Chapter

Exercise Therapy for Patients with Heart Failure: Focusing on the Pathophysiology of Skeletal Muscle

Nobuo Morotomi, Kunihiro Sakuma and Kotomi Sakai

Abstract

In patients with heart failure (HF), it is important to perform exercise therapy with a focus on the pathophysiology of skeletal muscle. Patients with HF have multiple clinical symptoms due to cardiac dysfunction. Recent studies demonstrated the mechanism and treatment strategy for HF, and multiple signaling pathways involved in HF result in reduced exercise capacity and skeletal muscle mass. On the other hand, exercise therapy for HF is known to inhibit the inflammatory cytokines and neurohumoral factors, and increase muscle mass. Therefore, in this chapter, we discuss the importance of exercise therapy for HF, with a focus on the pathophysiology of skeletal muscle.

Keywords: heart failure, skeletal muscle, muscle abnormality, exercise training, combination therapy

1. Introduction

1.1 Pathology of HF

HF is a condition characterized by cardiac decompensation due to organic or functional impaired pumping capacity. Reduced exercise capacity in patients with HF leads to numerous symptoms such as breath shortness, dyspnea, general fatigue, and edema in the foot [1]. One of the causes of reduced exercise capacity is the condition of HF. According to the JCS 2017/JHFS 2017 guidelines on the diagnosis and treatment of acute and chronic HF [1], HF is categorized into three groups by the left ventricular ejection fraction (LVEF). One is HF with LVEF <40%, termed heart failure with reduced ejection fraction (HFrEF). HFrEF develops due to left ventricular systolic dysfunction. HFrEF is a leading cause of ischemic heart disease and coronary sclerosis. Another group is HF with LVEF ≥50%, termed heart failure with preserved ejection fraction (HFpEF). HFpEF is known as diastolic dysfunction in HF. Diastolic dysfunction is mainly caused by hypertension. The last group is HR with LVEF from 40–49%, termed heart failure with mid-range ejection fraction (HFmrEF). HFmrEF can develop in the recovery process from HFrEF, but many other factors can cause HFmrEF. For example, arrhythmia with tachycardia, such

as atrial fibrillation, places strain on the left heart and causes HFmrEF. The exact mechanism of HFmrEF remains unclear.

Reduced exercise capacity in patients with HF can also cause organic and functional abnormality of skeletal muscle not only due to abnormal LVEF. Patients with HF can lose weight due to these abnormalities of skeletal muscle. A previous study reported that weight loss of 7.5% over six months was an independent predictor of long-term mortality in patients with HF [2]. In addition to the condition of HR and its related skeletal muscle abnormalities, reduced exercise capacity develops slowly with age. On the other hand, in 1998, Rosenberg proposed the term "sarcopenia" to describe age-related muscle decrease. Elderly patients with HF are included in "secondary sarcopenia" and advanced HF patients are defined as having "cardiac cachexia". The Asian definition of sarcopenia was established by the Asian Working Group for Sarcopenia in 2014 [3]. Sarcopenia is diagnosed by a low muscle mass and low muscle strength or low physical performance. Sarcopenia develops due to aging, undernutrition, sedentary lifestyle, and progression of inflammatory diseases, cancer, and chronic diseases such as HF and COPD. The reported prevalence of sarcopenia is between 4.1% and 11.5% in Asian older people. On the other hand, in 2013, Fülster reported a prevalence of 19.4% among 200 ambulatory patients with stable chronic HF in Germany [4].

The exact mechanism of the development of sarcopenia related to HF is unclear. However, previous studies noted specific changes in skeletal muscle in patients with HF. Kinugawa et al. reported that patients with HF have skeletal muscle abnormalities, including energy dysbolisms, fiber transformation from type 1 (*slow*-twitch muscle fibers) to type 2 (*fast*-twitch muscle fibers), and mitochondrial dysfunction [5]. Brown et al. demonstrated decreases in mitochondrial density, gene expression, and oxygenated capacity in skeletal muscle in patients with HF [6]. Using animal studies, Takada et al. found that chronic *heart failure (*CHF) model mice have a low level of protein expression of phosphorylated AMPKα, sirtuin-1, PGC-1, and mitochondrial transcription factor A (Tfam) in skeletal muscle [7].

In this review, we describe the molecular mechanisms in skeletal muscle and the treatment for HF.

2. Molecular mechanisms of HF

This section presents three representative skeletal muscle mechanisms unique to HF that cause organic and functional physical abnormalities.

