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MINIREVIEWS

Frailty, sarcopenia and cachexia in heart failure patients: Different clinical entities of the same painting

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Abstract

Heart Failure (HF) in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome. Cardiac cachexia, sarcopenia and frailty despite overlap in definitions are different clinical entities that frequently coexist in HF patients. However, these co-factors often remain unaddressed, resulting in poor quality-of-life, prolonged physical disability and exercise intolerance and finally with higher rehospitalization rates and mortality. Strategy aim to increase muscle mass and muscle strength and delay the occurrence of frailty state appear essential in this regard. Common HF drugs therapy (b-blockers, angiotensin-converting enzyme inhibitors) and prescription of physical exercise program remain the cornerstone of therapeutic approach in HF patients with new promising data regarding nutritional supplementation. However, the treatment of all these conditions still remain debated and only a profound knowledge of the specific mechanisms and patterns of disease progression will allow to use the appropriate therapy in a given clinical setting. For all these reasons we briefly review current knowledge on frailty, sarcopenia and cachexia in HF patients with the attempt to define clinically significant degrees of multiorgan dysfunction, specific "red alert" thresholds in clinical practice and therapeutic approach.

Key Words: Heart failure; Sarcopenia; Cachexia; Frailty; Terapheutic implication; Comorbidities

Core Tip: The last heart failure (HF) guidelines of the European Society of Cardiology dedicate a chapter each for cachexia, sarcopenia and frailty and several studies

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regarding these topics are coming up. This wealth of information highlights the importance of these co-factors in HF management and are each uniquely relevant to evaluate older patients with HF. It is time to routinely assess cachexia, sarcopenia and frailty that could help in personalized care plan, improve outcomes and reduce hospitalization and institutionalization. However, definitions, pathophysiology and treatment of all these conditions still remain unclear and we briefly summarize the most recent knowledge available in literature.

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INTRODUCTION

Heart failure (HF) in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome[1]. HF syndrome shows a significant impact on the health-care resources and its occurrence is ever increasing in the elderly[2]. Recently there are discussion regarding frailty and the common problems affecting skeletal muscle, both sarcopenia and cachexia. These comorbidities are crucial issue to plan health care resources for older patient with HF. After hospitalization for acute HF, these co-factors often remain unaddressed resulting in prolonged physical disability, poor quality-of-life, exercise intolerance and finally with higher rehospitalization rates and mortality. Besides, HF hospitalization independently and significantly increased the risk of limitations of Basic and Instrumental Activities of Daily Living (IADL)[3]. The complex relationship between frailty, muscle wasting and cachexia can coexist and different strategies and interventions need to be deeply investigated to improve outcome, quality of life and HF-related re-admissions. For all these reasons we briefly review current knowledge on frailty, sarcopenia and cachexia in HF patients with the attempt to define clinically significant degrees of multiorgan dysfunction, specific "red alert" thresholds in clinical practice and therapeutic approach.

FRAILTY IN HF

Frailty recognize a biologic basis and it is characterized by a loss of strength and physical ability with a progressive decline of cognitive function. Incorrect definition includes this syndrome as a comorbidity or a disability, but comorbidity is a risk factor and disability is an outcome of frailty state[4]. Frailty patients show a strong susceptibility to several endogenous and exogenous stressors. This vulnerability state contributes to risk of falls, hospitalization and death. Frailty is a common finding in HF patients and the prevalence is higher in older age and correlates significantly with HF severity, however frailty must not be considered only in older individuals and all patients with HF deserve a frailty assessment[5]. FRAIL-HF study reveal the presence of frailty state in 70% of patients with HF and ≥ 80 years old. On the other hand frail patients show an higher risk to develop HF[6]. Several frailty score and pre-fail status assessment are now available; Clinical Frailty Scale, gait speed test, PRISMA/7 questionnaire, Fried Score, FRAIL Score and Short Physical Performance Battery (SPPB) are routinely used in clinical practice with good agreement between methods[7-9]. Recently the HF Association/European Society of Cardiology establish a new frailty score that is the first elaborated in HF setting. This new score consider a 4-domain framework such as clinical, functional, cognitive-psychological and social variables, extremely useful and practical to diagnose frailty in HF patients[10] (Table 1). Nowadays an overall geriatric assessment that consider not only the frailty state but also depression, cognitive impairment and muscle wasting are each uniquely relevant to evaluate older patients with HF and significantly impact prognosis and treatment success (*i.e.*, transcatheter or surgical Aortic Valve Replacement)[11,12]. The SPPB is a set of objective measures of physical performance, highly predictive of disability, hospitalization, institutionalization, and mortality in community-dwelling older

