Multidomain Frailty as a Therapeutic Target in Elderly Patients with Heart Failure

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Summary

Heart failure and frailty share aging as a strong risk factor. The prevalence of frailty has been shown to be particularly high in elderly patients with heart failure. Moreover, it is important not to confine frailty to physical aspects. Rather, it should be considered to consist of multiple domains, including physical disability, psychiatric disorders, cognitive impairment, depression, and social disconnection. Development of interventions that can improve frailty domains are not well established, although observational studies have evaluated the association of various frailty domains and their prognostic impact. Some interventions, including resistance exercise, functional exercise, and respiratory muscle training have been demonstrated to hold potential for improving physical frailty. In terms of cognitive dysfunction, previous studies have demonstrated that exercise therapy is also effective for cognitive dysfunction. The social domain of frailty is one of the least investigated domains, particularly in patients with heart failure. However, heart failure is also strongly associated with physical frailty and cognitive impairment and has a poor prognosis in old patients. The prevalence of social frailty in elderly patients who need hospitalization due to heart failure is higher than previously thought. Very few studies have tested interventions targeting social frailty. Frailty and heart failure affect each other, and both are becoming increasingly important in society. In this article, we review the physical, cognitive, and social domains of frailty and the possible interventions to improve them in patients with heart failure.

Key words: Cognitive dysfunction, Cognitive frailty, Physical frailty, Resistance exercise, Respiratory muscle training, Social disconnection, Social frailty

Heart failure (HF) is a major public health burden worldwide that is associated with high medical costs. Recently, the population in Japan in particular, has been aging rapidly, leading to a marked increase in the number of patients with HF. Patients with HF often require repeated readmission, with a gradual decline in overall functionality. The clinical symptoms of HF are not characterized only by cardiac function, but also by neurohumoral factors triggered by myocardial damage, inflammation, respiratory control function, skeletal muscle mass, and skeletal muscle dysfunction.

Frailty is regarded as a geriatric syndrome associated with high vulnerability to stressors, causing adverse health outcomes, resulting from the decreased reserves of multiple physiological systems. The population prevalence of frailty in the community has been reported to be 3-7% among individuals aged 65-75 years and 20-26% in the 80-year age group. Several studies have shown a strong association between frailty and incident CVD and mortality in older individuals. On the other hand, it has also been reported that 25-50% of patients with CVD are frail.

As advanced age is among the strongest predictors of both HF and frailty, and frailty is particularly important in older patients with HF. Moreover, recently, several statements and/or position papers have underlined the importance of not confining frailty to physical aspects, and that frailty should be considered to consist of multiple domains, including physical disability, psychiatric disorders, cognitive impairment, depression, and social disconnection. Of note, recent studies have shown that these frailty domains are not independent, but are intertwined in patients with HF. In the FRAGILE-HF study, a prospective multicenter cohort study that enrolled consecutive hospitalized HF patients aged ≥ 65 years, the incidences of physical frailty, cognitive dysfunction, and social frailty...
(SF) were reported as 56.6%, 36.9%, and 66.4%, respectively. There are also notable overlaps between the areas of frailty, and patients with frailty in multiple areas have been shown to have higher mortality and rates of rehospitalization for HF, indicating the importance of a holistic evaluation of frailty in elderly patients with HF. Another study has shown that, in the general older population, individuals with physical frailty have significantly increased risk of cognitive impairment or dementia and are at a high risk of depression, compared to those without depression. Regarding psychological domains, it has been suggested that frailty is associated with apathy and anxiety in addition to depression and cognitive decline. These study results clearly suggest the strong association between frailty domains.

However, in contrast to the aforementioned observational studies evaluating the association of frailty domains and prognosis, interventions that can improve various frailty domains are not well established. In this review, we summarize the possible approaches for intervening in this vicious circle, with a view to improving the prognosis of patients with heart failure by improving each frailty domain, the currently available data on how promising the intervention is, and the future direction of this poorly established field.

**Interventions for Physical Frailty**

**Resistance exercise:** Skeletal muscle abnormalities contribute to a vicious cycle of disease progression, and have been recognized as one of the key factors aggravating the pathophysiology underlying HF. However, resistance exercise (RE) was largely overlooked for patients with HF before the 1990s, due to concerns about high cardiac afterload, which may contribute to left ventricular remodeling. Subsequently, the safety and efficacy of RE were confirmed and recommended in clinical guidelines for the management of patients with HF. A recent meta-analysis demonstrated that RE as a single intervention can improve muscle strength, exercise capacity, and quality of life (QoL) among patients with HF. Muscle-wasting and low muscle strength are strongly correlated with morbidity and mortality in patients with HF. Sarcopenia, or physical frailty, is also associated with disease progression, mobility, and QoL among patients with HF. Given the lack of standard treatment, RE represents a non-pharmacological strategy that shows potential for attenuating sarcopenia or physical frailty, in HF patients.