2.1 Inflammatory cytokines

Inflammatory cytokines are biologically active substances that exert a variety of functions by signaling through specific receptors on the cell surface. Inflammatory cytokines include interleukin (IL)-6, interferon, tumor necrotic factor (TNF) family, and colony-stimulating factor. The excess secretion of inflammatory cytokines due to HF disrupts the anabolic catabolic balance of skeletal muscle in HF patients. Impaired cardiac cell and vascular endothelial cells with high stress result in the secretion of inflammatory cytokines and myocardial infarction. Levine et al. reported that HF patients have a high circulating concentration of TNF-α [8].

In 2001, Reid et al. reported that secretion of TNF-α increased the production of reactive oxygen species through the mitochondrial electron transport system, resulting in the activated ubiquitin-proteasome system through the NF-κB signaling pathway [9]. This study suggested progressive skeletal muscle wasting through these systems in HF patients. In addition, Chojkier et al. reported that

TNF-α-injected mice had increased expression of nitric oxide synthase activity and the expression of their albumin synthesis genes was downregulated [10]. Schaap et al. reported that *high* expression of TNF-α and IL-6 led to a reduction of the quadriceps muscle area and grip strength in older people [11]. Langhaus et al. reported that the secretion of TNF-α induced appetite loss [12]. Saitoh et al. found that appetite loss caused malnutrition and resulted in the inhibition of protein anabolic action. Moreover, appetite loss was associated with a poor prognosis in HF patients in their study [13]. On the other hand, Hollriegel et al. reported that HF patients did not have high expression of atrogin-1 mRNA or protein in skeletal muscle [14]. Of note, there are few studies on this topic in human subjects [15]. Although TNF-α and IL-6 activity affect muscle abnormalities in HF patients, it remains unclear how inflammatory cytokine families influence each other in humans.

2.2 Renin–angiotensin–aldosterone system

The accelerated renin-angiotensin-aldosterone (RAA) system leads to skeletal muscle dysfunction in HF patients. Angiotensinogen is produced from the liver and is the first substrate of the RAA system. Thereafter, renin from the juxtaglomerular apparatus of the kidney is released into the blood. Angiotensin I is produced from angiotensinogen by activated renin. Then, angiotensin II is produced from angiotensin I by angiotensin-converting enzyme. Angiotensin II causes vasoconstriction and stimulates aldosterone secretion through *angiotensin* II *type 1 receptor.* Angiotensin II causes an accumulation of fibrosis in skeletal muscle through transforming growth factor-β (TGF-β)-dependent signaling [16]. Activation of the RAA system in HF patients causes the overproduction of angiotensin II. Their RAA system is activated regardless of the severity of HF [17]. This study also revealed that their renin activity is significantly higher than that in those without HF (3.0 ± 3.7 and 1.2 ± 1.2 ng/mL). In 2007, Cohn et al. investigated the effects of TGF-β neutralizing antibodies and angiotensin-receptor blockers (ARB) on skeletal muscle function. In this study, the intervention group using ARB had significantly reduced TGF-β signaling through angiotensin II and improved skeletal muscle function [18]. TGF-β is also known as a factor that elicits apoptosis of muscle satellite cells during the process of repairing damaged skeletal muscles. The author suggested that inhibition of the angiotensin II type1 receptor by ARB led to the low expression of TGF-β.

Fukushima et al. demonstrated that the phosphorylation of Akt (p-Akt) decreased in skeletal muscle from mice with HF after myocardial infarction and this decrease was caused by an increase in plasma angiotensin II [19]. Another study using HF model mice found that angiotensin II directly induced skeletal muscle abnormalities [20]. This study reported a significant decrease in the amount of p-Akt protein in angiotensin II-treated mice. In addition, angiotensin II induced fiber transformation from type I to type II, skeletal muscle atrophy, and weight loss. Based on these involved factors, the RAA system is considered to elicit skeletal muscle dysfunction in HF. In the future, studies on increased protein catabolism by the RAA system need to be conducted in humans.

2.3 Autophagy

Autophagy is an intracellular system that delivers cytoplasmic substrates to lysosomes for subsequent degradation and removal. Autophagy is divided into three types depending on the mechanisms; macroautophagy, microautophagy, and chaperone-mediated autophagy. The research area of macroautophagy is the most advanced of these three types. Fasting induces the autophagy system and

the isolation membrane is formed. The isolation membrane elongates, engulfing protein aggregates and organelles within the cytoplasm, and finally forms double-membraned structures called autophagosomes. Autophagosomes subsequently fuse with lysosomes to degrade their cargo by lysosomal enzymes.

