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Exercise training for patients with heart failure and preserved ejection fraction. 
A narrative review

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Abstract

Heart failure with preserved ejection fraction (HfPEF) remains a significant global health challenge, accounting for up to 50% of all heart failure cases and predominantly affecting the elderly and women. Despite advancements in therapeutic strategies, HfPEF’s complexity poses substantial challenges in management, particularly due to its high comorbidity burden, including renal failure, atrial fibrillation, and obesity, among others. These comorbidities not only complicate the pathophysiology of HfPEF but also exacerbate its symptoms, necessitating a personalized approach to treatment focused on comorbidity management and symptom alleviation. In heart failure with reduced ejection fraction, exercise training (ET) was effective in improving exercise tolerance, quality of life, and reducing hospitalizations. However, the efficacy of ET in HfPEF patients remains less understood, with limited studies showing mixed results. Exercise intolerance is a key symptom in HfPEF patients, and it has a multifactorial origin since both central and peripheral oxygen mechanisms of transport and utilization are often compromised. Recent evidence underscores the potential of supervised ET in enhancing exercise tolerance and quality of life among HfPEF patients; however, the literature remains sparse and predominantly consists of small-scale studies. This review highlights the critical role of exercise intolerance in HfPEF and synthesizes current knowledge on the benefits of ET. It also calls for a deeper understanding and further research into exercise-based interventions and their underlying mechanisms, emphasizing the need for larger, well-designed studies to evaluate the effectiveness of ET in improving outcomes for HfPEF patients.

Key words: heart failure with preserved ejection fraction, sarcopenia, exercise training, exercise tolerance.

Introduction

Despite significant advances in therapeutic strategies, heart failure (HF) persists as a leading cause of morbidity and mortality globally, affecting approximately 2% of the population in Western countries [1]. Heart failure with preserved ejection fraction (HfPEF) is characterized by typical HF signs and symptoms, normal left ventricular (LV) systolic function, and elevated LV filling pressure at rest or during exertion. HfPEF constitutes up to 50% of all HF clinical presentations and predominates among elderly and female demographics [2]. From a clinical perspective, HfPEF represents a complex and challenging condition, as underscored by the ongoing evolution of its diagnostic criteria [3]. Given its high prevalence among older
individuals, HFrEF frequently coexists with chronic comorbidities such as renal failure, atrial fibrillation, arterial hypertension, obesity, diabetes, chronic obstructive pulmonary disease (COPD), and sarcopenia [4,5]. These comorbidities not only contribute to the pathophysiology of HFrEF but also play a role in the onset of symptoms reported by patients. Consequently, HFrEF is marked by significant heterogeneity in pathophysiological mechanisms and clinical manifestations, necessitating a personalized treatment approach that prioritizes comorbidity management and symptom relief. The treatment of HFrEF remains a challenge, as there is a paucity of evidence supporting the effectiveness of pharmacological and non-pharmacological interventions in reducing mortality risk for these patients. Therefore, current treatment goals are centred on symptom relief, functional status improvement, and hospitalization risk reduction [6]. Exercise training (ET) is a well-established non-pharmacological intervention for patients with heart failure with reduced ejection fraction (HFrEF) and is a cornerstone of cardiac rehabilitation programs worldwide [7]. In HFrEF, ET improves symptoms, exercise tolerance, quality of life (QOL), and cardiac function. Through these improvements, ET has led to significant reductions in all-cause and cardiovascular hospitalization rates and, albeit less conclusively, it seems to positively influence all-cause mortality [8]. Conversely, the role of ET in patients with HFrEF remains unclear due to limited literature, predominantly characterized by small-scale studies with short follow-up periods. In this narrative review, we aim to synthesize current evidence supporting the utilization of ET in patients with HFrEF. The review is divided into two main sections: the first explores the mechanisms underlying exercise intolerance in HFrEF and describes the skeletal muscle (SM) pathological changes observed in these patients; the second part evaluates the benefits of exercise in HFrEF, comparing different exercise modalities.