Table 1 Current definitions of frailty, cachexia and sarcopenia

Institution/authors, journal, year	Frailty	Institution/authors, journal, year	Cachexia	Institution/authors, journal, year	Sarcopenia
British Geriatrics Society, Age UK and Royal College of General Practitioners Report[7]. *Age Aging* 2014	(1) A gait speed < 0.8 m/s; (2) Timed-up-and-go test > 10 s; (3) Score of ≥ 3 on the PRISMA 7 questionnaire. Falls, delirium and sudden immobility can used to indicate the presence of frailty	Argilés *et al*[19]. Consensus on cachexia definitions. *J Am Med Dir Assoc* 2010	Weight loss > 5% of body weight (or BMI < 20 kg/m^2) in ≤ 1 year in presence of chronic illness and three of five of these criteria. (1) Decreased muscle strength; (2) Fatigue; (3) Anorexia; (4) Low fat free mass index; (5) Anaemia (< 120 g/L), low serum albumin (< 32 g/L) and CRP > 5 mg/L, IL-6 > 4 pg/mL	Revised European consensus on definition and diagnosis[36]. *Age Aging* 2019	(1) Low muscle strength; (2) Evidence of low muscle quantity or quality; (3) Detection of low physical performance. The combination of three represent severe sarcopenia
Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure[10]. *Eur J Heart Fail* 2019	The frailty score in HF patients were built with the following variables: (1) Clinical: Comorbidities, weight loss, falls; (2) Psycho-cognitive: Cognitive impairment, dementia, depression; (3) Functional: ADL/IADL, mobility, balance; (4) Social: Living alone, no social support, institutionalisation	International Consensus on Cancer Cachexia Classification[65]. *Lancet* 2003	The agreed diagnostic criterion for cachexia was weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI < 20 kg/m^2) or skeletal muscle mass reduction	Society of Sarcopenia, Cachexia and Wasting Disorders[37]. *J Am Med Dir Assoc* 2011	Muscle loss with (1) walking speed equal or less than 1 m/s; (2) walks less than 400 m during a 6-minute walk. Appendicular lean mass/height2 > 2 SD below the mean mass of a healthy person (aged 20–30 yr)
Fried *et al*[4]. *J Gerontol A Biol Sci Med Sci* 2001	Frailty was defined with three or more of the following criteria: (1) Unintentional weight loss (4, 5 kgs in past year); (2) Self-reported exhaustion; (3) Weakness (reduced grip strength); (4) Slow walking speed; (5) Low physical activity. A pre-frail status is accordingly whit one or two criteria	SCRINIO working group[66]. *JPEN J Parenter Enteral Nutr* 2009	The patients were divided in 4 groups based on combinations of body weight loss < 10% in precachexia and ≥ 10% in cachexia; associated to the presence/absence of at least 1 symptom of anorexia, fatigue or early satiation	International working group on sarcopenia[39]. *J Am Med Dir Assoc* 2011	Gait speed of less than 1 ms (-1) and low muscle mass (appendicular mass relative to ht (2) that is ≤ 7.23 kg/m^2 in men and ≤ 5.67 kg/m^2 in women)
Canadian Study of Health and Aging[9]. *CMAJ* 2005	Clinical frailty scale is based on IADL, activity, mobility, energy, and symptoms all associated with clinical judgement			Special Interest Groups "Cachexia-Anorexia in Chronic wasting diseases" and "Nutrition in Geriatrics"[21]. *Clin Nutr* 2008	Reduced muscle mass, strength and function (low handgrip strength (men < 26 kg, women < 16 kg), gait speed ≤ 0.8 m/s, low appendicular lean mass/BMI)

BMI: Body mass index; IL-6: Interleukin-6; hg: Height; kgs: Kilograms; CRP: C-reactive protein; IADL: Instrumental activities of daily living.