Autophagy influences the muscle abnormalities in HF. There are two mechanisms. First, a maladaptive response for autophagy exacerbates the condition of HF, resulting in reduced muscle function. For example, the decrease in Beclin 1 expression weakens the macroautophagy system in patients with ischemic cardiac myopathy [21]. In contrast, Zhu et al. reported that pressure overload in mice markedly increased cardiac autophagy and load-induced autophagic activity remained significantly high for at least 3 weeks [22]. This study reported that Beclin 1 overexpression increased autophagic activity and promoted pathological remodeling. Using mice with pressure-overload heart failure, this study revealed that lysosome abundance calculated by measuring the lysosomal markers LAMP-1 and cathepsin D increased in wild-type hearts and to a greater extent in Beclin 1 transgenic hearts. Another study demonstrated that cardiac-specific deficiency of autophagy-related 5, a protein required for autophagy, leads to cardiac hypertrophy in adult mice [23]. Therefore, HF is exacerbated by dysfunctional autophagy and results in skeletal muscle abnormality.

Second, cardiac autophagy may directly cause skeletal muscle atrophy regardless of the progression of HF. Janning et al. investigated the autophagy pathway using myocardial infarction model mice [24]. Their study revealed that although myoatrophy in the soleus muscle and plantaris muscle progressed, the expression levels of autophagic markers, such as GABARAPL-1 and AtG7, increased in the plantaris but not in the soleus muscle. This study provides evidence of autophagy signaling regulation in HF-induced muscle atrophy. In addition, the selective degradation of mitochondria is termed mitophagy. Oka et al. reported that cardiac cells are abundant in mitochondria and dysfunctional mitophagy leads to reduced cardiac function through the inflammation inside the cells [25]. It is also possible that mitophagy causes skeletal abnormalities.

There is increasing evidence supporting a role of autophagy in age-related disease states of the cardiovascular system. Sasaki et al. reviewed autophagy in cardiovascular disease [26]. Their report states that autophagy is related to age-associated cardiovascular diseases, HF, ischemic heart disease, cardiomyopathy, hypertension, and atherosclerosis. However, the mechanisms of skeletal muscle dysfunction caused by autophagy in HF remain unclear.

3. Exercise training as treatment for HF

Exercise training improved the reduced exercise capacity and skeletal muscle power due to HF in several studies. There are two types of exercise; aerobic exercise and resistance training (RT). Aerobic exercise induced peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) expression and improved insulin resistance [27]. High-intensity aerobic exercise increases the ratio of type 1 muscle fibers. Gielen et al. investigated how the expression of cathepsin-L, E3 ligases MuRF-1, and MaFbx changed after exercise training among HF patients, and compared them with healthy subjects [28]. As a result, the expression of MuRF-1 in HF patients was significantly higher than that in healthy subjects. In addition, after four weeks of exercise training, the expression of MuRF-1 mRNA in HF patients was reduced by 32.8% and 37.0% in people aged ≤55 years and ≥ 65 years, respectively. In another study, they investigated the expression of inflammatory cytokines (TNF-α, IL-6, and IL-1-β) before and after exercise training in HF patients [29].

Exercise training did not affect the serum levels of TNF-α, IL-6, or IL-1-β, but it significantly reduced the expression levels of these cytokines and iNOS (by 52%) in skeletal muscle. Thus, exercise training may reduce the expression of inflammatory cytokines and maintain high-level muscle function.

St-Jean-Pelletier et al. investigated myofiber changes and mitochondrial density in the vastus lateralis in healthy subjects [30]. They found an increased ratio of type 2a myofibers and decreased mitochondrial density in people aged ≥65 years with low physical activity. Campos et al. investigated the effects of exercise training on mitochondrial dysfunction using myocardial infarction model mice [31]. This study suggested that the improvement in mitochondrial number, density, and oxygenation by exercise training aid in recovery from cardiac dysfunction. Although exercise training improved mitochondrial dysfunction in HF mice model, the exact mechanism in HF patients remains to be elucidated.

Aerobic exercise increases the exercise capacity, and RT improves skeletal muscle mass and strength. Pu et al. demonstrated the effects of resistance training on muscle function in HF patients [32]. In their study, the improvement of knee extensor muscle power was 43% higher and the six-minute walking distance was 49 m greater in HF patients than those in the control group. Another study also found that RT improved skeletal muscle mass and power more than aerobic exercise in dialysis patients [33]. Multimodal exercise programs, including aerobic exercise, RT, and respiratory muscle training, were reported to significantly improve dyspnea and the quality of life, in addition to quadriceps power and exercise time, in HF patients [34].