**RE and physical frailty:** The standard RE intervention is performing 1-3 sets of 6-8 types of moderate intensity REs targeting major muscle groups for more than 12 weeks, at 3 sessions per week. On the other hand, it has been recommended that a greater volume of RE is required to combat frailty in patients with HF. Several prior studies have suggested that RE combined with aerobic exercise may attenuate abnormalities in muscle quality and quantity in frail HF patients. However, older patients are underrepresented across these studies: few studies have examined the efficacy of RE in old and frail patients with HF. Although, in general, low-intensity RE is considered to be preferable for older patients with HF, the American College of Sports Medicine (ACSM) position recommends RE to improve motor performance and muscle strength, particularly in older adults. In contrast, low-to-moderate intensity and high-velocity RE, aimed at improving motor performance and muscle power, have appeared to be prouder in older frail patients. Needless to say, elderly patients with HF need a tailor-made exercise program according to their functional status, comorbidity status, and HF severity. Further studies are needed to provide clinical evidence of an individualized RE program for improving motor performance or muscle power in older frail patients with HF.

**Functional exercise training:** In older patients with cardiovascular disease, a decline in the functions of basic activities of daily living (ADL) (e.g., standing up quickly and safely, standing stably with good balance, and walking alongside a friend) is commonly observed. Therefore, in recent years, in addition to traditional aerobic exercise and resistance training, functional exercise training that incorporates elements of ADL has become increasingly important.

Kitzman, et al. conducted a multicenter, randomized, controlled trial of a progressive rehabilitation intervention focusing on 4 physical-function domains (strength, balance, mobility, and endurance). They found that a progressive rehabilitation intervention focusing on these 4 physical-function domains, started early after hospitalization and continued for 36 outpatient sessions after discharge, resulted in a significant improvement in the Short Physical Performance Battery (SPPB) scores at 3 months as compared to the usual care group. The SPPB, 1 of the standard frailty assessments, consists of 3 components: 1) a balance test, 2) a walking test, and 3) a chair-standing test that is scored 0-4 points according to functional ability in each component, which are summed to obtain a total score. We assessed 3 components of the SPPB (standing balance, walking speed, and leg strength), in addition to the walking distance (endurance), and found that implementation of an exercise program based on this 4-domain assessment resulted in physical rehabilitation of hospitalized older HF patients at Juntendo University Hospital.

Functional exercise training has also been shown to be effective in older patients after coronary artery bypass graft surgery. Busch, et al. found that the 6-minute walking distance (6MWD), timed up-and-go duration, and relative workload were improved significantly more than in those randomized to the control group, after 5 sessions per week of additional special balance training that was added to a standard inpatient cardiac rehabilitation program. Similarly, Tamulevičiūtė-Prascienė, et al. examined the effect of resistance and balance training (3 days per week) in patients who underwent valve replacement surgery and found that this intervention improved functional and exercise capacity, physical performance, and muscular strength, and reduced physical frailty levels in the short and medium terms. These study results may imply that functional exercise training, in addition to conventional aerobic exercise and machine resistance training, is important to overcome physical frailty in older patients with heart disease.
Respiratory muscle training: In patients with chronic HF, exercise tolerance and ADL may be limited by dyspnea, shortness of breath, and fatigue associated with exertion, to which respiratory muscle weakness is thought to be a contributing factor. Several studies have confirmed that maximal inspiratory mouth pressure (PImax) is decreased in patients with chronic HF, and it has been reported that in 30-50% of HF patients, the status is complicated by inspiratory muscle weakness, defined as PImax decreased to < 70% of the reference value. Although the mechanism of respiratory muscle weakness in HF patients is not clear, it has been suggested that changes in skeletal and respiratory muscles in chronic HF may be related to hypoxia, oxidative stress, low nutrition, systemic inflammation, medication, and disuse. In addition, recent studies have reported that decreased diaphragmatic function (decreased diaphragm muscle thickness and contractility) is associated with respiratory muscle weakness in patients with chronic HF. HF patients with reduced diaphragmatic function have reduced PImax and 6MWD. Reduced inspiratory muscle strength in HF patients is associated with reduced diaphragmatic function. HF patients with reduced PImax have worse long-term prognosis. Given that inspiratory muscle strength is a prognostic determinant in these patients, assessing respiratory muscle strength is extremely important clinically and suggests the value of respiratory muscle training.

