



Lean Mass Abnormalities in Heart Failure: The Role of Sarcopenia, Sarcopenic Obesity, and Cachexia

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Abstract: The role of body composition in patients with heart failure (HF) has been receiving much attention in the last few years. Particularly, reduced lean mass (LM), the best surrogate for skeletal muscle mass, is independently associated with abnormal cardiorespiratory fitness (CRF) and muscle strength, ultimately leading to reduced quality of life and worse prognosis. While in the past, reduced CRF in patients with HF was thought to result exclusively from cardiac dysfunction leading to reduced cardiac output at peak exercise, current evidence supports the concept that abnormalities in LM may also play a critical role. Abnormalities in the LM body composition compartment are associated with the development of sarcopenia, sarcopenic obesity, and cachexia. Such conditions have been implicated in the pathophysiology and progression of HF. However, identification of such conditions remains challenging, as universal definitions for sarcopenia, sarcopenic obesity, and cachexia are lacking. In this review article, we describe the most common body composition abnormalities related to the LM compartment, including skeletal

Funding: Salvatore Carbone is supported by a Career Development Award [19CDA34660318](#) from the American Heart Association. Danielle Kirkman is supported by a Career Development Award [19CDA34740002](#) from the American Heart Association.

Disclosures: The authors have no conflicts of interest to disclose.

Curr Probl Cardiol 2020;45:100417

0146-2806/\$ – see front matter

<https://doi.org/10.1016/j.cpcardiol.2019.03.006>

and respiratory muscle mass abnormalities, and the consequences of such anomalies on CRF and muscle strength in patients with HF. Finally, we discuss the potential nonpharmacologic therapeutic strategies such as exercise training (ie, aerobic exercise and resistance exercise) and dietary interventions (ie, dietary supplementation and dietary patterns) that have been implemented to target body composition, with a focus on HF. (Curr Probl Cardiol 2020;45:100417.)

Introduction

Individuals with heart failure (HF) have increased by near half million in the last 4 years, currently affecting 6.2 million Americans, with more than 8 million estimated to be diagnosed with HF by 2030.¹ The dramatic increase in the prevalence of the diseases has occurred despite improvements in the understanding of its pathophysiology and the development of pharmacologic and nonpharmacologic therapeutic strategies.² This would suggest that advancements in the pathophysiology of the diseases is highly needed to identify potential novel therapeutic strategies.

The role of body composition in the development and progression of HF has recently received intense scrutiny.^{3,4} In fact, in addition to cardiac dysfunction, which is clearly required for defining HF and a determinant of reduced cardiorespiratory fitness (CRF), patients with HF also present abnormalities in body composition, namely fat mass (FM) and fat-free mass (FFM),⁵ the latter being a surrogate for lean mass (LM), which is in turn the best surrogate for skeletal muscle mass.⁶ The most common conditions associated with abnormalities in LM and skeletal muscle mass are sarcopenia,⁷ sarcopenia obesity,⁸ and cachexia,⁹ (Fig 1)¹⁰ which highly affect CRF, muscle strength, and quality of life (QoL).¹¹⁻¹³

In this critical review article, we describe the definitions for sarcopenia, sarcopenic obesity and cachexia and how those body composition phenotypes affect CRF, QoL, and overall prognosis in patients with HF. Although other body composition phenotypes exist in relation to LM abnormalities (eg, dynapenia, myopenia, sarco-osteopenia, and sarco-osteoporosis),¹⁴ here we focus on sarcopenia, sarcopenic obesity, and cachexia, as such conditions have been recently investigated in HF. We also discuss potential interventions targeting body composition abnormalities, particularly LM, with the goal of improving CRF and muscle strength and, ultimately, clinical outcomes in HF.

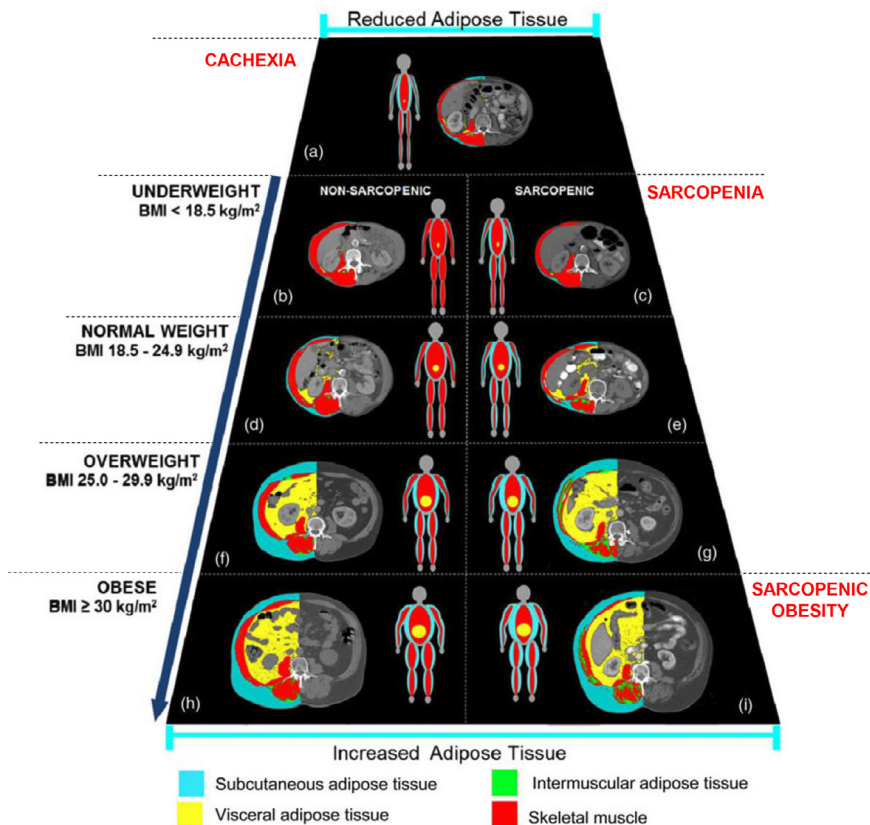


FIG 1. Body composition phenotypes. Individuals with a similar body mass index (BMI) can present with different body composition compartments resulting in different body composition phenotypes. On the left-side, nonsarcopenic individuals, including those with cachexia, are identified. On the right-side, individuals with sarcopenia alone and with sarcopenic obesity. (Modified with permission from Prado CM et al¹⁰) (Color version of figure is available online.)

Sarcopenia and Sarcopenic Obesity

Sarcopenia is defined as the reduction in skeletal muscle mass associated with a reduction in its strength and functionality, paralleled by a preservation of FM.⁷ When sarcopenia is associated with increased adiposity (ie, obesity), it is defined as sarcopenic obesity.⁸ Due to the lack of clear criteria in defining sarcopenia and sarcopenic obesity, as well as the tools used to assess body composition, the prevalence for both conditions in the general population ranges from 5%-20% in adults over 60 years of age and can reach up to 50% in those aged 80 years and older.¹⁵⁻¹⁷

While in the past sarcopenia was exclusively thought to be the progressive loss of LM due to aging (ie, primary sarcopenia), it has now been

Table 1. Criteria for the definition of sarcopenia.

	Probable Sarcopenia	Confirmed Sarcopenia	Confirmed Sarcopenia	Severe Sarcopenia
1) Low muscle strength	✓	✓	✓	✓
2) Low muscle quantity		✓		✓
3) Low physical performance			✓	✓

Modified with permission from Cruz-Jentoft et al.⁷

largely recognized that sarcopenia can also affect younger individuals, as many more factors other than aging seem to contribute to its development (ie, secondary sarcopenia).⁷ In both primary and secondary sarcopenia, 3 major criteria are required for its identification (**Table 1**). Early definitions used in identifying the presence of sarcopenia had suggested that a primary criterion was a reduction in the amount of appendicular LM,¹⁸ as opposed to the most recent definition, which emphasizes a reduction in muscle strength as the most important criteria for identifying sarcopenia.⁷ The cut-offs for the 3 above-listed criteria can vary depending on the different definitions utilized and proposed by several associations and sarcopenia-related working groups. The European Working Group on Sarcopenia in Older People (EWGSOP) recently provided guidance on what they consider the most appropriate cut-offs to define (1) reduced muscle strength; (2) reduced amount or quality of muscle mass; and (3) reduced physical performance,⁷ as summarized in **Table 2**. When criterion 1 is met (ie, reduced muscle strength), sarcopenia is likely present, but not confirmed. When an additional criterion between reduced muscle

Table 2. Cut-offs for sarcopenia criteria.

Test Utilized	Cut-off for Men	Cut-off for Women
Low Muscle Strength		
Handgrip strength	<27 kg	<16 kg
Chair stand	>15 s for 5 rises	
Low muscle quantity		
ALM	<20 kg	<15 kg
ALM index	<7.0 kg/m ²	<6.0 kg/m ²
Low physical performance		
Gait speed	≤0.8 m/s	
SPPB	≤8 points	≤8 points
TUG	≥20 s	≥20 s
400 m walk test	Noncompletion OR ≥ 6 min	Noncompletion OR ≥ 6 min

kg, kilograms; s, seconds; ALM, appendicular lean mass; SPPB, short physical performance battery; TUG, timed-up and go test; min, minutes.