Saitoh et al. suggested that combination therapy of exercise training with standard drugs, such as angiotensin-converting enzyme inhibitors, beta-receptor blockers, ghrelin agonists, and myostatin inhibitors, is better than exercise training and nutritional supplements for treating cardiac sarcopenia [35]. The following section explains the possibility of treatment for HF using combinations of exercise training and other therapies (**Figure 1**).

3.1 Combination of nutritional supplements and exercise training

3.1.1 Amino acids and micronutrients

Sufficient nutritional supplements improve skeletal muscle dysfunction accompanying HF. Aquilani et al. investigated the effects of exercise training with 8 g of daily essential amino acids (EAA) in 21 HF patients [36]. Based on the cardiopulmonary exercise test, the EAA group had no change in oxygen consumption but increased their exercise load. Although there was no significant change in the 6-minute walking distance in the control group, the EAA group increased their walked distance by 74 m on average. Rozentryt et al. reported that the intake of nutritional supplements with a high-calorie (600 kcal) and high-protein (20 g) diet increased the body weight by 2.0 kg at the 6-week follow-up and 2.3 kg at the 18-week follow-up [37]. In this study, oral nutritional supplementation did not affect the albumin concentration or peak oxygen consumption, but reduced the serum level of TNF-α.

β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of the amino acid leucine and has a positive effect on muscle protein anabolism. A study using rats reported that HMB supplementation resulted in greater expression of Akt, mTOR, and S6K1 than leucine [38]. Berk et al. investigated the effects of a mixture of HMB, glutamine, and arginine in advanced cancer patients. However, there were no significant differences in the 8-week lean body mass between the placebo and the HMB/Arg/Gln groups [39]. Another study examining chronic pulmonary patients

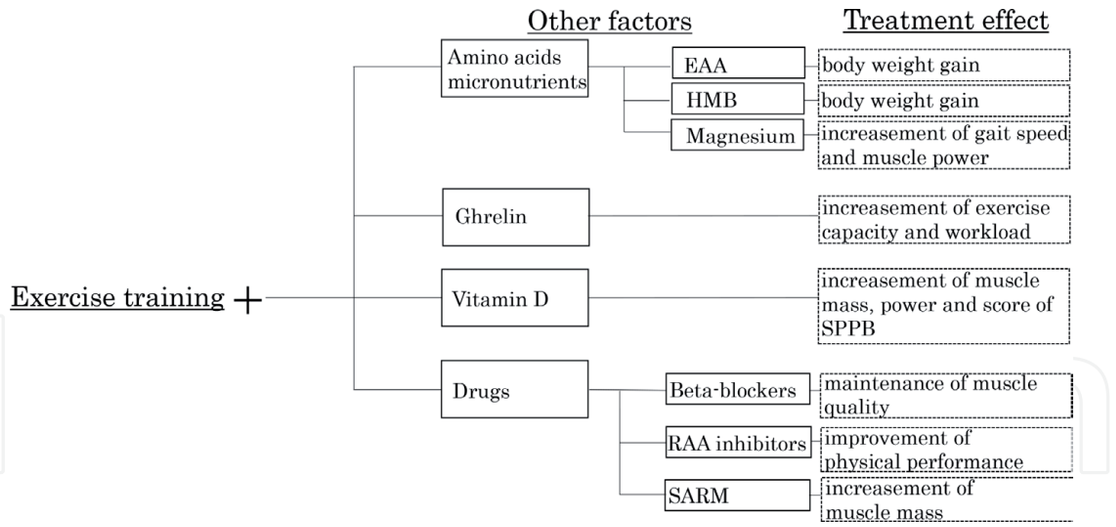

Figure 1.
It is thepossibility of treatment for HF using combinations of exercise training and other therapies. This figure presents the effects of exercise training added by other factors. The square box shows the other factors and the dotted box shows treatment effect. EAA: essential amino acids, HMB: β-Hydroxy-β-methylbutyrate, SPPB: short physical performance battery, RAA inhibitors: Renin-angiotensin-aldosterone inhibitors, SARM: selective androgen receptor modulators.

described that, in the group receiving pulmonary rehabilitation plus an oral nutritional supplement enriched with HMB, the mean and maximum handgrip and fat free mass significantly increased at 12 weeks [40]. The review of HMB supplementation in humans suggested that this agent has positive effects in patients with chronic pulmonary disease, hip fracture, and AIDS- related and cancer-related cachexia [41], but HF was not mentioned. However, a recent study suggested that a high-protein oral nutritional supplement containing HMB increased the body weight at day 30 in HF patients [42]. As described above, protein supplementation for HF patients increases the body mass and improves muscle function.