individuals[13,14]. The prognostic potential of the instrument has been proven in patients hospitalized for HF, pneumonia, chronic obstructive pulmonary disease (COPD) and minor stroke[15]. Furthermore, in a cohort of hospitalized elderly HF patients, a low physical performance status, as evaluated with SPPB, predicted mortality even after adjustment for left ventricle ejection fraction (LVEF), New York Heart Association (NYHA) Class and comorbidities[16]. Moreover, handgrip strength, serum albumin and IADL status are all associated with health outcome in elderly patients hospitalized for HF. Moreover, the pre-frailty state, a condition that is potentially reversible, identified by slow gait speed, exhaustion and low energy expenditure, is in the same way an independent predictor of new cardiovascular events in older adults[17]. For all these reasons closer follow up by HF team is highly necessary in frail patients. This approach could monitor HF symptoms, adjust medications and address reversible causes leading to worsening of frailty score and consequent HF decompensation.

CARDIAC CACHEXIA IN HF

Cachexia is a serious but underrecognized consequence of many chronic diseases such as cancers, COPD, malnutrition state, neurological disease, rheumatoid arthritis and kidney disease. It is considered a wasting process at multiorgan levels (skeletal muscle, fat and bone tissue)[18]. Cachexia is defined by a weight loss > 5% of body weight [or body mass index (BMI) < 20 kg/m^2] in ≤ 1 year in presence of chronic illness and three of five of these criteria (1) decreased muscle strength; (2) fatigue; (3) anorexia; (4) low fat free mass index; and (5) abnormal biochemistry [anaemia (< 120 g/L), low serum albumin (< 32 g/L), increased inflammatory markers (C-reactive protein > 5 mg/L), interleukin-6 (IL-6) > 4 pg/mL][19] (Table 1). The overall prevalence in Western World is still growing and affects around 1% of patients population[20,21]. Cachexia is more frequently common in end-stage HF, its prevalence ranges from 5%-15%[22], but surprisingly it is not clear a close relationship with LVEF, in particular the prevalence of the disease is the same in various HF phenotype[23]. In a prospective study that enrolled outpatients with LVEF ≤ 40%, 18% are cachectic and cardiac cachexia is associated with intestinal congestion irrespective of HF stage and cardiac function. Inflammation state, gastrointestinal discomfort, appetite loss provide probable mechanisms, by which intestinal congestion may trigger cardiac cachexia[24]. Instead right ventricular dysfunction and weight loss may have a pathophysiological linked (venous congestion, malabsorption, anorexia, gut bacteria translocation)[25]; improvement of right ventricular function may delay the occurrence of cachexia. Moreover, tricuspid regurgitation and pulmonary hypertension are associated with low BMI and they are accentuating risk factor for cachexia, together with hypoalbuminemia and hyponatremia due to protein-losing enteropathy[26,27].

Cachectic patients show an impaired functional capacity, more severe symptoms and low quality of life[28]. This serious complication is associated with frequent hospitalization increased length of in hospital stay and health care cost[29]. Weight loss displays an additional prognostic information beyond clinical features of HF severity with significant association with morbidity and mortality[30]. Wasting disorders is and independent risk factor for impaired survival in chronic HF patients (adjusting for age, sex, NYHA class, LVEF, and VO2 consumption); mortality at 18 months of followup is around 50% in patients with cachexia[31]. In hospitalized HF patients with cardiac cachexia factors such renal function, age, and haemoglobin are pivotal prognostic markers[32].

As opposite, obesity is an independent risk factor associated with HF, but recently it is well demonstrated that obesity in patients that have already developed HF (across a wide range of BMI) is related to lower mortality; highlighting the concept of "obesity paradox" also common in other chronic disease[33]. However, BMI does not reflect the body composition regarding the percentage of fat mass, fat-free mass and lean mass. Inside this different large spectrum of body composition, patients with preserved skeletal muscle mass show a better prognosis compared with patients with reduced lean mass due to increased stroke volume and consequent better tissue perfusion[34]. Thus, fat mass loss but not lean mass has a prognostic impact and it is a good indicator of enhanced catabolism and has a role of cardioprotection in advanced HF.