Modified with permission from Cruz-Jentoft et al.⁷

mass and reduced physical performance is present, the diagnosis of sarcopenia is confirmed, which becomes severe when all 3 criteria are met (Table 1). Of note, race-specific cut-offs have also been proposed in the literature, particularly for Caucasians⁷ and Asians,¹⁹ in which the most research on sarcopenia and sarcopenic obesity has been conducted. The EWGSOP has recently proposed an algorithm for the identification of sarcopenia and its related severity, which can be implemented in both clinical and research practice (Fig 2).⁷ The tests included in Figure 2 are further described in the subsequent paragraphs of this review. However, it is also important to indicate that there are other cut-offs to define sarcopenia and for sarcopenia classification proposed by other sarcopenia research communities.²⁰

In addition to sarcopenia, the definition of sarcopenic obesity requires the presence of excess adiposity. Several different cut-offs for FM have been also proposed in the literature to define obesity. The most commonly

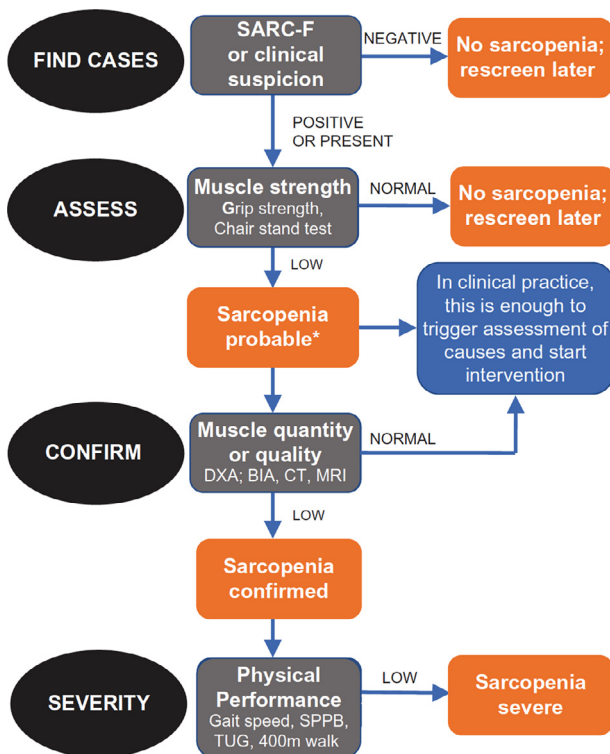


FIG 2. EWGSOP algorithm for identification, diagnosis and severity characterization of sarcopenia. DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging; SPPB, short physical performance battery; TUG, timed-up and go test; *: consider other potential reasons for low muscle strength. (Used with permission from Cruz-Jentoft et al⁷) (Color version of figure is available online.)

used tool to diagnose obesity, however, remains the body mass index (BMI) $\geq 30 \text{ kg/m}^2$.²¹ While an increase in BMI predicts an increase in total FM and/or FFM in healthy individuals^{22,23} maintaining its strong prognostic role in predicting the risk to develop cardiovascular diseases,²⁴ in those with cardiometabolic diseases the mere use of BMI without an assessment of FM or FM distribution (ie, waist circumference, waist-hip ratio) may lead to nutritional status misclassification.²⁵⁻²⁷ For such reasons, when available, an assessment of FM may help identifying those individuals with excess adiposity that may impair health. A FM $\geq 25\%$ in men and $\geq 35\%$ in women has been suggested to be used for defining obesity,^{28,29} however, sex, age, and race/ethnicity-specific cut-off have been proposed in the literature.³⁰ Importantly, sarcopenic obesity may develop following 2 different scenarios: 1 associated with weight gain, with a disproportional increase in FM compared to LM, and 1 associated with weight loss in individuals with obesity and severe obesity in which weight loss and FM loss may be paralleled with a significant amount of LM loss (**Fig 3**).^{8,31}

Cachexia

The terms cachexia and sarcopenia are often used interchangeably in the literature, however, they describe different body composition phenotypes, although they are both characterized by a reduction in LM. Cachexia is a multiorgan syndrome associated with several diseases, particularly cancer, chronic infection, and HF, and is generally defined as unintentional weight loss in the 6-12 months prior its assessment.^{5,32,33} Similar to the limitations in developing a consensus definition for sarcopenia and sarcopenic obesity, a universal characterization of cachexia is lacking. However, the most commonly used definition is a nonoedematous (ie, corrected for fluid retention) unintentional weight loss $\geq 5\%$ - 6% of body weight in the prior 12 months.^{33,34} Contrary to sarcopenia and sarcopenic obesity in which LM loss occurs concurrently with either a preservation of FM or increased FM, respectively, in cachexia it is typical to observe a reduction of FM. Cachexia is often associated with anorexia as well as the progressive worsening of functional capacity. Importantly, while in sarcopenia or sarcopenic obesity, energy expenditure is typically not increased or even reduced, in cachexia, energy expenditure resulting from an accelerated hypermetabolic state is, in fact, increased.^{35,36} Systemic inflammation is also increased, to a much greater degree, in cachexia as compared to sarcopenia and sarcopenic obesity.^{5,35,36}

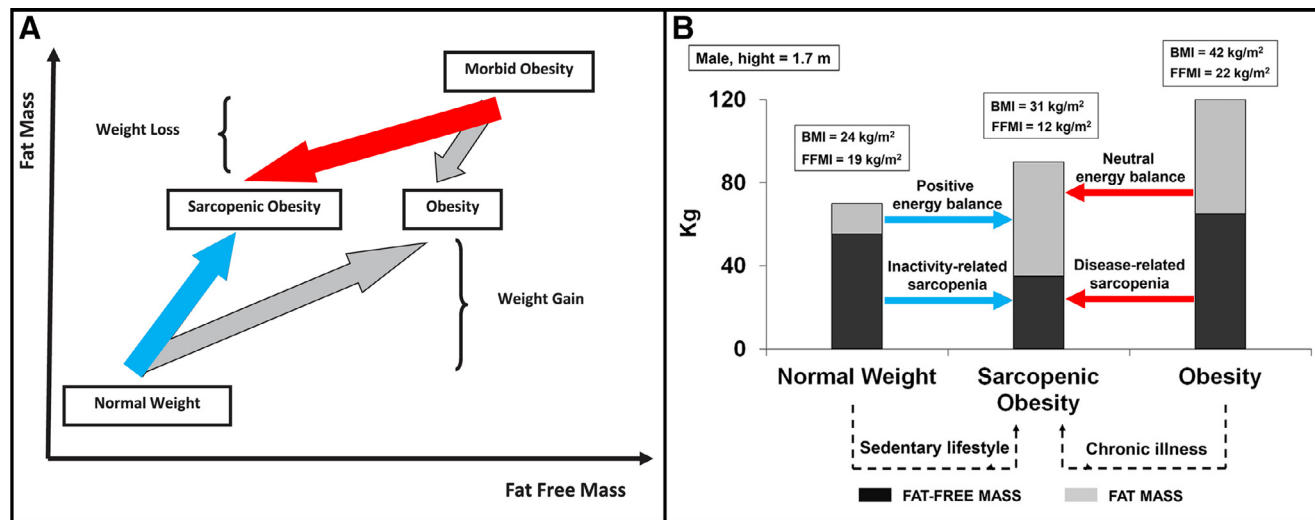


FIG 3. Development of sarcopenic obesity. (A) It proposes 2 theoretical trajectories resulting in sarcopenic obesity: (1) disproportional increase in FM compared to FFM that occurs in an individual with normal BMI (blue arrow) and (2) significant weight loss occurring in individuals with severe or morbid obesity, which may result in a disproportional loss of FFM compared to FM (red arrow). (B) Illustrates 2 proposed and 2 additional metabolic trajectories of sarcopenic obesity: (1) long-term physical inactivity and chronic positive energy balance may lead to excess FM without a concomitant increase or even a reduction in FFM index (FFMI) in normal BMI individuals (blue arrows); and (2) individuals with obesity may present weight loss induced by chronic diseases that contributes to muscle loss and muscle dysfunction and ultimately sarcopenic obesity (red arrows). Fat mass is preserved or only minimally reduced to the maintenance of a neutral energy balance. FM, fat mass; FFM, fat-free mass; BMI, body mass index; FFMI, fat-free mass index. (Modified with permission from Prado CM et al.⁸ and Biolo G et al.³¹) (Color version of figure is available online.)

