

# 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

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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.

## 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]. HF 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, HFpEF 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 HFpEF but also play a role in the onset of symptoms reported by patients. Consequently, HFpEF 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

HFpEF 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 HF 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 HFpEF 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 HFpEF. The review is divided into two main sections: the first explores the mechanisms underlying exercise intolerance in HFpEF and describes the skeletal muscle (SM) pathological changes observed in these patients; the second part evaluates the benefits of exercise in HFpEF, 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 QOL in this population [9]. In patients with HFpEF, aerobic exercise capacity, as measured by peak oxygen consumption at peak exercise ( $\text{VO}_2$  peak) during cardiopulmonary testing, has been estimated to be 34-50% lower compared to healthy age-matched subjects [10,11]. This reduction in  $\text{VO}_2$  peak is similar to that observed in patients with HFrEF [12]. The etiology of exercise intolerance in HFpEF is multifactorial, with defects identified at multiple stages of the  $\text{O}_2$  pathway, where both central and peripheral mechanisms frequently coexist [13-15]. Pavley *et al.* 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  $\text{VO}_2$  peak [16]. The underlying mechanisms for impaired chronotropic responsiveness in HFpEF are multifactorial. A diminished heart rate (HR) response to increasing plasma isoproterenol concentrations, indicating decreased sinus node  $\beta$ -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  $\beta$ -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, relates to the decreased LV compliance and leads to an upstream increase in left atrial pressure. This, in turn, affects pulmonary circulation, resulting in lung capillary stress failure, arterial system remodeling, and, ultimately, pulmonary hypertension. Alterations in the pulmonary vascular bed compromise alveolar  $\text{O}_2$  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.* studied elderly HFpEF patients and found that impaired ability to increase arteriovenous oxygen difference (a- $\text{vO}_2$  difference) during peak exercise was the strongest independent predictor of  $\text{VO}_2$  peak [25]. Dhakal *et al.* observed that impaired peripheral  $\text{O}_2$  extraction, alongside peak HR, were the most important predictors of  $\text{VO}_2$  peak in HFpEF, with impaired peripheral  $\text{O}_2$  extraction being the most significant cause of exercise intolerance in approximately 40% of patients [13]. These findings underscore the role of the impaired SM oxygen utilization due to muscle mass loss and muscle-damaging changes as a cause of exercise intolerance in HFpEF [26]. This hypothesis was further supported by studies demonstrating a linear correlation between  $\text{VO}_2$  peak, total lean mass, and SM quality [27-29]. Respiratory muscle dysfunction has been described as well in HFpEF. Yamada *et al.* found inspiratory muscle weakness in 27% of HFpEF patients [30]. Subjects with inspiratory muscle weakness presented lower knee extensor strength and shorter distance walked at the 6-minute walk test (6MWT) compared to those with normal inspiratory muscle strength. Additionally, adverse changes in the vascular bed have been observed in HFpEF patients, including increased central arterial stiffness [31,32], impaired nitric oxide-mediated vasodilation [33], and microvascular dysfunction [34]. Hundley *et al.* showed that arterial stiffness was positively correlated with  $\text{VO}_2$  peak in HFpEF [35]. 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 a normal increase of cardiac output during low-intensity submaximal exercise [37]. Impaired peripheral oxygen utilization and pathological changes in  $\text{VO}_2$  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 and is associated with negative health outcomes, including disability, hospitalization, and mortality [39,40]. 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 HFrEF and controls [44]. Konishi *et al.* found a similar prevalence of sarcopenia between

patients with HFpEF and HFrEF, and sarcopenia had a comparable impact on mortality in both patient groups [45].

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<sub>2</sub> peak in multivariate analyses. Haykowsky *et al.* showed an inverse relationship between the ratio of intermuscular fat to SM and VO<sub>2</sub> peak [43]. Experimental studies in animal models of HFpEF provided additional insights. Bowen *et al.* 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 [46]. 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- $\alpha$ , interleukin (IL)-1 $\beta$ , 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 and atrogin 1 [51], with gene expression controlled by nuclear factor- $\kappa$ B 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/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- $\beta$  superfamily 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 [44]. 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 causes 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, the 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.* found that mitochondrial content in vastus lateralis fibers of HFpEF patients was 46% lower, and citrate synthase activity was 29% lower, than in controls [28]. Additionally, the expression of the mitochondrial fusion regulator, mitofusin 2, 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 and significantly decreased maximal mitochondrial oxidative capacity in the SM of HFpEF patients compared to controls. Kelley *et al.* found that maximal mitochondrial respiration was 40% to 55% lower in a postmenopausal rat model of HFpEF compared to controls [63]. Similarly, reduced maximal capacity and respiration linked to complexes I and II have 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 evidence shows that supervised ET improves exercise tolerance and 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.* included 276 patients enrolled in 6 randomized controlled trials (RCTs) [65]. The authors found that VO<sub>2</sub> peak increased by 2.72 mL/kg/min in the group undergoing ET *vs.* the control. They also documented significant improvements in QOL (assessed through the Minnesota living with HF score) in the ET group compared to the 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 VO<sub>2</sub> peak was limited to 8 studies, while two were excluded due to the absence of a control group, and another for not measuring VO<sub>2</sub> peak. Findings revealed a mean increase in VO<sub>2</sub> 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 VO<sub>2</sub> peak (corresponding to a decrease of 0.3 mL/kg/min). Additionally, the duration of the ergometric test increased by 21%, and the distance covered in the 6MWT improved by 9%. These improvements in exercise tolerance were accompanied by improve-