**Exercise intolerance in patients with heart failure with preserved ejection fraction**

Exercise intolerance is a prominent symptom among all HF patients and is the primary driver of morbidity and reduced quality of life in this population [9]. In patients with HFrEF, aerobic exercise capacity, as measured by peak oxygen consumption at peak exercise (VO₂ peak) during cardiopulmonary testing, has been estimated to be 34-50% lower compared to healthy age-matched subjects [10,11]. This reduction in VO₂ peak is similar to that observed in patients with HFrEF [12]. The etiology of exercise intolerance in HFrEF is multifactorial, with defects identified at multiple stages of the O₂ pathway, where both central and peripheral mechanisms frequently coexist [13-15]. Pavley et al. [16] assessed several hemodynamic variables related to exercise tolerance and identified reduced chronotropic reserve and abnormal increase in pulmonary capillary wedge pressure as having the
strongest association with reduced VO2 peak. The underlying mechanisms for impaired chronotropic responsiveness in HfPEF is multifactorial. A diminished heart rate (HR) response to increasing plasma isoproterenol concentrations, indicating decreased sinus node β-adrenoceptor responsiveness, has been reported in these patients [17]. Alternatively, it has been proposed that a subset of HfPEF patients, due to their limited capacity for incremental exercise, may not achieve an adequate level of sinus node β-adrenoceptor stimulation; in this case chronotropic incompetence would be secondary to premature cessation of exercise for other reasons [18]. The pronounced increase in pulmonary capillary wedge pressure, inherent to the definition of HfPEF; it relates to the decreased left ventricular compliance and leads to an upstream increase in left atrial pressure. This, in turn, affects pulmonary circulation, resulting in lung capillaries stress failure, arterial system remodeling, and, ultimately, pulmonary hypertension. Alterations in the pulmonary vascular bed compromise alveolar O2 diffusion and lead to a ventilation-perfusion mismatch, causing inefficient ventilation [19,20]. Pulmonary dysfunction in HfPEF extends beyond these vascular changes and lung dysfunctions may result from concomitant distinct lung diseases: the prevalence of COPD was 15-20% in different cohorts [21,22] while the prevalence of restrictive lung diseases was 7%. [22]. Moreover it has been estimated that at least one spirometry anomaly or sign of impaired alveolar diffusion capacity is present in over 94% of HfPEF patients [23]. Recently, exercise-induced desaturation was observed in HfPEF patients without known pulmonary conditions and underlying mechanisms remain to be explained [24] suggesting the presence of underlying undiagnosed lung diseases. Overall the pulmonary involvement during HfPEF appears to be sizable as well as its role in the onset of exercise intolerance in HfPEF. Peripheral "non-cardiopulmonary" factors contributing to reduced exercise tolerance have also been identified. Haykowsky et al. [25] studied elderly HfPEF patients and found that impaired ability to increase arteriovenous oxygen difference (a-vO2 difference) during peak exercise was the strongest independent predictor of VO2 peak. Dhakal et al. [13] observed that impaired peripheral O2 extraction, alongside peak heart rate, were the most important predictors of VO2peak in HfPEF, with impaired peripheral O2 extraction being the most significant cause of exercise intolerance in approximately 40% of patients. These findings underscored the role of the impaired SM oxygen utilization due to muscle mass loss and muscle detrimental changes as cause of exercise intolerance in HfPEF [26]. This hypothesis was further supported by studies demonstrating a linear correlation between VO2 peak, total lean mass, and SM quality [27-29]. Respiratory muscle dysfunction has been described as well in HfPEF. Yamada et al [30] found inspiratory muscle weakness in 27% of HfPEF patients. Subjects with inspiratory muscle weakness presented lower knee extensor strength
and shorter distance walked at six-minute walk test (6MWT) compared to those with normal inspiratory muscle strength. Additionally, adverse changes in the vascular bed have been observed in HFrEF and HFpEF patients, including increased central arterial stiffness [31,32], impaired nitric oxide-mediated vasodilation [33], and microvascular dysfunction [34]. Hundley et al. [35] showed that arterial stiffness was positively correlated with VO\textsubscript{2} peak in HFpEF. Similarly, in the study of Mahfouz et al. [36], microvascular dysfunction was linked to exercise capacity. These vascular changes may contribute to exercise intolerance in HFpEF by limiting oxygen supply to muscular effectors during exercise and represent potential therapeutic targets. During submaximal exercise, the limitations in exercise tolerance among HFpEF patients appear to be independent of central hemodynamic mechanisms. Unlike HFrEF, HFpEF individuals consistently demonstrate normal increase of cardiac output during low-intensity submaximal exercise [37]. Impaired peripheral oxygen utilization and pathological changes in VO\textsubscript{2} kinetics have been suggested as potential causes for the reduced tolerance to submaximal exercise [13].