Sarcopenia, Sarcopenic Obesity and Cachexia, and CRF in HF

In addition to obesity, which is a known independent risk factor for HF as well as one of its most common comorbid condition, muscle wasting (ie, sarcopenia, sarcopenic obesity, and cachexia), is also highly prevalent in HF.^{5,11-13} The clinical syndrome of HF can be divided based on left ventricular ejection fraction (LVEF) in 2 major forms: HF with reduced LVEF (HFrEF, LVEF <50% or <40%, depending on the definition used) and HF with preserved LVEF (HFpEF, LVEF>50%). The 2 conditions differ not only on LVEF, but also on their pathophysiology and related therapeutic strategies. The distinction of HFrEF versus HFpEF is important considering that several pharmacologic strategies proven to be beneficial for CRF and clinical outcomes in HFrEF have failed to result in positive outcomes in HFpEF. While both forms of HF require the presence of cardiac dysfunction (systolic dysfunction for HFrEF, also known as systolic HF, and diastolic dysfunction for HFpEF, also known as diastolic HF), are both characterized by abnormal body composition compartments. This is particularly true in HFpEF, in which abnormalities in body composition have been recently suggested to play an even more pronounced role than cardiac diastolic dysfunction,^{37,38} at least in regard to reduced CRF.³⁹ The significant contribution that abnormal body composition compartments present in HFpEF may, at least in part, explain the numerous therapeutic failures of the last decades in this population, which have primarily targeted cardiac dysfunction alone.³⁹

The body composition abnormalities described above are associated with impaired CRF and muscle strength in HF, likely contributing to poor prognosis. Due to its strong ability in predicting health outcomes, the American Heart Association has defined CRF a vital sign.⁴⁰ The gold standard assessment of CRF is a maximal cardiopulmonary exercise testing (CPX) that utilizes gas-exchange analysis that allows to measure peak oxygen consumption (VO₂).⁴¹ However, in absence of gas-exchange analysis, CRF can be estimated using metabolic equivalents (METs).⁴⁰ The consumption of oxygen in both healthy individuals and in patients with HF relies on different contributors, often described as determinants of CRF.⁴¹⁻⁴³ Apart from the reduced cardiac reserve, reduced CRF in HF can result from 1 or a combination of multiple factors such as reduced pulmonary reserve, vascular dysfunctions, skeletal muscle abnormalities, but also obesity, anemia, and iron deficiency, unhealthy diet and many others, as presented in **Figure 4** and described at length in a recent state-of-the-art review.⁴¹ In regard to sarcopenia, sarcopenic obesity, and

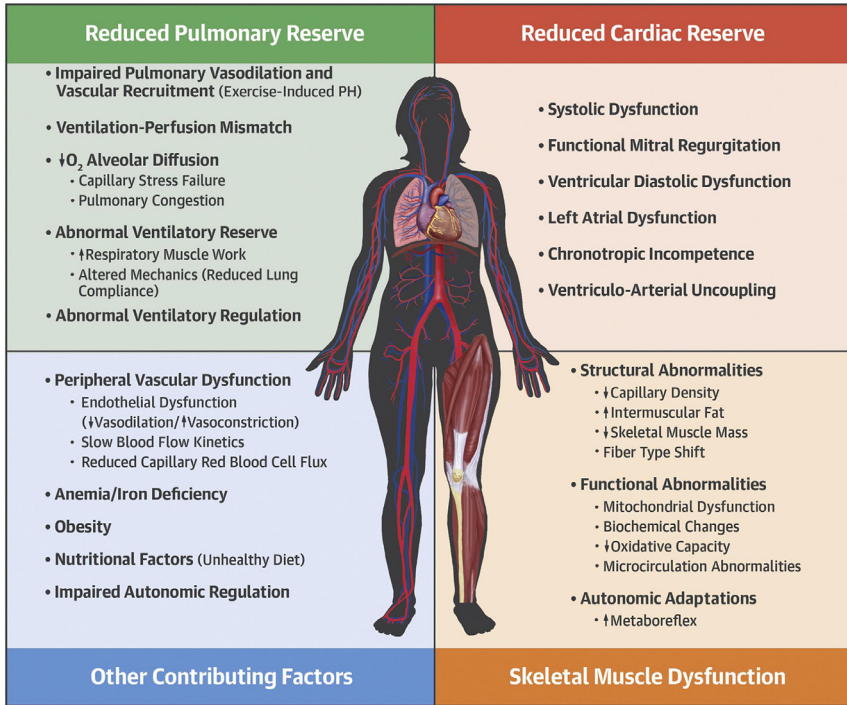


FIG 4. Determinants of exercise intolerance in heart failure. The Figure shows the multiple determinants for reduced CRF in patients with heart failure, which includes abnormalities in respiratory and skeletal muscle amount, quality, composition, and functionality. CRF, cardiorespiratory fitness. (Used with permission from Del Buono MG et al.⁴¹) (Color version of figure is available online.)

cachexia in the setting of HF, such conditions can further contribute to the impairment in CRF,^{4,44} which has been suggested to be, at least in part, independent of cardiac function. The amount of appendicular LM is a major determinant of CRF in both HFrEF⁴⁵ and HFpEF,¹² but also of handgrip strength (HGS) and quadriceps strength.

In an analysis of the SICA-HF (Studies Investigating Comorbidities Aggravating Heart Failure) evaluating 200 individuals with HF (68.8% HFrEF and 31.2% HFpEF), 19.5% of the patients presented muscle wasting,¹³ defined as having an appendicular LM 2 standard deviations below the mean value of a healthy young reference group (18-40 years of age). Muscle wasting was associated with a significantly lower HGS, quadriceps strength and 6-minute walk test (6MWT) distance.¹³ In addition, individuals with muscle wasting presented a lower absolute peak VO_2 and exercise time. Importantly, the abnormalities in exercise capacities (ie, absolute peak VO_2) persisted after adjustments for comorbidities,

age, sex, New York Heart Association (NYHA) class, hemoglobin, LVEF, and the distance of the 6MWT.¹³ This study, however, did not differentiate the effects of sarcopenia versus cachexia, as the definition of muscle wasting only required the presence of reduced LM, which is as mentioned above, characteristic of both conditions.

In a separate analysis of the SICA-HF, the investigators compared the effects of sarcopenia with cachexia in male patients with HF.¹¹ While the definition of sarcopenia remained the same as the previously described analysis,¹³ in this study cachexia was defined as unintentional weight loss of $\geq 6\%$ in the prior 12 months. Importantly, cachexia and/or sarcopenia were present in about 32% of the individuals ($N = 69$).¹¹ Of these, 30 individuals presented sarcopenia alone, 25 cachexia alone, and 14 sarcopenic cachexia, which combined both reduced LM and unintentional weight loss. Interestingly, while both peak VO_2 and quadriceps strength were significantly reduced in sarcopenia and cachexia, the 6MWT, HGS, and QoL questionnaires were only reduced in patients with sarcopenia, as compared to those with cachexia, suggesting that at least in the setting of HF, sarcopenia may be responsible for a more severe impairment of CRF and muscle strength compared to cachexia. As expected, when sarcopenia and cachexia coexisted (ie, sarcopenic cachexia), CRF, muscle strength, and QoL were impaired more so than either condition alone.

It is important to note that the role of sarcopenic obesity was not investigated in these studies. Nevertheless, measures of adiposity such as FM index, have been associated with reduced CRF in HF, particularly in HFpEF,^{46,47} which would suggest that in presence of both sarcopenia and obesity (ie, sarcopenic obesity), CRF may be further reduced (Fig 5).⁴⁸ Further studies to confirm this hypothesis are urgently needed. Taken together, these data suggest the therapies targeting changes in body composition (ie, increased LM, reduced FM) can exert beneficial effects on CRF in patients with HF and concomitant sarcopenia, sarcopenic obesity, and cachexia. Of note, the BMI of the individuals enrolled in the SICA-HF was significantly lower than the typical BMI reported in studies performed in the United States, clearly requiring confirmatory studies comparing the effects of sarcopenia with cachexia in different populations.

Skeletal Muscle Abnormalities and Endothelial Dysfunction in HF

In instances where skeletal muscle oxygen demand is increased, the HF profile is associated with a greater reliance on glycolytic,^{49,50} as opposed to oxidative,⁵¹⁻⁵⁴ pathways to produce energy (ie, ATP). This is

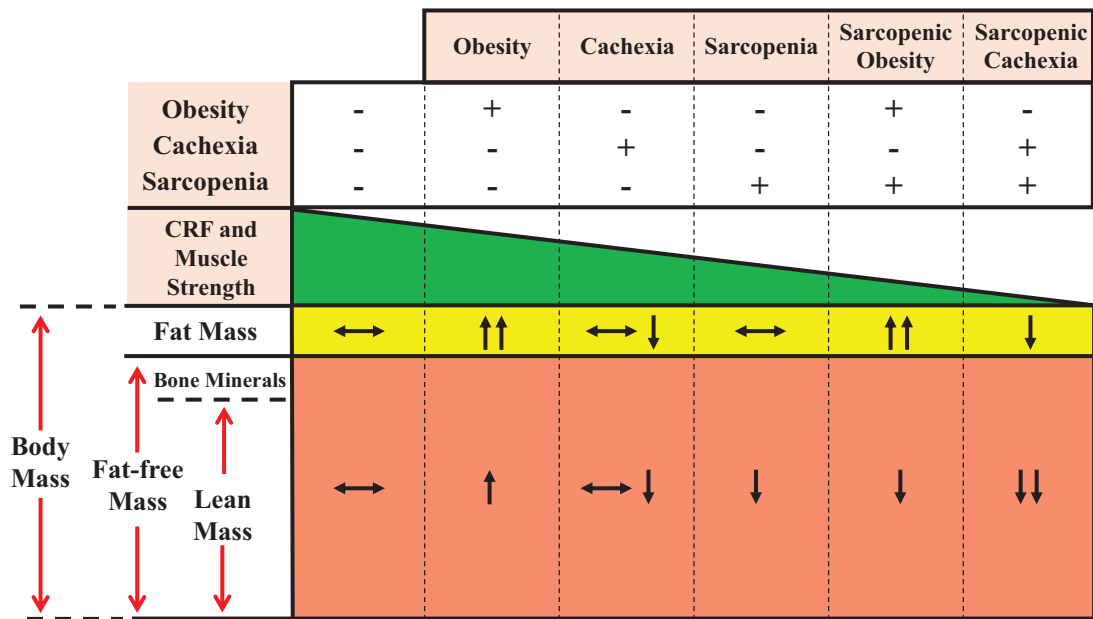


FIG 5. Body composition phenotypes and progressive reduction of cardiorespiratory fitness and muscle strength in heart failure. CRF, cardiorespiratory fitness. (Used with permission from Ventura HO et al.⁴⁸) (Color version of figure is available online.)