In recent years, the role of microelements has gained attention. Magnesium insufficiency increase the risk of HF. Sasiwarang et al. examined the relationship between the onset of HF and magnesium concentration in healthy subjects for 15 years [43]. Serum magnesium was inversely related to the risk of incident of HF. Moreover, HF patients with hypomagnesemia had high levels of IL-6 and von Willebrand factor (VWF). VWF is a marker for endothelial dysfunction and the serum level of VWF in HF patients is high. The author suggested that the magnesium concentration influences the inflammatory reaction. Microelements also play an important role in the treatment of sarcopenia [44]. Magnesium supplementation was reported to possibly improve the functional indices such as quadriceps torque [45]. In addition, the walking speed of healthy elderly women in the magnesium supplementation group became significantly faster than that of those in the control group (the supplementation group:Δ 0.21 ± 0.27 m/s, the control group Δ 0.14 ± 0.003). However, there are no studies on the effects of combination therapy of exercise training and magnesium supplementation in HF patients. As magnesium is commonly used for the treatment of arrhythmia and HF, it may be useful for the treatment of muscle dysfunction in HF.

3.1.2 Ghrelin

Ghrelin can improve the physical function of patients with HF. Ghrelin is produced in the fundic gland of the stomach, and stimulates *gastric* acid secretion and *motility.* Ghrelin has anabolic, orexigenic, and anti-inflammatory effects [46]. Ghrelin levels are lower in older people, especially in those with sarcopenia [47].

A study on anamorelin, a selective ghrelin receptor agonist, demonstrated a significant effect on body weight and food intake, but not on muscle strength in patients with cancer cachexia [48]. Nagaya et al. reported that the injection of synthesized ghrelin (2 μg/kg twice a day for 3 weeks) to HF patients increased the LVEF without adverse events, and increased the peak workload and oxygen consumption during exercise [49]. On the other hand, rikkunshito, a Japanese herbal medicine, is a ghrelin potentiator. Fujitsuka et al. reviewed the promotion of ghrelin activity by rikkunshito [50]. Several clinical trials demonstrated that the administration of rikkunshito increased the plasma ghrelin levels. These studies support the potential use of rikkunshito for improving skeletal muscle function and exercise capacity. However, rikkunshito and dipotassium glycyrrhizinate are structural components of licorice extract. The accumulation of dipotassium glycyrrhizinate in the body may cause pseudo aldosteronism and exacerbate the condition of HF. Thus, rikkunshito should be administered carefully. The satisfactory amount of rikkunshito should be investigated to manage HF effectively and safely.

3.1.3 Vitamin D

Vitamin D administration improves the exercise capacity in HF patients. The role of vitamin D is to maintain homeostatic function of the calcium-phosphorus balance and regulate bone metabolism. In recent years, vitamin D was confirmed to play an essential role in skeletal muscle function. Vitamin D deficiency or mutated vitamin D receptor causes skeletal muscle atrophy [51]. Vitamin D receptors are involved in gene expression in skeletal muscle, and regulate muscle anabolism and metabolism. The receptors act on calcium channels and directly regulate muscle contraction. Therefore, vitamin D deficiency results in lipid accumulation in skeletal muscle and atrophy of type 2 myofibers. Hayakawa et al. reported that the administration of 1α25 (OH)2D3 to human muscle cells inhibited the gene expression of MaFbx and MuRF-1 [52]. Antoniak et al. examined the effects of combination therapy of vitamin D administration and exercise training in comparison with exercise training and vitamin D alone [53]. They found that *lower extremity muscle power* increased more in the combination therapy group than in the exercise training alone group. In addition, the score of the short physical performance battery, skeletal muscle power, and femur density increased more in the combination therapy group than in the vitamin D alone group.