**Sarcopenia in heart failure with preserved ejection fraction**

Sarcopenia is a muscle disorder characterized by the progressive loss of SM mass, accompanied by adverse changes in SM that occur throughout life [38]. It contributes to frailty in older adults [39] and is associated with negative health outcomes, including disability, hospitalization, and mortality [40]. Approximately 18-20% of patients with HFpEF exhibit sarcopenia [41,42]. In these patients, the reduction in total lean mass is significantly more pronounced than in age-matched healthy controls [43], while muscle strength is notably lower compared to those with heart failure with reduced ejection fraction (HFrEF) and controls [44]. Konishi et al. [45] found a similar prevalence of sarcopenia between patients with HFpEF and HFrEF, and sarcopenia had a comparable impact on mortality in both patient groups.

Several functional and structural alterations in the SM of patients and animal models with HFpEF have been identified. Microscopic analyses of vastus lateralis muscle biopsies revealed a decreased percentage of oxidative type-1 fibers and an increased percentage of glycolytic type-2 fibers; inflammation, fibrosis, adipose infiltration, reduced capillary density with a diminished capillary-to-fiber ratio, mitochondrial reduction, and dysfunction [27,28]. These changes were closely associated with reduced aerobic capacity: In the study by Kitzman et al. [27], HFpEF patients demonstrated a lower percentage of type I fibers and a higher percentage of type II fibers, as well as a reduced capillary-to-fiber ratio compared to controls, both of which were significantly correlated with VO\textsubscript{2} peak in multivariate analyses. Haykowsky et al. [43] showed an inverse relationship between the ratio of intermuscular fat
to skeletal muscle and VO2 peak. Experimental studies in animal models of HFpEF provided additional insights. Bowen et al [46] demonstrated maladaptive muscle changes affecting both oxidative and glycolytic fibers in rats with HFpEF, including a 40% reduction in fiber cross-sectional area and a 15% reduction in capillarity of the oxidative slow-twitch soleus, with similar changes observed in the glycolytic fast-twitch extensor digitorum longus. These changes were related to strength reduction in both muscles. Selective involvement of locomotor muscles was suggested by Espino-Gonzalez et al. [47], who found blunted SM blood flow during contractions, alongside microvascular structural remodeling, fiber atrophy, and isotonic contractile dysfunction in locomotor muscles of a cardiometabolic obese-HFpEF rat model, whereas the diaphragm maintained its structure and function.

**Muscle atrophy**

In HFpEF, muscle atrophy is driven by a catabolic process initiated by a persistent pro-inflammatory state characterized by elevated levels of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-12 [48,49]. Cytokines activate protein degradation pathways, notably the ubiquitin-proteasome system [50]. This system's activity is regulated by muscle-specific ring finger protein 1 (MURF1) and atrogin 1 [51], with gene expression controlled by nuclear factor-kappa B (NF-κB) and forkhead box O (FoxO) family members [52], which, in turn, are upregulated by inflammatory cytokines. Additional pathways contributing to muscle atrophy include the insulin growth factor-1 (IGF-1)/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt1) pathway [53], increased gene expression of myostatin-2 (MSTN-2) [54], and autophagy [46]. Akt1 activation, promoted by IGF-1, leads to protein synthesis via activation of the mammalian target of rapamycin (mTOR) and inhibits FoxO transcriptional activity. Conversely, in catabolic conditions with IGF-1 deficiency, FoxO translocates to the nucleus to promote protein degradation gene transcription [55]. MSTN-2 is a member of the transforming growth factor-β superfamily [Bekfani 2020] that binds to the activin type IIB receptor and leads to intracellular phosphorylation of mothers against decapentaplegic (Smad) 2 and 3, which form a complex with Smad4. This complex then translocates to the nucleus where it regulates the transcription of genes involved in the protein degradation pathways [56]. The activation of Smad2 and 3 by MSTN-2, also cause the inhibition of the Akt/mTOR pathway in response to pro-growth signals (e.g. insulin and IGF-1) suppressing protein synthesis via FoxO. [57]. Changes in autophagy markers have been observed. The autophagic process involves the conversion of microtubule-associated protein 1A/1B-light chain 3 (LC3)-I to LC3-II through its conjugation with phosphatidylethanolamine. This modification targets LC3-II to autophagosomal membranes, facilitating the encapsulation of cellular debris [58].
Subsequent fusion of autophagosomes with lysosomes forms autolysosomes, where lysosomal hydrolases break down the autophagosomal contents, including LC3-II. The ratio of LC3-II to LC3-I serves as a quantitative marker of autophagy, reflecting the dynamic balance between autophagosome formation and degradation within the cell [59]. In a rat model LC3 II/I ratio showed a 15% reduction in HfPEF compared to control rats [60].