SARCOPENIA IN HF

Recently the 12th Cachexia Conference held in Berlin in December 2019 highlights preclinical and clinical studies in the field of wasting disorders[35]. The definition of sarcopenia remains a matter of discussion, however for the first time it is recognized that strength is better than mass to evaluate adverse outcomes and actually the European consensus on definition and diagnosis Sarcopenia define the disease with three criterion: (1) Low muscle strength, that is considered the most accurate parameter to evaluate sarcopenia; (2) Evidence of low muscle quantity or quality; and (3) The detection of low physical performance (Table 1). The presence of all three criteria permit to define ad advance sarcopenia status. Several tests and different tools are widely described to assess sarcopenia in practice and in research with specific description of each method used[36-39]. Sarcopenia is age related and old muscle mass is reduced by 1%-2% annually after 50 years old with a contemporary decline in muscle strength by about 1.5%[40]. Its prevalence increases around 3% annually after the 60 years old[41]. For the first time the European Society of Cardiology in the guidelines of 2016 dedicate a chapter to cachexia and sarcopenia recognizing as important comorbidities of HF[42]. The prevalence of sarcopenia is around 20% in HF with

reduced ejection fraction (HFrEF) and HF with preserved ejection fraction patients without clear difference in prevalence across different HF phenotype. A monotonic association existed between increasing sarcopenia prevalence and other comorbidities, in particular sarcopenia correlates with the decline of glomerular filtration rate[43,44]. Six-minutes-walk test and spiroergometry show lower Vitamin E/VCO2 (VO2) and shorter exercise time in sarcopenic HF patients, highlighting the impact of muscle wasting in lower muscle strength and lower physical performance in HF population. Bekfani *et al*[45] find better quality of life in patients with higher values of muscle strength/muscle mass ratio (evaluated by Visual Analogue Scale derived from the EQ-5D)[45]. Emami *et al*[46] demonstrate a percentage of overlap (6.7% in HF population studied) of both sarcopenia and cachexia. The lowest values of muscle strength and function, as assessed by handgrip and quadriceps strength, 6 min walking test, SPPB score and peak VO2, are observed only in sarcopenic groups[46]. Moreover, sarcopenia significantly impact the functional capacity of HF patients; and it is associated with increased likelihood of adverse events including falls, fractures, worst neurocognitive profile and low physical performance that may precipitate a relative clinical HF stable condition. In older patients low physical activity is strictly related with the occurrence of sarcopenia and it is an independent factor in prolonging hospital stay among patients admitted to hospital care[47]. However, muscle wasting might be present also in younger patients with HF and non-ischemic dilated cardiomyopathy, particularly in those with advance clinical status[48]. In literature, some discordant opinions are evident regarding the recovery of skeletal muscle after heart transplantation (HT) or left ventricle assistant device implantation[49]. Skeletal muscle impairment seems to persist after months from HT and contribute to the impaired exercise capacity[50], however a recent study demonstrates the recovery of muscle mass and strength after 1.5-3 years of follow up after HT. Moreover, HT and ventricular assist device therapy lead to an improvement in frailty score during follow up highlighting that sarcopenia and frailty are both dynamic and not a fixed entity[51].

BASIC PATHOPHYSIOLOGICAL OVERVIEW

Cardiac cachexia, sarcopenia and frailty in HF patients recognize similar pathophysiological features (Figure 1). Systemic inflammation and hypermetabolism play a pivotal role; cachectic patients display an increased cortisol/dehydroepiandrosterone ratio and higher cytokine levels such as tumor necrosis factor (TNF)-alpha, soluble TNF-receptor 1 and IL-6. Higher levels of hormones and cytokines activities are both associated with muscle wasting, reduced fat tissue and bone mass. Few hormones are implicated in the pathophysiology in cachexia and sarcopenia. Growth hormone, insulin resistance and insulin-like growth factor-1 levels are all associated with muscle mass loss and consequently with a significant reduction of physical performance[52]. Triiodothyronine in cachectic oncologic patients is increased compared to non-cachectic cancer patients and it is also normal in patients with benign weight loss. Ghrelin significantly inhibits the production of cytokines with inflammatory pathway and exhibits anti-cachectic activity both with growth hormone dependent and independent mechanisms. Low testosterone levels are usually common in all HF patients and contribute to the progression of cardiac cachexia, sarcopenia and frailty through altered peripheral vascular resistance, increased cardiac afterload, and decreased cardiac output. Nutritional alterations and gastrointestinal malabsorption lead to an abnormal calorie uptake, protein balance and insulin resistance[53]. Advanced HF status is linked to gastroenteropathy secondary to intestinal edema that result in protein losing enteropathy which causes malabsorption and anorexia[54]. Catabolic/anabolic imbalance change the substrate utilization in tissues. Moreover, cachexia in HF is associated with an increase in adiponectin concentration strictly related to type B natriuretic peptide levels[55]. All these reasons exacerbate the wasting process and muscle cells apoptosis, and therefore result in muscle atrophy and lower muscular strength favoring the occurrence of frailty[56].