On the other hand, a meta-analysis demonstrated that vitamin D administration reduced the levels of TNF-α, CRP, and thyroid hormone, but did not improve exercise performance [54]. Bauer et al. reported the effects of combination therapy using vitamin D and leucine-enriched whey protein on physical function in older people with sarcopenia [55]. The active group (n = 184) received vitamin D at 800 IU, 20 g of whey protein, and 9 g of leucine twice a day for 13 weeks. In the active group, the score for the chair-stand test (1.0 second on average) and muscle mass (0.19 kg on average) significantly improved when compared with the control group. Other several studies using healthy elderly subjects reported the improvement of physical functions using a combination of vitamin D and amino acids, but not in HF patients.

3.2 Combination with standard therapeutics for HF

Standard therapeutics for HF can improve the skeletal function in HF patients. This section explains the three types of medicines for HF that may be useful for skeletal muscle.

3.2.1 Beta-blockers

Beta-blockers can prevent weight loss in HF patients. Beta-blockers, which have inhibitory action against left ventricular remodeling, are used for the treatment of HF and hypertension. Bisoprolol is a beta one-selective blocker and carvedilol is an alpha-beta blocker, and they are commonly used in the treatment of HF.

Beta-blockers were recently reported to inhibit muscle atrophy. A study using cancer cachexia model mice revealed that the administration of bisoprolol inhibited the loss of skeletal muscle mass [56]. This study also reported that bisoprolol improved physical activity and oral intake. In patients with rectal cancer or small cell carcinoma, the administration of espindolol twice a day improved their life prognosis and weight loss [57].

Clark et al. investigated the effects of the administration of carvedilol on body weight loss in patients with HF [58]. Carvedilol was initially administered at 3.1 mg (twice a day) and later increased to a maximum of 25 mg per dose (twice a day). As a result, the administration of carvedilol resulted in body weight gain (1 kg on average) after one year.

Based on these studies, beta-blockers may maintain skeletal muscle quality and improve skeletal muscle mass in HF patients.

3.2.2 Renin-angiotensin-aldosterone (RAA) inhibitors: angiotensin converting enzyme inhibitors (ACEI)/angiotensin-receptor blockers (ARB)

RAA inhibitors can improve muscle function in HF patients. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are commonly used for the treatment of hypertension. Saitoh et al. reported the protective action of ACEI for muscle function [59]. Several studies reported that ACEI prevent body weight loss due to HF, and improved muscle power and physical functions [60, 61]. Sumukadas et al. investigated the effects of a combination of ACEI therapy and exercise training on physical functions in older people [62]. However, the 6-minute walk distance, score of the Short Physical Performance Battery, handgrip and quadriceps strength, and QOL at 10-week and 20-week follow-up did not improve in the intervention group. In this study, some bias was considered to have caused the insufficient effects of combination therapy.

RAA inhibitors have direct positive effects on muscle function in HF patients. Thus, high-quality studies examining both RAA inhibitors and exercise training in HF patients are warranted.

3.2.3 Selective androgen receptor modulators (SARM)

Testosterone may have a positive effect on skeletal muscle mass. On the other hand, serious side effects, such as increased risks of developing prostate cancer and myocardial infarction, have been reported [63]. Therefore, selective androgen receptor repair agents known as selective androgen receptor modulators (SARM) were developed. They exert testosterone-induced muscle mass gain effects with less stimulation of the prostate. SARM may increase skeletal muscle mass in HF patients. The clinical trial SARMsMK-0773 examined their effects on skeletal muscle in female patients with sarcopenia [64]. Muscle mass in the intervention group increased significantly compared with that in the placebo group, but no effects on physical functions or muscle power were observed in this study.

No studies have investigated the effects of combination therapy of SARM and exercise training on skeletal muscle mass and physical function in HF patients.

4. Conclusions

The pathophysiology of skeletal muscle in patients with HF is complex and remains unclear. However, recent studies clarified several points. The mechanisms do not function independently and instead interact with each other. In the management of HF, it is important to assess skeletal muscle and physical functions, and to consider treatment combinations including exercise training, electrical stimulation, medicine, and supplements. Large-scale, high-quality studies are warranted to elucidate the pathophysiology and establish effective treatments for HF patients.

Conflict of interest

I do not have any conflict of interest.

Author details

Nobuo Morotomi[1*], Kunihiro Sakuma[2] and Kotomi Sakai[3]

1 Department of Rehabilitation medicine, Shin-Yurigaoka General Hospital, Kawasaki, Kanagawa, Japan

2 Institute for Liberal Arts, Environment and Society, Tokyo Institute of Technology, Tokyo, Japan

3 Setagaya Memorial Hospital, Department of Rehabilitation Medicine, Tokyo, Japan

*Address all correspondence to: uoratubon@gmail.com

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