**Mitochondrial dysfunction**

There is growing evidence of significant structural and functional abnormalities in SM mitochondria in HfPEF. Rat models have demonstrated impaired diaphragmatic mitochondrial respiration and reduced activity of citrate synthase, a key enzyme in the Krebs cycle [61]. Molina et al. [28] found that mitochondrial content in vastus lateralis fibers of HfPEF patients was 46% lower, and citrate synthase activity was 29% lower, than in controls. Additionally, the expression of the mitochondrial fusion regulator, mitofusin 2 (Mfn2), was 54% lower in HfPEF patients compared to controls. Using 31P magnetic resonance spectroscopy, Weiss et al [62] showed early depletion and delayed recovery of phosphocreatine (PCr) and significantly decreased maximal mitochondrial oxidative capacity in the skeletal muscle of HfPEF patients compared to controls. Kelley et al. [63] found that maximal mitochondrial respiration was 40% to 55% lower in a postmenopausal rat model of HfPEF compared to controls. Similarly, reduced maximal capacity and respiration linked to complexes I and II has also been observed in HfPEF patients compared to controls [64].

**Effects of exercise training in heart failure with preserved ejection fraction and underlying mechanisms**

Current evidences show that supervised ET improves exercise tolerance and quality of life (QOL) in HfPEF patients. These results are highlighted by some systematic reviews and meta-analyses that have been published on this topic in the last decade [65-68]. The meta-analysis of Pandey et al [65] included 276 patients enrolled in 6 randomized controlled trials (RCTs). Authors found that VO₂ peak increased of 2.72 ml/kg/min in the group undergoing ET versus control. They also documented significant improvements of QOL (assessed trough Minnesota living with heart failure score) in the ET group compared to control. A wider systematic review included 11 RCTs published from 2010 onward with a total of 324 patients participating in ET programs [69]. Included studies varied significantly in terms of exercise duration and modality: exercise protocols ranged from 1 to 8 months; moderate-intensity continuous training (MCT) and high-intensity interval training (HIIT) emerged as the predominant exercise modalities utilized. The evaluation of changes in VO₂ peak was limited to 8 studies, while two were excluded due to the absence of a control group and another for
not measuring VO₂peak. Findings revealed a mean increase in VO₂ peak of 14%, corresponding to an increase of 2.2 mL/kg/min in patients undergoing ET; in contrast the control group presented a 0.2% reduction of VO₂peak (corresponding to a decrease of 0.3 mL/kg/min). Additionally, the duration of ergometric test increased by 21%, and the distance covered in the 6-minute walk test (6MWT) improved by 9%. These improvements in exercise tolerance were accompanied by improvements in QOL assessments. Further meta-analyses have showed similar results with the increase in peak VO₂ ranging from 1.7 to 2.7 mL/kg/min. Mechanisms by which ET exerts these beneficial effects in HFpEF patients are still poorly understood. Schematically, we can distinguish central (cardiac) and peripheral (vascular, muscular) effects.

