, inflammatory, and metabolic parameters of HF-related frailty. However, no studies to date have specifically addressed the impact of these molecular changes with specific respect to frailty reversibility or mortality.

As discussed above, in addition to predicting incident HF, inflammation is associated with both primary frailty and frailty secondary to HF. However, attempts to alter the inflammatory milieu of HF have met with disappointing results. Small studies of patients with moderate to severe HF found that TNF α -inhibition with infliximab or etanercept improved both functional status and ejection fraction. However, larger randomized trials found no such benefit; in fact, there was a trend toward harm, as TNF α -inhibition seemed to increase HF-related hospitalization and death.^{80,81} The reason for this lack of benefit remains unclear. One theory suggests that the redundancy of the inflammatory pathway allows TNF α -specific elements to be bypassed with few downstream consequences.⁸¹ Another is that inhibition may ultimately result in a “rebound effect” or a potentiation of TNF α activity over the long term.^{80,81} However, these medications are safe and effective in other inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis. They have never been applied to treatment or prevention of primary frailty or the *de novo* development of HF in this population, nor is there an understanding of their impact on HF-related frailty.

With respect to HF-related frailty, GDMT targeting the neurohormonal and autonomic nervous system dysfunction of systolic HF may pose complex advantages and disadvantages. Treatment recommendations for systolic HF include β -blockers (BB), ACE inhibitors or angiotensin receptor blockers, aldosterone antagonists, and diuretics to improve morbidity, hospitalizations, and mortality.⁸² The β -adrenergic signaling pathway stimulates an anabolic response in skeletal muscle via increased protein synthesis and decreased degradation⁸³; and administration of low-dose β -agonists in animal models increases muscle mass and force (for review, see Lynch & Ryall 2008),⁸³ a seemingly beneficial effect with respect to the muscle wasting process of frailty. Therefore, the BB recommendation of GDMT would be assumed to have deleterious consequences. Somewhat counterintuitively, but perhaps due to indirect effects on the renin–angiotensin system, Scherer and colleagues (2013) found that appropriate up-titration of BBs improves HRQoL in elderly HF patients with reported benefits in general health, vitality, and physical function, although physical capacity was not objectively quantified.⁸⁴ Regarding the renin–angiotensin–aldosterone system, as discussed above, administration of ACE inhibitors in normal aging may have a modest effect in slowing the progression of muscle-related weakness, although results are variable.^{41–43} In HF, early studies showed that 12 weeks of ACE inhibitor



administration increased exercise tolerance and improved NYHA functional class by one grade,⁸⁵ and therefore indirectly suggest that ACE inhibition may improve frailty status. However, these results preceded current recommendations for GDMT. There has been no direct assessment of GDMT on HF-related frailty.

Theoretically, the recipients of heart transplants or artificial circulatory support are the best population to assess for potential improvement of HF-related frailty. On a molecular level, data from Lund and colleagues (2012) show reversibility of some hormonal derangements common in HF-related frailty after transplant, including a normalization of the GH/IGF-1 axis,⁸⁶ although the relationship of this molecular change to reversal of the frailty phenotype was not addressed in this study. Functionally, heart transplant patients undergo some improvement in peak VO₂, but do not improve to levels equal to control populations. Interestingly, reported factors affecting exercise capacity changed from dyspnea to leg fatigue in a post-transplant population,⁸⁷ implying an element of permanence to some musculoskeletal consequences of HF. With respect to components of frailty, reversal of weight loss has been consistently documented in this setting. After undergoing heart transplant, patients gain an average of 10 kg in the first year.^{88,89} This does not appear to be a consequence of glucocorticoid use, as increased steroid dose is actually inversely related to weight gain and likely a marker of rejection episodes. It is important to note, however, that age is inversely correlated with weight gain after transplant, as younger patients (<48 years of age) gain significantly more weight than older ones,^{88,89} suggesting a spectrum of frailty reversibility based on patient age.

If there is an age-related spectrum of frailty reversibility, understanding the impact of circulatory support in an elderly HF population is crucial. Toward this end, Khawaja et al (2014) addressed some molecular, cellular, and functional elements of frailty reversibility in a slightly older population of patients receiving an LVAD as a bridge to transplant.⁹⁰ Study participants were on average 62 years old, as compared to an average age of 50 years in the heart transplant population. By LVAD explant, GH levels decreased significantly, accompanied by a normalization of the GH/IGF-1 ratio. Rectus abdominis muscle biopsies at explant showed a decreased proportion of type II muscle fibers with relative increase of type I muscle fibers as compared to implant, and grip strength improved over time. The results of this small study suggest that circulatory support with an LVAD has the ability to reverse some of the metabolic, structural, and functional derangements associated with HF and frailty in a slightly older population than previously analyzed.

Given that frailty is a risk factor for morbidity and mortality in the elderly advanced HF population, the potential for frailty reversibility is an important element of management decisions. Although evidence supports that some frailty components may improve in response to physical therapy, GDMT,

and more advanced circulatory support, how this relates to the entire frailty phenotype, as well as future risk for morbidity and mortality, is unknown. Also unknown is whether these results hold true for elderly patients (ie, over age 65) with advanced HF. Additional work to address the relationship between age, HF management, and frailty reversibility may help to improve outcomes as well as enhance conversations between clinicians and patients with respect to treatment options and goals of care (Fig. 1).