evident with increase lactate production at submaximal workloads in HF patients when compared to age matched controls.⁵⁵ This increased glycolytic state during periods of augmented oxygen demand may be driven by numerous factors such as skeletal muscle fiber type shifts or reduced oxygen delivery. The examination of slow, oxidative type I muscle fibers and fast, glycolytic type II muscle fibers in HF patients has revealed substantial reduction in the ratio of type I to type II fibers. It has been revealed that this may result from a decline in type I fibers,⁵⁶⁻⁶⁰ an increase in type II fibers,⁵⁶ and/or a shift from type I to type II fibers.^{59,61,62} The reported downregulation of mitochondrial transcription factor proliferator-activated receptor γ coactivator 1- α ^{53,63} may be a contributor to these substantial shifts in fiber type and subsequent reliance on glycolytic pathways. In addition, considerable reductions in oxygen delivery to the skeletal muscle may modulate this change in fiber type ratio due to the resulting limited oxygen availability. In HF_{rEF} patients, central limitations (ie, reduced cardiac output)⁶⁴ coupled with endothelial dysfunction,⁶⁵⁻⁶⁷ augmented sympathetic vasoconstriction, enhanced heterogeneity of blood flow,^{68,69} and lower capillary density^{56,70} effectively prevent adequate oxygen delivery during instances of increased oxygen demand. In HF_{pEF} patients, oxygen delivery to the skeletal muscle is limited by observed reductions in microvascular vasodilatory capacity^{71,72} and blunted capillary blood flow due to reduced capillary density and diameter, decreases in red blood cell flux into existing capillaries,⁷³⁻⁷⁵ and inadequate perfusion pressure gradient secondary to increased central venous pressures.

Another major issue regarding altered muscle metabolism during instances of increased skeletal muscle oxygen demand is the blunted oxygen kinetics at the onset of activity. Oxygen supply and demand is tightly coupled, and the onset of exercise/activity presents a great challenge to this coupling. Indeed, the speed to which metabolic demand can be met is crucial for reducing skeletal muscle fatigue. Greater fatigue is present when oxygen and thus, blood flow kinetics,⁷⁶ are slowed, as reported in HF patients, and this is thought to be due to greater depletion of high-energy phosphagen stores (ATP/phosphocreatine) and a greater reliance on glycolytic pathways to produce energy. Taken together, the depletion of glycogen and phosphagen stores,⁵⁰ coupled with slower resynthesis of ATP and phosphocreatine stores⁷⁷ and negative changes in pH, can lead to early-onset skeletal muscle fatigue and reduced CRF in HF patients.

Potential contributors to the aforementioned alterations in skeletal muscle function in HF patients are plentiful. Inflammation, oxidative stress, and neurohormonal factors such as angiotensin-II, epinephrine, and norepinephrine can all act individually or in concert when affecting

skeletal muscle function in HF. In addition to the above listed contributors to skeletal muscle maladaptation in HF patients, other factors have also been implicated such as myofilament dysfunction secondary to reduced calcium cycling in skeletal muscle myocytes,^{78,79} capillary rarefaction,⁸⁰ skeletal muscle fibrosis,⁸¹ and greater protein catabolism^{79,82-88} modulated by a disruption in the balance between protein synthesis^{79,82,89-94} and degradation.^{79,83-85,95,96} Therefore, the skeletal muscle maladaptation reported in HF patients results in significant barriers to adequately meeting the oxygen demand of the skeletal muscle resulting in greater fatigability and reduced CRF.

Mitochondrial Dysfunction

Mitochondria dysfunction is central to the dysregulation of myocyte function and viability and is therefore sentinel in the pathogenesis of sarcopenia.⁹⁷ The pathophysiological pathways linking mitochondrial dysfunction and chronic muscle atrophy are highly complex, but ultimately involve an imbalance between fission and fusion that alters cellular signaling, accelerated mitochondrial mediated apoptosis, and impaired autophagy.⁹⁷ Reductions in skeletal muscle mitochondrial density and impairments in mitochondrial morphology, function, and oxidative capacity are consistently reported in HF.⁹⁸⁻¹⁰¹ Chronic adrenergic stimulation that is characteristic of HF is a likely contributor to this aberrant mitochondrial function.^{86,98,99} In this respect, patients treated with beta-blockers or angiotensin-converting enzyme inhibitors appear to confer some degree of skeletal muscle mitochondrial protection.^{54,102,103} Sustained sympathetic activity is linked with excessive mitochondrial, NADPH oxidase, and xanthine oxidase derived reactive oxygen species production that outpaces the endogenous antioxidant capacity,^{90,98,99} further contributing to mitochondrial damage, muscular protein dysfunction, and degradation.^{104,105}

As changes in mitochondrial function occur in parallel with changes in muscle function throughout the spectrum of sarcopenia,¹⁰⁶ it would be expected that mitochondrial dysfunction is implicated in the reduced CRF that is characteristic of HF. Indeed, alterations in mitochondrial morphology, biogenesis, and fission regulation are correlated with maximal and submaximal exercise capacity in both HF_{rEF} and HF_{pEF}.^{59,107} In contrast, other studies suggest that although mitochondrial enzyme activity and oxidative capacity is diminished in HF, the limitations to CRF in this population lie upstream of the mitochondria.^{54,108} Therefore, the role that sarcopenia-related skeletal muscle mitochondrial dysfunction

and bioenergetic failure plays in HF-related exercise intolerance remains equivocal and warrants further investigation.

Independent of muscle function, aberrant skeletal mitochondrial bioenergetics may also contribute to muscle quality in terms of intermuscular fat content. In the presence of increased circulating free fatty acids and triglycerides, incomplete fatty acid oxidation and insulin resistance, an impairment in mitochondrial oxidative capacity could result in substrate overload with subsequent accumulation of lipid intermediates in the muscle.¹⁰⁹ An increased intermuscular fat/skeletal muscle mass ratio, particularly of the thigh, has previously been associated with reduced CRF.¹¹⁰ In support to this association, a reduced intermuscular fat/skeletal muscle mass ratio has been associated with favorable changes in CRF in HFpEF patients.¹¹¹ The mechanisms through which increased intermuscular fat/skeletal muscle mass ratio may impair CRF requires further investigation. It has been suggested that intramuscular fat may shunt blood flow away from the muscle, ultimately reducing skeletal muscle perfusive oxygen delivery.

Respiratory Muscle Abnormalities

Muscle fatigue and dyspnea are 2 major symptoms commonly reported by patients with HF, limiting their normal daily activities.¹¹² Interestingly, the pathophysiology behind these phenotypes is not just limited to peripheral muscular and cardiac dysfunction. Preclinical animal studies and human HF studies have described numerous anomalies in the respiratory muscles that contribute to the observed exacerbated fatigue.^{59,112-116} Histological, structural, biochemical, and functional changes in the diaphragm contribute to reduced respiratory strength and endurance in HF.^{117,118} Notably, the consequences of diaphragm myopathy in this population are not limited to fatigue and dyspnea. Associations between the degree of respiratory muscle weakness and the severity of cardiac dysfunction have been previously described.¹¹⁹ Furthermore, reduced respiratory muscle strength and endurance exacerbate dyspnea and directly contributes to reduced CRF in HF.¹¹⁵

Patients with HF typically experience higher minute ventilation and an increased workload of the respiratory muscles after light exertion resulting in congestion, edema, and lung stiffness.¹¹² Specifically, during exertion, there is an increase in lactic acid from the skeletal muscle that is buffered by bicarbonate, resulting in the synthesis of carbon dioxide and thus, stimulating the brain stem respiratory center.^{112,120,121} In addition,

during physical activity, the pulmonary dead space of patients with HF almost doubles when compared with healthy individuals, increasing the ratio between dead space and tidal volume. This detrimental characteristic is neutralized through an increased workload of the respiratory muscles aggravating the rapid and shallow breathing.¹²²

Multiple studies have shown that, apart from changes in peripheral muscles, patients with HF also exhibit structural changes in respiratory muscles that contribute to exertional fatigue and dyspnea.^{59,113-116} Studies completed in the diaphragm of different animal models with HF have revealed overall atrophy of type I, type IIa, and IIb fibers as well as an increase in the proportion of type I fibers.^{123,124} Similar alterations have been found in diaphragm samples of patients with HF with increases in the proportion of type I fibers and decreased type IIb fibers.¹²⁴ This shift in respiratory muscle fiber type also contributes to a change in metabolism losing more fatigable fibers toward a slower, less fatigue profile with greater oxidative capacity.^{124,125} Although this shift may seem initially an advantage, type I fibers generate lower cross-sectional tension than type IIb fibers compromising the strength ability of the diaphragm.^{125,126} This situation exerts an overwhelming demand to enhance respiratory muscle endurance compromising respiratory muscle load¹²⁷ and predisposing the patient to lung hyperinflation.^{116,128}

In conclusion, respiratory muscles in HF exhibit a different histological phenotype that affects their structure and function and therefore, contributes to their generalized weakness.^{114,116} Importantly, dysfunctions in the inspiratory muscles play a critical role in the response to exertion with an exacerbate fatigue and dyspnea response that directly contributes to exercise intolerance in HF.