ments in QOL assessments. Further meta-analyses have shown similar results with the increase in peak  $\text{VO}_2$  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 mainly focused on diastolic function and have produced mixed results. The meta-analysis of Fukuta *et al.* included 8 RCTs with a total of 436 patients [69]. In the pooled analyses, ET did not significantly change LV diastolic function parameters compared to control. Furthermore, no changes in structural parameters as LV end-diastolic volume and LV mass, were observed in ET or control. Similar results were shown by a more recent meta-analysis that included 7 RCTs with a total of 346 participants. Interestingly, in both studies, patients undergoing ET obtained a significant improvement in  $\text{VO}_2$  peak than controls. The neutral effect of ET on LV structure and function allows to hypothesize that the ET-mediated improvement of  $\text{VO}_2$  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 the 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  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  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 adaptations might imply ET-induced epigenetic modulations. Liu *et al.* demonstrated a different pattern of RNA methylation in trained HFpEF rats compared to untrained, with modulatory effects on proteins involved in myocardial energy metabolism and the apoptosis pathway [78].

### Peripheral effects of exercise training

While ET appears to have little effect on central parameters, peripheral factors seem to play a prominent role in determining the  $\text{VO}_2$  peak increases in HFpEF observed after ET programs. It has been estimated that increases in peak exercise  $\text{a-vO}_2$  difference account for >90% of the improvement in  $\text{VO}_2$  peak obtained after ET [79]. These findings suggest that increases in  $\text{VO}_2$  peak following ET in HFpEF may be mediated primarily by SM and/or arterial function. However, studies examining changes in SM morphology and oxidative capacity following ET in HFpEF are scant. In the study of Bowen *et al.* [46], 8 weeks of exercise (HIIT or MCT) were ineffective in counteracting fiber atrophy and in improving capillary density in rats; however, ET attenuated the activity of the glycolytic enzyme LDH. In the only study performed on SM specimens of HFpEF patients, ET showed only mild effects on muscle atrophy, and mitochondrial function was documented [80]. Consequently,

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 in endothelial function and arterial stiffness following ET. [81-83]. Short ET interventions have proved ineffective: Kitzman *et al.* assessed carotid arterial stiffness and brachial artery flow-mediated dilation (FMD) in HFpEF patients undergoing MCT [83]. 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 HFpEF. In this study, performing ET maintained the expression of endothelial nitric oxide synthase 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 HFpEF, both aerobic ET and caloric restriction proved effective in enhancing  $\text{VO}_2$  peak, 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 with 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, endurance training, and caloric restriction could prevent the loss of SM mass in comparison to a double intervention (endurance exercise plus caloric restriction). It was found that both interventions led to similar significant enhancements in  $\text{VO}_2$  peak. The triple intervention increased leg strength and muscle quality without attenuating SM 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.* observed that after 4 weeks, patients performing HIIT presented a significant increase in  $\text{VO}_2$  peak (from  $19.2 \pm 5.2$  to  $21.0 \pm 5.2$  mL/kg/min;  $p=0.04$ ) and improvement in diastolic markers, while no significant changes were observed in patients performing MCT [86]. These findings paved the way for considering short-term HIIT protocol in HFpEF patients. Donelli da Silveira *et al.* observed that, after 12 weeks of training, the increase in  $\text{VO}_2$  peak was two times higher in the HIIT compared to MCT [HIIT=+3.5, 95% confidence interval (CI) 3.1 to 4.0; MCT=+1.9, 95% CI 1.2 to 2.5 mL/kg/min,  $p<0.001$ ] [87]; no differences in diastolic function and QoL were found between the two groups. However, in the OptimEx-Clin, changes in  $\text{VO}_2$  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.* included only three RCTs comprising a total of 150 patients (HIIT=77; MCT=73), with a majority being female [89]. The mean duration of follow-up was 12 weeks. The analysis indicated that HIIT significantly improved peak  $\text{VO}_2$  compared to MCT, though no significant differences were observed between HIIT and MCT in terms of the ventilatory efficiency ( $\text{VE}/\text{VCO}_2$  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.* investigated the cardiac effects of HIIT vs. MCT on cardiomyocyte  $\text{Ca}^{2+}$  homeostasis and LV function in a mouse model of HFpEF [90]. They found that both exercise modalities improved cardiomyocyte  $\text{Ca}^{2+}$  homeostasis, with an increase in stroke volume observed only in rats subjected to MCT.

### Respiratory muscle 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.* conducted a small-scale trial to evaluate the effects of IMT in elderly patients with HFpEF [91]. They found that the IMT group exhibited significant improvements in maximal inspiratory pressure,  $\text{VO}_2$  peak, oxygen uptake at the anaerobic threshold,  $\text{VE}/\text{VCO}_2$  distance walked in the 6MWT, and QOL. A subsequent systematic review, which included 17 studies examining IMT in HF patients, revealed that only four of these studies specifically investigated the impact of IMT on HFpEF 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 HFpEF population yet. Scientific research in this regard is still in an embryonic stage, and therefore, there is a lack of robust evidence in favor of the utilization of ET in the management of HFpEF patients. This is clearly confirmed by the fact that there is no mention of ET interventions, in reference to HFpEF, 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 HFpEF patients is particularly timely since cardiac-oriented drug interventions in large-scale clinical trials in HFpEF have proven to be largely ineffective in terms of improving patient outcomes. Moreover, the understanding of the mechanisms underlying the skeletal myopathy of HF, and specific therapies targeting these abnormalities, can be developed.

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