Conclusion

The frailty phenotype is associated with both advancing age and progressive HF and increases the risk for morbidity and mortality in both populations. At this time, clinical differentiation of the primary frailty of aging and frailty secondary to HF is not possible. In both, a propensity for an anabolic-catabolic imbalance appears to be driven by similar molecular mechanisms of systemic inflammation, oxidative stress, mitochondrial dysfunction, and neurohormonal dysregulation. These molecular derangements result in first structural and then functional musculoskeletal consequences. This process lays the foundation for the weight loss, weakness, fatigue, and functional deterioration that define the frailty phenotype.

Using the available data, it appears that there are subtle differences between the pathophysiology and recovery potential of primary frailty and HF-related frailty, which could have implications for management decisions. The prevalence of HF-related frailty is higher than that of age-matched community-dwelling elderly, demonstrating an earlier age of onset of frailty in this population. Perhaps, circulatory derangements trigger the neurohormonal and inflammatory milieu, which in turn initiates the underlying catabolic process of frailty. Interestingly, as compared to muscle loss associated with aging, fiber changes in HF favor a slow-to-fast twitch fiber shift due to higher overall percentage of type II fibers. The reason for this difference is unknown. Additionally, this population appears to have a more robust response to physical therapy as compared to those with primary frailty. Finally, there is a potential role for GDMT beyond preservation of left ventricular function, with some suggestion that BBs and ACE inhibitors improve frailty status. The caveat, however, is that the majority of evidence related to frailty in the HF population is extrapolated from studies of weight loss and cachexia, not frailty per se, in this population. Continuing to tease apart true differences between primary frailty and HF-related frailty may ultimately improve success with respect to therapeutic and pharmacological interventions.

However, primary frailty and HF-related frailty are most likely not mutually exclusive. Whether the elderly HF population manifests components of both primary and secondary frailty is unknown. About 30% of patients receiving LVADs are over age 65, the majority of whom receive the device as destination therapy. Although preliminary data suggest that circulatory support positively affects some elements

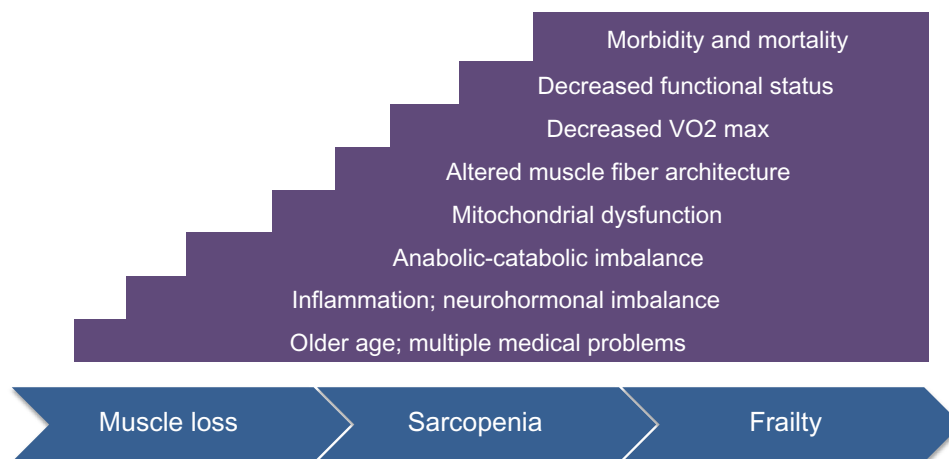


Figure 1. Progression to frailty in aging and heart failure. The primary frailty of aging and HF-related frailty have significant similarities. Older age and multiple medical problems are risk factors for the development of both types of frailty. The pathophysiological mechanisms of both include elevated inflammatory markers (ie, $\text{TNF}\alpha$ and IL-6), as well as dysregulated neurohormonal systems (ie, cortisol and insulin signaling). With respect to skeletal muscle, both groups have evidence of mitochondrial dysfunction and a shift in the cellular architecture of the muscle fibers. These molecular and structural changes result in decreased aerobic capacity, impaired functional status, and ultimately increased morbidity and mortality.

of HF-related frailty, there is no information with respect to this very elderly cohort. If primary and secondary frailty coexist, potentially the balance between the two will contribute to reversibility potential. To assist with clinical differentiation, perhaps assessments may be aided by additional tests, such as muscle biopsies, to define frailty etiology and predict the potential for reversibility. Ongoing investigations are addressing the prevalence of frailty in this population as well as the potential for LVAD-mediated frailty reversibility. These results will further the discussion with respect to the risks and benefits of advanced circulatory support in an elderly HF population. Until that time, continued use of a standardized frailty definition and systematic operationalized approach to pre- and post-procedural frailty assessments will add to our knowledge. Ultimately, understanding the interaction between aging, HF, and frailty and clarifying the distinction between primary and secondary frailty will help guide difficult life-altering decisions for elderly HF patients.

List of Abbreviations

ACE: angiotensin-converting enzyme
 BB: β -blockers
 COPD: chronic obstructive pulmonary disease
 CRP: C-reactive protein
 ESRD: end stage renal disease
 GDMT: guideline-directed medical therapy
 GH: growth hormone
 HF: heart failure
 HRQoL: health-related quality of life
 IGF1: insulin-like growth factor-1
 IL: interleukin
 LVAD: left ventricular assist device
 $\text{NF}\kappa\text{B}$: nuclear factor kappa B
 NYHA: New York Heart Association

$\text{TNF}\alpha$: tumor necrosis factor alpha
 VO₂: peak oxygen uptake

Author Contributions

Analyzed the data: DG, SP. Wrote the first draft of the manuscript: DG, SP. Contributed to the writing of the manuscript: DG, SP. Agree with manuscript results and conclusions: DG, SP. Jointly developed the structure and arguments for the paper: DG, SP. Made critical revisions and approved final version: DG, SP. Both authors reviewed and approved of the final manuscript.

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