In a systematic review and meta-analysis of the effects of inspiratory muscle training (IMT) in chronic HF patients, it was reported that IMT improved cardiopulmonary function (6MWD, peak VO2, PImax, VE/VCO2 slope) and QOL (Minnesota Living with Heart Failure Questionnaire). In addition, a systematic review and network meta-analysis of 31 RCTs (1,499 subjects) found that IMT with high pressure (60% maximal inspiratory pressure or maximal inspiratory pressure plus aerobicics) had the highest effect size for peak VO2 and 6MWD, and IMT with medium pressure (30-40% maximal inspiratory pressure) had the highest effect size on QOL. In addition, a recent systematic review and meta-analysis reported that IMT alone can improve respiratory comfort, increase walking distance, and improve QOL without combining it with other exercises. These study results have consistently suggested that IMT is effective in improving inspiratory muscle strength, exercise tolerance, and QOL in HF patients.

It is recommended that providing IMT to patients with HF should be initiated at 30% of PImax and can be titrated up to 60%, with a frequency of 3-5 times/week, for at least 8 weeks, at about 20-30 minutes/set. In future, it may become an alternative therapy for HF patients before they transition to exercise training, or could be a major training tool for HF patients who cannot undergo conventional exercise training. However, the prognostic impact of IMT in elderly patients with HF has not been evaluated yet, and should be clarified in future studies.

Interventions for Cognitive Dysfunction

In terms of cognitive impairment, no intervention specifically aimed at improving cognitive function has been demonstrated to be effective. Instead, exercise therapy, among the interventions most widely examined, has been reported not only to improve physical function, but also to improve cognitive function. A randomized controlled trial from Japan in patients with mild cognitive impairment showed that a combined exercise intervention was effective for improving Mini-Mental State Examination (MMSE) scores and memory scores. Moreover, the atrophy level of the cerebral cortex, measured by magnetic resonance imaging, was lower in the group that performed combination of physical and cognitive exercise. Another study showed that cognitive training alone does not improve cognitive function, but cognitive function improves when combined with exercise. These findings indicate that exercise interventions may be a key to improving cognitive function in those with cognitive frailty, as these 2 conditions do not overlap in terms of prevalence, but also seem to interact with each other in terms of the disease pathophysiology. This point is also supported by the results of prospective observational studies. Raji, et al. prospectively followed 942 community-dwelling older adults for 10 years and reported that lower MMSE scores at the beginning of follow-up were associated with a greater likelihood of developing frailty at 10 years. In addition, a prospective observational study that followed 2,737 patients for 4 years found that a decrease in MMSE scores during the 4 years correlated significantly with a decrease in muscle mass and walking speed in men, and a decrease in muscle strength in women. Conversely, it has also been revealed that cognitive impairment is related to physical frailty. In a 6-year cohort study of 594 subjects (assessed between the ages of 70 and 76 years), executive function speed (and its decline), as a marker of cognitive function, was found to be predictive of physical frailty at 6 years.

Recently, the new construct called cognitive frailty was defined as the presence of both physical frailty and cognitive impairment without dementia or cerebrovascular diseases. There is no universally accepted definition of cognitive frailty; however, cognitive impairment in cognitive frailty is considered to be primarily due to physical deterioration, rather than neurodegenerative processes. An International Consensus Group on “Cognitive Frailty” was organized by the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics on April 16th, 2013, in Toulouse, France and cognitive frailty was defined as a heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment. In particular, the key factors defining such a condition included: 1) presence of physical frailty and cognitive impairment (CDR = 0.5); and 2) exclusion of concurrent Alzheimer’s dementia or other dementias.

Previous studies have shown that exercise training may be effective for cognitive frailty. Yoon, et al. demonstrated that 16 weeks of high-speed RE using elastic exercise bands improved processing speed and executive functions in older adults with cognitive frailty. A hypothesis for the pathophysiological background of cognitive frailty is that the prefrontal cortex is heavily involved in both frailty and motor function; this has yet to be clarified.
Nevertheless, patients with cognitive frailty may be a good target for appropriate interventions, including physical exercise, and they may improve not only motor function but also their cognitive function, considering the association between physical and cognitive dysfunction. Indeed, it has been shown that physical activity frequency, type, and total volume were positively associated with processing speed, memory, mental flexibility, executive function, and overall cognitive function. However, the efficacy of RE for cognitive frailty in older patients with HF is currently unknown and randomized controlled trials with sufficient sample sizes are needed to clarify the effects of RE on cognitive function and physical function in older HF patients with cognitive frailty.