Screening and Evaluation of Body Composition Phenotypes

Body Composition Assessment

Magnetic resonance imaging (MRI) and computed tomography (CT) are currently considered the gold standard methods to measure muscle mass and muscle quality.¹²⁹⁻¹³¹ The high resolution and contrast of MRI makes it particularly useful in separation of fat and muscle tissue and provides reproducible and reliable images.¹²⁹ However along with CT, these clinical techniques of assessment are expensive, immobile, require highly trained personnel, and importantly, protocols for analysis are not standardized and cut-offs for low muscle mass are not universally defined.¹²⁹⁻¹³¹ Dual

Energy X-Ray Absorptiometry (DXA) is relatively quick with a minimal exposure of radiation, it is commonly utilized in research, and presents a lower cost than MRI or CT. Importantly body composition assessment with DXA highly correlates with those of MRI and CT.

Current cut-offs for low muscle mass such as those defined by the EWGSOP and the Asian Working Group for Sarcopenia (AWGS) are DXA-based.^{130,132} However, limitations of utilizing DXA exist such as the inability to assess intermuscular fat, which can only be estimated.¹²⁹ Additionally, though DXA is widely available there are inconsistent results among different brands of machinery and it is not easily mobilized.¹²⁹⁻¹³¹ Other methods aimed at assessing muscle mass include bioelectrical impedance analysis (BIA) and ultrasound.¹³⁰ These options are quick, portable, affordable, and easier to operate than MRI, CT, and DXA. BIA is an accepted technique by major consensus statements such as AWGS and EWGSOP and provides an estimate of total or appendicular skeletal muscle mass based on equations, which should be validated in the specific population of use.^{130,133} Estimates from BIA may vary between machines and type of BIA (single-frequency, multifrequency, bioelectrical impedance spectroscopy)¹³⁴ and are affected by subject's hydration.^{130,133} Lastly, ultrasound correlates well with reference methods such as MRI, however, the technique for assessment is not completely standardized and cut-offs for low muscle mass are not well established.¹³⁵

Functional Testing

Performance-based testing provides a functional, as opposed to structural, assessment of skeletal muscle function. These tests can focus on strength development from only 1 muscle group (ie, HGS) or multiple muscle groups employing strength/force development to complete certain tasks similar to what is expected with activities of daily living (short physical performance battery [SPPB]) or tolerance of exercise (ie, CPX), or physical activity (ie, 6MWT).

HGS is often employed alone or in combination with other tests¹³⁶⁻¹³⁸ to determine global reduction in muscle function. Indeed, HGS highly correlates with strength measures obtained from the arm, leg, and trunk.¹³⁹ The HGS method is simple to administer and involves a maximal isometric contraction of the forearms performed multiple times. The ease of the test is also coupled with its appropriateness for patients who are bed-ridden or have severe physical impairment and cannot participate in the SBBP, a peak oxygen uptake test, or the 6MWT. In HF and non-HF populations, HGS has been reported to predict various health

outcomes and mortality.^{137,138,140} Specific to HF patients, HGS is associated with reductions in muscle mass that can substantially lower other functional outcomes (peak VO₂, exercise time, 6MWT, or 4-meter walk test).¹³ In absence of HGS assessment, the chair stand test or the chair rise test can be implemented for an estimate of skeletal leg muscle strength.¹⁴¹⁻¹⁴³ The chair stand test measures the time needed for an individual to rise 5 times from a seated position, while the chair rise test counts the number of times an individual can rise and sit completely in 30 seconds.¹⁴¹⁻¹⁴³

The SPPB provides additional functional assessments that are scored together and involve the evaluation of standing balance, gait speed, and a 5-repetition sit and stand test.¹⁴⁴ In HF patients, the SPPB correlates with peak oxygen uptake values, total and limb-specific LM,¹⁴⁵ as well as with mortality risk.¹⁴⁶ When comparing across HF phenotypes, utilization of the SPPB revealed similar outcomes for both HF_{rEF} and HF_{pEF} patients.¹⁴⁷ The Timed-Up and Go Test (TUG) can also be used to assess physical function.¹⁴⁸ To perform the TUG, individuals are asked to stand up from a chair, walk for 3 meters, turn around, walk back to the chair and sit again.

Cardiopulmonary testing, such as a ramped exercise protocol or 6MWT, are commonly employed in HF patients with reductions in peak oxygen uptake or distance covered, which are considered hallmarks of the HF etiology.^{37,149,150} Although poor performance in these functional tests can be correlated back to skeletal muscle maladaptation in HF patients,^{145,151} these types of tests are reliant on adequate oxygen delivery and therefore can be altered by the numerous factors other than skeletal muscle dysfunction (ie, reduced cardiac output, endothelial dysfunction) associated with HF.

Biomarkers

Currently, there exist no easily identifiable biomarkers for sarcopenia and cachexia due to the complex and multifactorial pathophysiology of these syndromes.¹⁵² Many biomarkers have been suggested in the literature, but ongoing work focuses on identifying biomarkers, which may be the most useful in providing value to clinical assessment of the patient.^{152,153} Current suggestions include biomarkers of systemic inflammation, nutritional status, oxidative stress, endocrine activity, muscle protein turnover, and neuromuscular function.^{153,154}

The BIOMarkers associated with Sarcopenia and PHysical frailty in Elderly pERsons (BIOSPHERE) study is an ongoing case-control,

cross-sectional study, which seeks to address the lack of distinct biomarkers to detect and track clinical progress of sarcopenia and frailty.¹⁵² Approximately half of the 200 subjects currently enrolled meet the criteria for physical frailty and sarcopenia (PF&S) as defined under the Foundation for the National Institute of Health's Sarcopenia and Physical Frailty IN older people: multi-compartment Treatment strategies project¹⁵⁵ and the other half serve as age-matched healthy controls.¹⁵² The first released results from the project show a distinct amino acid profile associated with PF&S: higher levels of asparagine, aspartic acid, citrulline, ethanolamine, glutamic acid, sarcosine, and taurine while patients without PF&S had higher levels of α -aminobutyric acid and methionine.¹⁵⁶ Twelve other candidate biomarkers are being analyzed in BIOSPHERE of which 10 are markers of inflammation (ie, C-reactive protein, tumor necrosis factor- α , and interleukin-6), and the remaining biomarkers are C-Terminal Agrin Fragment (CAF, a marker of neuromuscular junction dysfunction) and Procollagen III N-terminal peptide (P3NP, a marker of muscle remodeling).¹⁵² Importantly, a major barrier to identifying a sarcopenia biomarker remains its specificity as many inflammation markers are not specific to muscle tissue.^{153,157}

An important feature of a candidate biomarker for sarcopenia would be the ability to demonstrate response to treatment. A small randomized controlled exercise training study examined the effects of 6 weeks of resistance training on hypothesized sarcopenia biomarkers CAF and P3NP.¹⁵⁸ At the end of the intervention, individuals in the exercise group showed nonsignificant increases in both P3NP and CAF, along with an increase in muscle strength and quality without an increase in LM. However, only the increase in CAF was deemed to be clinically meaningful.¹⁵⁸ Notably, this increase is paradoxical, as higher CAF is associated with the presence of sarcopenia, including in HF.¹⁵⁹ Nevertheless, in the case of this resistance training intervention, it may reflect positive remodeling to the exercise training stimulus.¹⁵⁸

Questionnaires

A number of scoring tools and questionnaires have been developed for the quick clinical assessment of sarcopenia and cachexia. The SARC-F is one such tool that is composed of 5 questions aimed at muscle strength and functionality and can be easily and quickly used in the clinical setting.¹⁶⁰ However, when compared to sarcopenia criteria provided by the International Working Group on Sarcopenia, EWGSOP, and AWGS, the SARC-F was found to have high specificity, but poor sensitivity.¹⁶⁰ Notably, no questions regarding muscle mass are included within this tool as

muscle mass is not easily assessed in the extremely short time that the SARC-F was designed to be implemented.¹⁶⁰ To address this gap, calf circumference has been added as a surrogate of muscle mass.¹⁶¹ This tool, termed the SARC-calF, is able to greatly improve the sensitivity of the original test with EWGSOP, International Working Group on Sarcopenia, AWGS, and FINH criteria.¹⁶²

Another quick clinical assessment, the Mini Sarcopenia Risk Assessment (MSRA), asks 7 questions related to dietary intake, age, weight history, physical, and hospitalization based on existing literature regarding sarcopenia risk factors.¹⁶³ In a recent study comparing the MSRA and SARC-F using AWGS criteria, the SARC-F was found to have superior specificity for sarcopenia while the MSRA had superior sensitivity.¹⁶⁴ Currently, neither the MSRA nor the SARC-F has been validated in the HF population.