Central effects of exercise training

Several small studies have investigated the effects of ET on cardiac structure and function in HFpEF patients [70-73]: they have been mainly focused on diastolic function and have produced mixed results. The meta-analysis of Fukuta et al [69] included 8 RCTs with a total of 436 patients. In the pooled analyses, ET did not significantly change LV diastolic function parameters compared to control. Furthermore, no changes on structural parameters as LV end-diastolic volume LV mass were observed in ET or control. Similar results were showed by a more recent meta-analysis that including 7 RCTs with a total of 346 participants. Interestingly in both researches patients undergoing ET obtained a significant improvement of VO₂ peak than controls. The neutral effect of ET on LV structure and function let hypothesize that the ET-mediated improvement of VO₂ peak in HFpEF is almost exclusively mediated by peripheral mechanisms. However same caution should be used in interpreting available data: exercise interventions were in most cases short and it is possible that longer ET programs are needed in order to induce structural myocardial adaptations. For example, in the study of Hieda et al. [74], a year of ET reversed abnormal LV myocardial stiffness in patients with HFpEF. Moreover differences in exercise intensities and modalities, among included studies, could have affected results of meta-analyses. Further hints regarding central effects of ET come from studies performed on animal models. Chronic low-intensity interval ET attenuated diastolic impairment, preserved myocardial oxygen balance, and promoted a physiological molecular hypertrophic signaling phenotype in a rat model of HFpEF [75]. In swine with HFpEF interval ET prevented coronary vascular dysfunction mediated by large-conductance Ca²⁺-activated K⁺ channels [76]. In the same animal model, ET reduced coronary stiffness by preventing the secretion of advanced glycation end products (AGE) in the perivascular adipose tissue [77]. These described myocardial adaptation might imply ET-induced epigenetic modulations. Liu et al [78] demonstrated different pattern of RNA
methylation in trained HFP EF rats compared to untrained, with modulatory effects on protein involved in myocardial energy metabolism and apoptosis pathway.

**Peripheral effects of exercise training**

While ET appears to have little effects on central parameters, peripheral factors seem to play a prominent role in determining theVO2 peak increases in HFP EF observed after ET programs. It has been estimated that increases in peak exercise a-vO2diff accounts for >90% of the improvement in VO2peak obtained after ET [79]. These findings suggest that increases in VO2 peak following ET in HFP EF may be mediated primarily by SM and/or arterial function. However, studies examining changes in SM morphology and oxidative capacity following ET in HFP EF are scant. In the study of Bowen et al. [46], eight weeks of exercise (HIIT or MCT) were ineffective in counteracting fiber atrophy and in improving capillary density in rats; however ET attenuated activity of the glycolytic enzyme LDH. In the only study performed on SM specimens of HFP EF patients ET showed only mild effects on muscle atrophy and mitochondrial function were documented [80]. As a consequence, further studies are needed in order to clarify what changes in SM morphology and function can be obtained through ET. Several studies have investigated changes on endothelial function and arterial stiffness following ET. [81-83]. Short ET interventions have proved ineffective: Kitzman et al. [83] assessed carotid arterial stiffness and brachial artery flow-mediated dilation (FMD) in HFP EF patients undergoing MCT. The authors documented no significant changes in these parameters after 8 or 16 weeks of training. Conversely 28 weeks of ET improved endothelium-dependent and independent vasodilation in a rat model of HFP EF. In this study performing ET maintained the expression of endothelial nitric oxide synthase (eNOS) and prevented the increase of matrix metalloproteinase activity and of AGE-modified proteins [82]. In a recent meta-analysis, aerobic ET, for more than 24 weeks, improved FMD and reduced pulse wave velocity by small effect sizes; ET for more than three times per week improved FMD by moderate effect sizes [83].

In a specific group of obese patients with HFP EF, both aerobic ET and caloric restriction proved effective in enhancing VO2peak, with the greatest improvement observed when the two interventions were combined [84]. However, it was noted that 35% of the weight loss with caloric restriction was due to SM mass reduction, and this result was also observed in the group in which caloric restriction was associated to ET. This outcome raised concerns, as the reduction in SM mass could potentially impede gains in exercise capacity and is associated with an elevated risk of frailty, physical disability, injuries, hospitalizations, and mortality. In a subsequent study, the same group investigated whether a triple intervention including resistance training (RT), endurance training and caloric restriction could prevent
the loss of SM mass in comparison to a double intervention (endurance exercise plus caloric restriction). The found that both interventions led to similar significant enhancements in VO$_2$peak. The triple intervention increased leg strength and muscle quality without attenuating skeletal muscle loss [85].