TERAPHEUTIC IMPLICATION

Physical inactivity due to the progression of HF syndrome are common in frailty patients. Sarcopenic, cachectic and frailty patients show impaired exercise capacity and limitations in common activity such as food preparation and eating, contributing to disability and muscle loss. Skeletal muscle improvement after exercise training

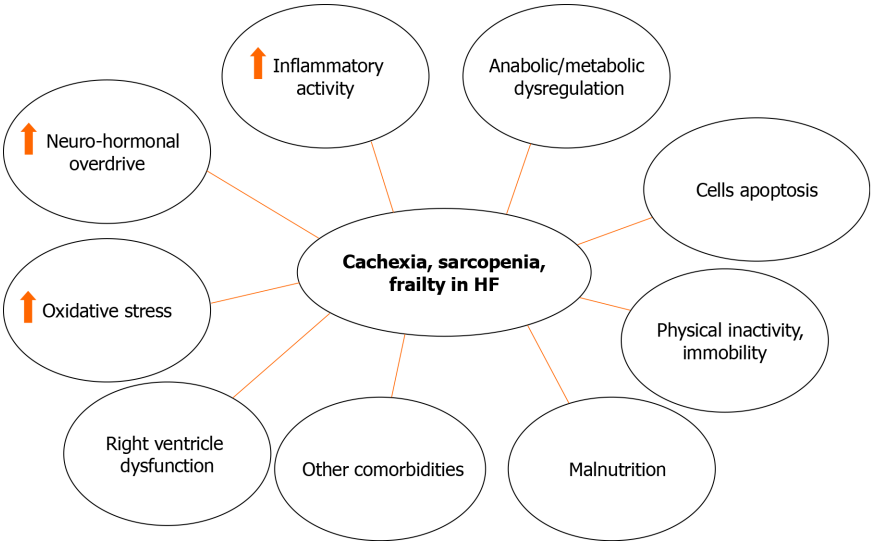

Figure 1 Pathophysiological mechanism and contributing factors leading to cachexia, sarcopenia and frailty in heart failure. HF: Heart failure.

explain the reduction of maximal oxygen consumption demonstrating how physical activity is the major treatment of these patients[57]. Physical exercise program and nutritional supplementation are more effective in individuals with low functional level and increased number of frailty criteria[58]. Growing evidence show a potential benefit from oral supplementation in terms of protein and energy intake in HF patients with the aim to avoid the loss of lean mass[59,60], this personalized dietary intervention results in a potential benefit with significant impact in reducing mortality and hospital readmission. In sarcopenic patients potential treatments may include appetite stimulants and anabolic agents, including testosterone, in combination with the application of nutritional supplements and anti-catabolic interventions, although none is of proven benefit and their safety is unknown[61]. However, scientific data are scarce and the quality of the evidence is low, and no strong recommendations can be currently made in HF setting[62].

In patients with HFrEF and sinus rhythm, b-blockers significantly improve the outcome due its effect on weight gain counterpoising the sympathetic activation that it is an important determinant of cardiac cachexia[63]. Moreover treatment with an angiotensin-converting enzyme (ACE) inhibitor (enalapril) reduces the risk of weight loss in patients with HFrEF[64-66].

CONCLUSION

Cardiac cachexia, sarcopenia and frailty despite overlap in definitions are different clinical entities that frequently coexist in HF patients. All these conditions are serious complications in HF patients and are associated with increasing hospitalization and mortality rates[1]. It is time to produce an important effort to include a routinely assessment in clinical practice of cachexia, sarcopenia and frailty for HF patients that could help in earlier therapeutic decision, personalized care plan, improve outcomes and reduce hospitalization and institutionalization. Strategy aim to increase muscle mass and muscle strength and delay the occurrence of frailty state appear essential in this regard. Common HF drugs therapy (b-blockers, ACE inhibitors) and prescription of physical exercise program remain the cornerstone of therapeutic approach in HF patients with new promising data regarding nutritional supplementation. However, the treatment of all these conditions still remain debated and only a profound knowledge of the specific mechanisms and patterns of disease progression will allow to use the appropriate therapy in a given clinical setting.

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