Alternatively, the Mini Nutritional Assessment Short Form (MNA-SF) is a 6-question tool developed for a rapid clinical assessment of nutrition status in elderly populations.¹⁶⁵ Though not developed specifically for cachexia or sarcopenia, an analysis of the SICA-HF examined the use of the MNA-SF in a cohort of 130 HFREF subjects.¹⁶⁶ This analysis defined muscle wasting as an appendicular skeletal muscle mass 2 standard deviations below the mean of a healthy reference group 18-40 years old and found that a MNA-SF cutoff value of 12.5 demonstrated good sensitivity, but lacked specificity.¹⁶⁶ Lastly, the Sar-QoL is a 22-question QoL questionnaire specific to individuals with sarcopenia, recently validated also in English.¹⁶⁷ It also has not yet been evaluated in a HF population.¹⁶⁸

Current Treatments and Future Directions

Aerobic Exercise Training

Exercise has proven to be a highly beneficial adjunct therapy for improving skeletal muscle function and exercise capacity in HF patients. As aerobic exercise is a powerful stimulus for cardiovascular adaptations, it is the more frequently prescribed modality of exercise in this patient population. Although aerobic activity is not deemed the most effective mode of exercise to elicit an anabolic response, it may still infer benefits for sarcopenia via mechanisms that prevent skeletal muscle catabolism. In human subject trials of HF, favorable structural, metabolic, hormonal, antioxidant, and anti-inflammatory adaptations that are local to skeletal muscle have been observed following chronic aerobic exercise interventions.¹⁶⁹ Specifically, high intensity aerobic interventions have been

shown to increase types I and II fiber cross-sectional area, in addition to a predominant shift from glycolytic to oxidative fiber types.^{170,171} These exercise-related structural changes in cross-sectional area and fiber type have been accompanied by increased capillary densities and capillary/fiber ratios, thus augmenting oxygen and nutrient delivery.^{171,172} With regards to sarcopenia-related pathways, aerobic exercise has been shown to block ubiquitin protease system activation by attenuating the expression of the E3-ligase muscle ring factor-1, thus preventing down-stream protein degradation.¹⁷³ Additionally, in patients with HF, aerobic exercise induces an increase in expression and sensitivity of the hypertrophic regulator, insulin-like growth factor-1.¹⁷⁴

In respect to the inflammatory and oxidative stress contributors to sarcopenia, local decreases in cytokine and inducible nitric oxide synthase expression have been observed following training, thus providing evidence for an enhanced anti-inflammatory environment within the muscle.¹⁷⁵ Evidence of the antioxidant effects of aerobic training appear to be predominantly mediated by increases in enzymatic antioxidants superoxide dismutase, catalase, and glutathione peroxidase.^{176,177} Finally, while exercise related improvements in skeletal mitochondrial structure,¹⁷⁰ density,¹⁷¹ and oxidative capacity¹⁷⁸ have previously been reported the effects of aerobic exercise on mitochondrial bioenergetics and apoptosis are relatively unexplored in the HF population.

Despite these positive effects on markers of skeletal muscle hypertrophy, the effect of aerobic exercise on muscle quantity and quality assessed via recommended endpoints of nutritional status¹⁷⁹ in sarcopenic HF are yet to be fully elucidated and warrant investigation in future studies.

Resistance Exercise Training

The main principles of exercise programs specifically designed for patients with HF rely on training peripheral muscles effectively without producing great cardiovascular stress. Traditionally, aerobic training has been the modality of choice given its ability to increase exercise capacity.¹⁸⁰⁻¹⁸² Although endurance training is able to partially counteract the histochemical and metabolic abnormalities observed in skeletal muscle,^{170,178} improvements in muscle strength and endurance can mostly be achieved after specific resistant training.¹⁸³ Remarkably, muscle mass is directly associated with exercise capacity,^{45,184} emphasizing the role that resistance exercise may contribute to improving CRF in HF.¹⁸⁵

Similar to any other chronic condition, prescribing physical activity to a patient with HF should involve extra caution in order to minimize any

potential harmful event. Despite multiple positive evidences,¹⁸⁶⁻¹⁹² resistance exercise and especially isometric or static exercise have not been routinely prescribed to patients with HF due to the potential detrimental effect on cardiovascular response.¹⁹³⁻¹⁹⁵ Increasing evidences indicate that this modality of physical activity is safe and well-tolerated in this population without major complications.^{186,189,190,196-198} Indeed, the aforementioned studies have evaluated the preexisting concerns with left ventricular remodeling,^{182,199} discarding any safety concern from a cardiovascular perspective.^{189,197}

A scientific statement from the American Heart Association endorses resistance training as part of the health and fitness suggestions for people with cardiovascular disease.²⁰⁰ However, the majority of these recommendations are not specifically derived from patients with HF. As a result, most of specific HF recommendations are based on different systematic reviews and meta-analysis that have evaluated the role of resistance training on patients with HF.^{183,201,202} Accordingly, there is a general consensus that resistance training is safe for patients with HF classified as NYHA classes I-III with a clinically stable presentation for at least 2 months.^{187,190,203} Although specific contraindications have not been reported, a debate still exists surrounding the prescription of resistance exercise for patients classified as NYHA IV.¹⁸³

Positive results have been observed in multiple trials using resistance training designed with different length (8-12 weeks), frequency (1-3 days per week), and intensity (40%-80% of 1 repetition maximum).^{186,187,190,203-208} Improvements in maximal strength are the most characteristic benefit described in most of the trials with improvements ranging from 15%²⁰⁷ to 43%¹⁹⁰ of maximal strength. Such changes are frequently accompanied by greater muscle endurance ranging from 18%²⁰³ to even 299%.¹⁹⁰ Notably, these studies have also described improvements in exercise capacity up to 19% of peak VO₂ in just 8 weeks of training.²⁰⁸ Resistance training programs in HF can also improve skeletal muscle metabolism,²⁰⁹ muscle fiber composition¹⁹⁰ and can enhance blood flow and vascular function.^{186,206,210} Taken together, resistance exercise represents an important tool to improve exercise tolerance and overall, health status in patients with HF.

Current recommendations to design an appropriate exercise program for HF primarily depend on the overall health status of the participant. As in any other chronic disease, a training session for the patient with a good overall condition is significantly different from any physical activity plan for those individuals awaiting heart transplantation with very low cardiac reserve. Although several studies have completed resistance exercise programs in patients with a fragile health state,^{196,211,212} emerging evidence

suggests to exclude them from engaging in resistance training programs.¹⁸³ For the rest of the patients with HF (NYHA classes I-III), a resistance training session should require strength exercises using dynamic movements with machines, small free weights, or elastic bands.²⁰¹

Patients with an overall good health condition (NYHA class I) can engage in whole body resistance exercises^{186,190,206,207,210} while those with greater limitations (NYHA classes II-III) should complete unilateral muscular training.^{187,192,203} In addition, current recommendations suggest dividing the session into short phases, including a small number of repetitions^{183,213,214} and short duration (20-30 minutes per session). Designing a program that applies the principles of interval training will allow patients with HF to train at a higher power output with lower left ventricular stress and reduced hemodynamic requirements.²¹⁵ In terms of intensity, recommendations range from 40% to 60% of an individual's 1-repetition maximum and a perceived exertion from "fairly light" (rating of 11 Borg scale) to "somewhat hard" (rating of 13 Borg scale).^{198,203,207,210,212,216} However, it is important to note that multiple studies have used higher intensities that have been well-tolerated among the participants.^{186-188,190,203,207} Finally, current recommendations suggest completing resistance training 2 times per week if combined with aerobic exercise or 3 times per week if it is the sole exercise modality utilized.¹⁸³

Increasing evidence indicates that resistance training in combination with aerobic exercise represents a beneficial approach to counteract the negative peripheral side effects commonly observed in patients with HF.^{203-205,208,211} Certainly, the combination of strength and endurance programs results in greater improvements in exercise capacity than either modality alone.^{203,205,206,210} Considering the critical clinical value that VO₂ has in predicting QoL within this population, combining both modalities of exercise may represent an important tool to enhance prognosis and survival in HF.²¹⁷

Dietary Supplementation

Among suggested dietary supplementation therapies for sarcopenia and cachexia, protein, amino acids and their metabolites remain the key nutrients of interest. It is commonly accepted that older adults have higher dietary protein requirements to help counteract a reduced response to anabolic stimuli, which often leads to a loss of muscle mass and function over time.²¹⁸ Additionally, a recent scientific statement from the Heart Failure Society of America (HFSA) recommended a goal protein

intake of at least 1.1 grams of protein per kilogram of body weight per day for HF patients with identified cachexia or malnutrition.²¹⁹ However, while most trials include older adults with reduced muscle mass or strength, criteria for entry is highly variable as are the dosing of protein or amino acids assigned.