**High intensity interval training**

High intensity interval training emerges as a particularly appealing exercise modality for patients with HFpEF. Indeed, compared to MCT, HIIT may necessitate fewer weekly sessions and shorter durations per session to achieve significant physical conditioning, potentially making it more suitable for patients leading socially active lives. However, there are limited trials directly comparing these two exercise modalities in HFpEF patients. Angadi et al. [86], they observed after 4 weeks patients performing HIIT presented a significant increase in VO$_2$peak (from 19.2 ± 5.2 to 21.0 ± 5.2 mL/kg/min; p = 0.04) and improvement in diastolic markers, while no significant changes were observed in patients performing MCT. These findings paved the way for considering short-term HIIT protocol in HFpEF patients. Donelli da Silveira et al. [87] observed that, after 12 -weeks of training, the increase in VO$_2$peak was two times higher in the HIIT compared to MCT [HIIT= +3.5, 95%CI3.1 to 4.0;MCT=+1.9, 95% CI1.2 to 2.5) mL/kg/min, p < 0.001]; no differences in diastolic function and QoL were found between the two groups. However, in the OptimEx-Clin, changes in VO$_2$ peak were not significantly different at 3 or 12 months between HIIT and MCT. Moreover neither group met the a priori–defined minimal clinically important difference of 2.5 mL/kg/min compared with the control group [88]. Results of a sub-study of the OptimEx-Clin trial that involves patients undergoing SM biopsies, suggested that HIIT induced more pronounced changes in SM of HFpEF patients than MCT. Changes included: reduced synthesis of proteins related to muscle atrophy such as MURF-1; greater expression of mitochondrial complex proteins I-IV; increased amount of satellite cells [80]. The recent meta-analysis by Siddiqi et al. [89] included only three RCTs comprising a total of 150 patients (HIIT=77; MCT=73), with a majority being female. The mean duration of follow-up was 12 weeks. The analysis indicated that HIIT significantly improved peak VO2 compared to MCT, though no significant differences were observed between HIIT and MCT in terms of the ventilatory efficiency (VE/VCO2 slope), respiratory exchange ratio, and left atrial volume index. As a result of data scarcity, the impact of HIIT on HFpEF patients remains largely unexplored, with most evidence on its benefits derived from animal models. For instance, in a Dahl salt-sensitive rat model of HFpEF, HIIT was shown to preserve endothelial function and prevent the decline of endothelium-dependent vasodilation [82]. Bode et al. [90] investigated the cardiac effects of HIIT versus MCT on cardiomyocyte Ca2+ homeostasis and left ventricular function in a
mouse model of HFrEF. They found that both exercise modalities improved cardiomyocyte Ca2+ homeostasis, with an increase in stroke volume observed only in rats subjected to MCT.

**Respiratory muscles training**

Inspiratory muscle training (IMT) is a technique aimed at strengthening the muscles involved in inspiration, primarily the diaphragm, to enhance muscle strength, endurance, and cardiopulmonary function. Palau et al. [91] conducted a small-scale trial to evaluate the effects of IMT in elderly patients with HFrEF. They found that the IMT group exhibited significant improvements in maximal inspiratory pressure, VO2 peak, oxygen uptake at the anaerobic threshold, VE/VCO2distance walked in the 6MWT, and quality of life (QoL). A subsequent systematic review, which included 17 studies examining IMT in heart failure (HF) patients, revealed that only four of these studies specifically investigated the impact of IMT on HFrEF patients [92]. This indicates that current data are insufficient to conclusively determine the overall effectiveness of IMT on symptomatic improvement in this patient population.

**Conclusions**

While the clinical impact of ET has been systematically studied in HFrEF it has not been adequately investigated in the HFrEF population yet. Scientific researches to this regard are still in an embryonic stage and therefore there is lack of robust evidences in favour of the utilization of ET in the management of HFrEF patients. This is clearly confirmed by the fact that there is no mention of ET interventions, in reference to HFrEF, in the latest European guidelines on HF management published in 2021 [93]. This remains a critical area for future research. The relevance of assessing the effects of ET on the prognosis of HFrEF patients is particularly timely since cardiac-orientated drug interventions in large-scale clinical trials in HFrEF have proven to be largely ineffective in terms of improving patient outcomes. Moreover the understanding of the mechanisms underlying the skeletal myopathy of HF, specific therapies targeting these abnormalities can be developed.
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