**Interventions for Social Frailty (SF)**

The social domain of frailty is among the least investigated fields. As social activity often requires the integration of physical and mental capacities, SF may develop at a relatively early stage in the progressive trajectory of frailty. A prior study on community-dwelling older adults showed that SF caused decline in physical and cognitive function. The prevalence and prognostic impact of a weak social network among patients with HF are featured in prior research; however, the results are inconsistent. The impact of social and environmental issues on clinical outcomes may only become apparent following the discharge of patients with HF from the hospital. SF is not an adequately studied concept; therefore, to develop a better understanding, a broad and systematic evaluation of the existing insights is required.

We recently reported that approximately two-thirds of hospitalized patients with HF aged > 65 years in Japan had SF. They were diagnosed with SF by 5 simple questions that have already been verified to be associated with the risk of future disability among community-dwelling older adults without disability. Those with SF were older and more symptomatic at baseline and had a worse clinical prognosis, including mortality, than those without SF. These results demonstrated that information regarding the presence of SF has an additive prognostic value over that of pre-existing factors.

Patients with SF may have less physical activity, experience depression, or utilize less social support for disease management, each of which can lead to poor long-term outcomes. Therefore, SF can be considered an intervenable domain via HF self-care and social support. One randomized study showed that a group-based social support program could enhance social connections. Although many studies have demonstrated the effects of interventions on physical frailty, the number of studies targeting SF is very limited.

Among the limited number of interventions, the results of the existing trials have been inconsistent. One study examining the impact of providing opportunities for social interaction to older adult residents found that participation in gatherings, such as salon activities promoting social interaction, reduces the need for elderly care. Participation in such gatherings may promote the maintenance or improvement of physical, cognitive, and mental functions. Interestingly, studies that have assessed exercise-based interventions have found, for example, that supervised group exercises not only improve the physical aspects of frailty, but also promote social interaction, which in turn may lessen or resolve SF. Regional studies in Spain have shown that social support interventions, such as visits from non-specialist volunteers, improved the nutritional condition and frailty status of those who were visited. In this study, visits from volunteers took place twice-weekly over 12 weeks. The study primarily focused on social aspects, including the encouragement of excur- sions and conversational exchanges, all serving to activate cognitive functions. Additionally, in a preliminary report investigating a social support intervention involving problem-solving training in patients with HF, significant improvements were seen in self-care maintenance and self-care confidence, without assessing clinical outcomes. However, a collaborative intervention, including both nursing and social worker care for HF symptoms and psychosocial symptoms, resulted in no difference in the quality of life between the intervention and control groups, with decreased depressive symptoms and fatigue in the intervention group. Moreover, another trial investigating reciprocal peer support in patients with HF observed no difference in time-to-HF hospitalization, mortality, or measures of HF-specific QoL or social support. The discrepancies in these interventional trials may be due to poor participant engagement, lack of a control group, and high drop-out rates.

Facilitation during index hospitalization for the transition from the hospital to the home and the subsequent intentional establishment of social connections between discharged patients and their community might be effective in decreasing mortality and preventing rehospitalization due to HF. Specifically, information technology, such as communication via smartphone applications, video-calling, and social networking services, may be promising interventions. Additionally, a previous randomized clinical trial showed that a multicomponent exercise program improved not only physical performance, but also the cognitive, emotional, and social networking parameters. This may imply that frailty domains, including SF, do not occur in isolation. Moreover, a previous study showed that those with SF but without physical frailty are at a greater risk of developing physical frailty. Hence, screening for SF is important, as it can potentially identify frail older adults, that would not be captured otherwise. It may be possible to reverse frailty by using focused interventions, thereby preventing the future risk of incident disability. Therefore, the prevalence and prognostic value of SF should be routinely evaluated in daily clinical practice. Further prospective investigations directly examining the efficacy of interventions on SF in patients with HF are warranted to demonstrate their effectiveness.

**Conclusions**

Frailty and HF affect each other and are becoming increasingly important in society. In this article, we reviewed physical, cognitive, and social frailty and the possible interventions to improve them in patients with HF.
In recent studies, multi-domain frailty has been described as the complex interaction of each frailty, and the same is true for HF patients. Recent studies have suggested several possible interventions for improving frailty and subsequently decreasing mortality and morbidity; however, very few of them have been tested in patients with HF in terms of their efficacy. Further research, particularly a well-powered randomized clinical trial, is needed to test the hypothesis of whether improvement in frailty can subsequently improve the prognosis of old patients with HF.

**Disclosure**

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