Some of the earlier protein and amino acid supplementation strategies were specifically evaluated in HF populations. One study examined the effect of 8 grams of essential amino acids (EAA) for 2 months in 38 stable HFREF patients with adequate protein-energy intake.²²⁰ Subjects were enrolled based on the severe depletion of muscle mass defined by arm muscle area measured by triceps skinfold thickness and mid-arm muscle circumference.²²⁰ Following the randomization to either the EAA supplement or no supplement, a 7-day food records and a nitrogen balance test was used to assess dietary intake. Subjects also performed a 6MWT and cycle-ergometer-based CPX to assess CRF.²²⁰ After 2 months, individuals in the EAA group showed a better CRF by improvements in both their peak VO_2 and peak work during CPX, as well as distance covered during the 6MWT.²²⁰ No improvements were observed in the control group.

Another study examined the effects of a 6-week high calorie, high protein oral nutrition supplement in subjects with HFREF versus a low-calorie, protein-free placebo supplement.²²¹ The intervention supplement supplied 600 calories and 20 grams of protein daily, while the texture and taste matched placebo supplied only 12 calories.²²¹ Enrolled subjects were screened for cardiac cachexia defined as edema-free weight loss $>7.5\%$ over a period of at least 6 months.²²¹ Subjects underwent body composition measured by DXA, a 6MWT as well as a treadmill CPX to assess peak VO_2 at baseline, 6 weeks and 18 weeks.²²¹ Of note, dietary intake was not measured.²²¹ After 6 weeks of daily supplementation, individuals significantly increased their total mass (ie, body weight), FM, and LM. Interestingly, at 18 weeks, weight was maintained and only FM remained significantly elevated.²²¹ Distance covered during the 6MWT was significantly greater at 6 weeks and trended toward an increase at 18 weeks, however, peak VO_2 was not increased at either timepoint.²²¹

More recently, a study of 66 subjects with HF were randomly assigned to either resistance exercise or resistance exercise with 10 grams of BCAA for 3 months.²²² Resistance exercise was performed for 1 hour twice per week in a supervised setting.²²² Subjects underwent body composition with BIA, treadmill stress tests, HGS with dynamometer and anthropometric measurement of waist, hip, and arm at both baseline and 12 weeks.²²² Subjects also underwent standardized nutritional counseling and evaluation with 24-hour dietary recall at baseline and 12 weeks with

a research dietitian.²²² After 3 months, between group differences were not observed, with the exception of a lower hip circumference in the BCAA group.²²² Both groups of subjects increased HGS, but neither had changes in CRF nor FM and LM.²²² Notably, there were no criteria of reduced muscle mass, strength, or weight loss to be enrolled in this trial.²²² It is plausible that the participants were not in a depleted state at baseline and therefore, would not have benefitted from additional BCAAs. Additionally, in the aging population, maintaining an adequate protein intake alone may not be sufficient to protect against a loss of muscle mass. Recently, an analysis of a longitudinal cohort of 1561 individuals aged 70-79 followed over a 6-year span, showed that higher protein intake was not associated with protection against thigh muscle loss measured by CT scan at baseline and 6-year timepoints. This was the case even for those consuming above 1.2 grams per kilogram body weight of protein per day, which is greater than the HFSA's recent recommendation for protein intake.^{219,223} Overall, more evidence is needed to identify the ideal dosing of protein supplementation in HF patients with both sarcopenia or cachexia. There is perhaps a greater protein need in sarcopenic patients who have a reduced HGS and peak VO_2 compared to cachectic patients.²²⁴ Further work is also warranted on protein supplementation in HFpEF patients as the presented work has mostly focused on HFrEF.

Recently, trials have utilized other supplements with theorized effects on muscle within protein supplements. Beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of the amino acid leucine, has been shown to increase muscle mass gain in older adults.²²⁵ Vitamin D has also been shown to have effects to skeletal muscle, most notably muscle strength and higher serum levels may enhance ability to gain muscle mass.^{226,227} A double-blind, placebo controlled, randomized trial looked at the effects of supplementing a high protein oral nutrition supplement with both HMB and Vitamin D twice daily during admission and for 90 days post discharge in 652 elderly (>65) HF patients.²²⁸ The patients were classified as malnourished by the Subjective Global Assessment (SGA) upon admission, but were not screened for sarcopenia or cachexia and body composition was not performed.²²⁸ Though the primary endpoint was not met (a composite of readmission and mortality at 90 days), a significantly reduced risk of mortality and improved odds of better nutrition status as measured by the SGA were observed at 90 days compared to placebo.²²⁸

Notably, a multicenter, double-blind, randomized placebo controlled trial with an interventional nutrition supplement containing both vitamin D and HMB was supplemented for 24 weeks in free living individuals.²²⁹ The 330 elderly subjects enrolled were classified as sarcopenic based on

EWGSOP guidelines and malnourished by SGA, but did not have HF.²²⁹ The interventional and placebo supplements were isocaloric, each providing 330 calories.²²⁹ The interventional oral nutritional supplements contained 20 grams protein, HMB and 499 international units vitamin D while placebo had 14 grams of protein, no HMB and 147 IU vitamin D.²²⁹ Peak torque leg strength, HGS by dynamometer, gait speed, body composition by DXA and 3-day food diaries were performed at baseline, 12 and 24 weeks.²²⁹ At 24 weeks, subjects in both groups demonstrated improved leg and HGS, gait speed as well as improved muscle quality with no statistical difference between groups.²²⁹ Sarcopenia was staged and those with mild-moderate sarcopenia had a greater improvement on the interventional oral nutritional supplements in respect to HGS and leg strength than those with severe sarcopenia, possibly due to better blood flow and nutrient delivery to the muscle.²²⁹ Subjects in both groups demonstrated increases from baseline in body weight and FM with no observed differences between groups.²²⁹ Another double-blind, placebo controlled randomized trial examined the effect of a once daily oral nutrition supplement with 112 calories, 22 grams of protein, and 100 IU Vitamin D versus an isocaloric maltodextrin supplement in 130 sarcopenic elderly subjects admitted to a physical rehabilitation center.²³⁰ As the patients were admitted, they consumed a standardized diet and their dietary intake was measured for 3 days at the beginning and end of the study period.²³⁰ At the end of the 12 week period, subjects receiving the intervention supplement increased their FFM, skeletal muscle mass, MNA-SF score, HGS, insulin-like growth factor-1 and decreased their C-reactive protein in comparison to those receiving the isocaloric maltodextrin supplement.²³⁰ Importantly, the effects of vitamin D and HMB individually versus protein are not clearly elucidated in the aforementioned trials, as the placebo supplements either provide a different amount of these supplemental nutrients (Vitamin D and HMB) than the interventional supplements⁽²²⁹⁾ or does not include them at all.^{228,230} Furthermore, when both interventional and placebo supplements contained significant amounts of protein, differences between groups were reduced, suggesting that protein quantity may have been the major driving factor for the observed improvements within the trials.²²⁹ Of note, while vitamin D supplementation has been considered an appealing strategy in HF, in a randomized-controlled trial of 400 patients with advanced HF, 3 years of daily supplementation with 400 IU, did not result in reduced mortality.²³¹ Moreover, vitamin D supplementation was associated with a greater need for mechanical circulatory support implants, questioning the safety of vitamin D in this population.²³¹

Other supplements of interest in the treatment of cachexia and sarcopenia in HF include the use of creatine, nitrates, and omega-3 polyunsaturated fatty acids (N-3 PUFA). HF subjects demonstrate reduced skeletal muscle creatine and thus supplementation has been studied for its effects on CRF and muscle strength.²³² In a randomized, double-blind, placebo-controlled, crossover trial of 20 subjects with HFrEF, supplementation of 4 × 5 grams of creatine daily for 6 weeks increased body weight and muscle strength versus placebo.²³² Post intervention however, the patients reverted to baseline and weight gain was postulated to be an effect of fluid retention secondary to creatine use, an important consideration in HF patients.²³² There were no effects on CRF measured by peak VO₂ or distance covered in the 6MWT.²³² This was reflected by a later trial that showed no effect of 5 grams creatine per day for 6 months in an HFrEF cohort on 6MWT or peak VO₂.²³³ Notably, neither trial screened for sarcopenia or cachexia at baseline nor assessed body composition and therefore effect on these specific individuals is not known.^{232,233}

Inorganic nitrates are converted to nitric oxide, a potent vasodilator, which has been hypothesized to improve CRF in HF. While initial finding suggested that inorganic nitrates would be beneficial on CRF in HFpEF patients,²³⁴ in a larger randomized controlled trial of 105 individuals with HFpEF, inorganic nitrate administered by inhaler 3 times daily versus placebo did not improve peak VO₂.²³⁵ Similarly, inorganic nitrates failed to improve CRF in HFrEF patients.²³⁶ N-3 PUFA can increase FM and decrease inflammatory markers such as tumor-necrosis factor α and Interleukin-1 in advanced HF population.²³⁷ In a small randomized controlled trial in 31 patients with HFrEF, a 3-month intervention with a supplement combining N-3 PUFA and dipeptide L-alanyl-L-glutamine was associated with increased LM measured with DXA, and a favorable trend toward an increase in peak VO₂ compared to placebo.²³⁸ No differences between groups were observed in 6MWT distance, HGS, isolated arm, and leg muscle function and echocardiography measures at follow-up.²³⁸ Further work is clearly warranted in creatine, N-3 PUFA, and nitrates to establish their effects on muscle mass and strength in HF patients with confirmed sarcopenia or cachexia.

Dietary Patterns

Currently, no evidence exists to show that a change in dietary pattern can reverse loss of muscle mass and strength. The HFSA supports the adoption of a Mediterranean dietary pattern (MedDiet) or Dietary Approaches to Stop Hypertension diet as reasonable for those with HF or

at risk of developing HF, but also underlined a need for greater evidence.²¹⁹ For the prevention of sarcopenia, the MedDiet has accrued more evidence than any other dietary pattern.²³⁹⁻²⁴³ The MedDiet is recognized as the traditional dietary pattern of countries surrounding the Mediterranean Sea, rich in fruit, vegetables, whole grains, nuts, fish, and extra-virgin olive oil (EVOO), with moderate intake of poultry, dairy, and red wine and low intake of refined sugar and red meat.²⁴⁴ The MedDiet was first recognized as being protective against the development of cardiovascular disease,²⁴⁵ which accruing evidence such as the landmark *Prevencción con Dieta Mediterránea (PREDIMED)* trial has continued to support.^{246,247} Mixed results currently exist on the ability of the MedDiet to reduce risk of developing HF,²⁴⁸⁻²⁵⁰ but recent work has shown that higher adherence to the MedDiet reduces hospital readmissions for HF.^{251,252} The preventative benefits of the MedDiet are likely synergistic as it is a nutrient-rich dietary pattern, but a particularly important role may be played by its enrichment in unsaturated fatty acids (UFA) originating from dietary sources, such as EVOO, nuts, and fatty fish.²⁵³

Inflammation is a shared characteristic of HF and sarcopenia²⁵⁴ and an early analysis of the PREDIMED trial demonstrated that supplementation of nuts and EVOO in the context of a MedDiet resulted in a reduction in inflammatory markers over the control low-fat diet.²⁵⁵ In a cross-sectional analysis of subjects with HFpEF, a greater consumption with UFA was associated with an enhanced peak VO_2 , while sugars consumption was inversely correlated.²⁵⁶ Additionally, in this analysis, greater consumption of UFA was correlated with more favorable body composition including greater FFM/FM ratio and overall FFM.²⁵⁶ Of note, we have recently completed the UFA-Preserved pilot study aimed at increasing UFA intake in a population with obesity and HFpEF, showing that dietary UFA supplementation is feasible and has the potential to improve CRF in this population.²⁶¹

In contrast to the MedDiet, the Western dietary pattern is characterized by high saturated fatty acid and refined sugar content and increased markers of systemic inflammation.²⁵⁷ In an analysis of 757 British subjects over 85 years of age, those who consumed adequate protein in the context of a traditional British diet (defined as being rich in potatoes, butter, gravy and red meat) demonstrated increased risk for sarcopenia (as defined by EWGSOP criteria) at both baseline and after 3 years of follow up compared to those consuming adequate protein with a low butter consumption.²⁵⁸ In an additional cross-sectional analysis of 300 subjects over 55 years of age, those who adhered to a more MedDiet pattern had a reduced risk of sarcopenia, defined by EWGSOP criteria, while contrary

to the previously discussed study,²⁵⁸ following a Western dietary pattern was not associated with an increased risk for sarcopenia.²³⁹

Further work is needed to define the role of the pro-inflammatory Western diet in the development and progression of sarcopenia as well as the preventative mechanisms behind the MedDiet and whether a dietary pattern intervention can improve strength and quantity of muscle mass. There is also a need for evaluation of other healthy dietary patterns such as the Dietary Approaches to Stop Hypertension, which has been recently associated with a favorable trend in reducing hospitalizations in patients with an event of acute decompensated HF,²⁵⁹ and nutrient quality scoring systems such as the Alternate Healthy Eating Index on risk reduction for sarcopenia and cachexia.

Combination of Dietary Intervention and Exercise Training

The role of a combined intervention with both exercise training and dietary intervention has been rarely investigated in HF. To date, the available data related to combined exercise and dietary interventions rely on a single randomized controlled trial in patients with obesity and HFpEF.¹¹¹ In this study, 100 patients were randomized to either 20 weeks of exercise (ie, aerobic exercise), diet (ie, caloric restriction), exercise and diet, or to a control, with 92 individuals completing the trial. The exercise training regimen included a 3 times per week 1-hour supervised aerobic exercise session, at a walking intensity which varied based on the individual CRF measured at baseline and progressively increased based on tolerability and heart rate reserve. The dietary intervention included a caloric restriction of about 400 kcal/day in the caloric restriction alone, and 350 kcal/day in the combined caloric restriction and exercise, with 1.2 g of protein per kg of ideal body weight, 25%-30% of total daily calories from fat, and the remaining kcal from carbohydrates. A daily calcium supplement (600 mg) was provided and a food diary monitored weekly to verify adherence to the dietary intervention. Importantly, the meals were prepared under supervision of a dietitian and provided to the participants by the investigators.¹¹¹

At the end of the study, both caloric restriction and exercise resulted in improved peak VO_2 , which was further improved with the combined intervention compared to the control group. The coprimary endpoint measured with the Minnesota Living with HF Questionnaire to assess changes in QoL was not improved in any of the interventional groups. For exploratory purposes, other assessments of QoL such as the Kansas City Cardiomyopathy Questionnaire, were shown to improve with the dietary intervention, but not with the exercise intervention.¹¹¹ Importantly, neither exercise or caloric restriction were associated with major clinically

relevant improvements in cardiac function, aside from a small, although statistically significant reduction in LV mass (-4 g) by MRI, reduction in LV relative wall thickness assessed by echocardiography and an increase in E/A velocity ratio ($+0.10$) with caloric restriction. In fact, changes in peak VO_2 were for the most part associated with changes in body composition compartments and markers of systemic inflammation. However, after multiple regression analysis, only sex and total body mass remained as independent predictors for the changes in CRF (ie, peak VO_2).¹¹¹

The study has shown that caloric restriction and/or aerobic exercise training are efficacious strategies to improve CRF in obesity and HFpEF, however, caloric restriction is typically associated with a reduction of FM and concomitant LM,²⁶⁰ which in the long-term could result in an increased risk for sarcopenia and sarcopenic obesity, especially when such intervention are implemented in older adults. For such reasons, the investigators of the trial described above are currently testing the hypothesis that adding resistance training to caloric restriction and aerobic exercise may result in a further improvement in CRF by preserving and perhaps even increasing LM (NCT02636439).

Conclusion

Abnormalities in body composition compartments, particularly of LM, leading to the development of sarcopenia, sarcopenic obesity and cachexia, are highly prevalent in patients with HF. However, universal definitions for such conditions are desperately needed to identify the exact prevalence in the general population and particularly in patients with HF, in which such conditions are associated with impaired CRF and reduced muscle strength, further contributing to the poor prognosis of the disease.

Nonpharmacologic therapeutic strategies targeting changes in body composition (ie, exercise and nutritional strategies), with and without improvements in cardiac function may, therefore, exert beneficial effects. Such interventions have the potential to improve CRF in HF, particularly in HFpEF. Larger randomized controlled trials testing the effects of these interventions individually or combined on clinical outcomes in patients with sarcopenia, sarcopenic obesity and cachexia are required.

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The role of body composition in patients with heart failure has been the focus of attention in the past few years

Salvatore Carbone et al et al performed a very extensive and clinically oriented review of several aspects body composition and implementation of therapies in patients with heart failure

Several inferences can be delineated from this excellent review

First, abnormalities in body composition compartments, specially of LM, leading to the development of sarcopenia, sarcopenic obesity and cachexia, are highly prevalent in patients with heart failure

Second, definition of this abnormalities in body composition are needed to identify, first the exact prevalence in the general population and particularly in patients with heart failure

Third, clearly these abnormalities of lean mass are associated with abnormal cardiorespiratory fitness and muscle strength contributing to the poor prognosis of patients with heart failure.

Nutritional strategies as well as exercise programs may exert clinical benefits, specially in patients with heart failure and preserved systolic function.

Radomized controlled trials testing the effects of these interventions on clinical outcomes in patients with sarcopenia, sarcopenic obesity and cachexia in patients are needed.

I want to congratulate the authors for a very nice review of the clinically important subject.
