Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Caminiti G, Volterrani M, Iellamo F, et al. **Exercise training for patients with heart failure and preserved ejection fraction. A narrative review.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.3030

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

Giuseppe Caminiti,[1,2] Maurizio Volterrani,[1,2] Ferdinando Iellamo,[3] Giuseppe Marazzi,[2] Marco Silvestrini,[3] Domenico Mario Giamundo,[4] Valentina Morsella,[2] Deborah Di Biasio,[2] Alessio Franchini,[2] Marco Alfonso Perrone[3]

[1]Department of Human Science and Promotion of Quality of Life, San Raffaele Open University, Rome; [2]Cardiology Rehabilitation Unit, IRCCS San Raffaele, Rome; [3]Division of Cardiology and Sports Medicine, Department of Clinical Sciences and Translational Medicine, Tor Vergata University, Rome; [4]Department of Systems Medicine, Tor Vergata University, Rome, Italy

Correspondence: Giuseppe Caminiti, Cardiology Rehabilitation Unit, IRCCS San Raffaele, Rome via della Pisana 235, 00163, Rome, Italy.
Tel.: +390652252487.
E-mail giuseppe.caminiti@uniroma5.it

Contributions: all the authors made a substantive intellectual contribu-tion. All the authors have read and approved the final version of themanuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: waived ethical committee approval.

Patient consent for publication: not applicable.

Funding: this work was supported by funding from the Italian Ministry of Health (Ricerca Corrente).

Availability of data and materials: the data used to support the find-ings of this study are available from the corresponding author uponreques

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, 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 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 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 patientsand is the primary driver of morbidity and reduced quality of life in this population pro [9]. In patients with HFpEF, aerobic exercise capacity, as measured by peak oxygen consumption at peak exercise (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 VO_2peak 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 theO_2 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-vO_2 difference) during peak exercise was the strongest independent predictor of VO_2 peak. Dhakal et al. [13] observed that impaired peripheral O_2 extraction, alongside peak heart rate, were the most important predictors of VO_2peak in HFpEF, with impaired peripheral O_2 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 VO_2 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 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_2peak in HFpEF. Similarly, in the study ofMahfouz 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_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 withHFpEF 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_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 VO_2 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 of324 patients participating in ET programs [69].Included studiers 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_2 peak was limited to 8 studies, while two were excluded due to the absence of a control group and another for

not measuring VO_2peak. Findings revealed a mean increase in VO_2 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_2peak (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 $V\,o_2$ 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 been mainly focused on diastolic functionand 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 bothresearches patients undergoing ET obtained a significant improvement of VO_2 peak than controls. The neutral effect of ET on LV structure and function let hypothesize that the ET-mediated improvement of VO_2 peak in HFpEF isalmost 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 Ca^{2+}-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 HFpEF 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 theVO_2 peak increases in HFpEF observed after ET programs. It has been estimated that increases in peak exercise a-vO_{2diff} accounts for >90% of the improvement in VO_2peak obtained after ET [79]. These findings suggest that increases in 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], 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 HFpEF 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 HFPEF 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 HFpEF. 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 HFpEF, both aerobic ET and caloric restriction proved effective in enhancing VO_2peak, 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_2peak, 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_2peak (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_2peak 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 HFpEF. 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 HFpEF. They found that the IMT group exhibited significant improvements in maximal inspiratory pressure, VO_2 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 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 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 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-orientated 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, specific therapies targeting these abnormalities can be developed.

References

1. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA2003;289:194-202.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation 2021;143:e254-743.
3. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297-317.
4. Gomez-Soto FM, Andrey JL, Garcia-Egido AA, et al. Incidence and mortality of heart failure: A community-based study. Int J Cardiol 2011;151:40-5.
5. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev 2017;3:7-11.
6. Gard E, Nanayakkara S, Kaye D, Gibbs H. Management of heart failure with preserved ejection fraction. Aust Prescr 2020;43:12-7.
7. Morris JH, Chen L. Exercise training and heart failure: a review of the literature. Card Fail Rev 2019;5:57-61.
8. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.
9. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Exercise intolerance in heart failure with preserved ejection fraction: more than a heart problem. J Geriatr Cardiol 2015;12:294-304.
10. Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991;17:1065-72.
11. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure Withpreserved ejection fraction: diagnosing and ranking its causes using personalized O_2pathway analysis. Circulation 2018;137:148-61.
12. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286-94.
13. Hearon CM Jr, Sarma S, Dias KA, et al. Impaired oxygen uptake kinetics in heart failure with preserved ejection fraction. Heart 2019;105:1552-8.

14. Salzano A, De Luca M, Israr MZ, et al. Exercise intolerance in heart failure with preserved ejection fraction. Heart Fail Clin. 2021;17:397-413.
15. Montero D, Diaz-Cañestro C. Determinants of exercise intolerance in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Int J Cardiol 2018;254:224-9.
16. Pandey A, Khera R, Park B, et al. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. JACC Heart Fail 2018;6:117-26.
17. Sarma S, Stoller D, Hendrix J, et al. Mechanisms of chronotropic incompetence in heart failure with preserved ejection fraction. Circ Heart Fail 2020;13:e006331.
18. Dominguez E, Palau P, Nunez E, et al. Heart rate response and functional capacity in patients with chronic heart failure with preserved ejection fraction. ESC Heart Fail 2018;5:579-85.
19. Nayor M, Houstis NE, Namasivayam M, et al. Impaired exercise tolerance in heart failure with preserved ejection fraction: quantification of multiorgan system reserve capacity. JACC Heart Fail 2020;8:605-17.
20. Olson TP, Johnson BD, Borlaug BA. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. JACC Heart Fail 2016;4:490-8.
21. Mooney L, Hawkins NM, Jhund PS, et al. Impact of chronic obstructive pulmonary disease in patients with heart failure with preserved ejection fraction: insights from PARAGON-HF. J Am Heart Assoc 2021;10:e021494.
22. Eckhardt CM, Balte PP, Barr RG, et al. Lung function impairment and risk of incident heart failure: the NHLBI Pooled Cohort Study. Eur Heart J 2022;43:2196-208.
23. Andrea R, Lopez-Giraldo A, Falces C, et al. Lung function abnormalities are highly frequent in patients with heart failure and preserved ejection fraction. Heart Lung Circ 2014;23:273-9.
24. Omar M, Omote K, Sorimachi H, et al. Hypoxaemia in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2023;25:1593-603.
25. Haykowsky MJ, Brubaker PH, John JM, et al. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol 2011;58:265-74.
26. Middlekauff HR. Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. Circ Heart Fail 2010;3:537-46.
27. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the case for skeletal muscle myopathy and its contribution to exercise intolerance in heart failure with preserved ejection fraction. Circ Heart Fail 2017;10:e004281.

28. Molina AJA, Bharadwaj MS, Van Horn C, et al. Skeletal muscle mitochondrial content, oxidative capacity, and Mfn2 expression are reduced in older patients with heart failure and preserved ejection fraction and are related to exercise intolerance. JACC Heart Fail2016;4:636-45.
29. Tucker WJ, Haykowsky MJ, Seo Y, et al. Impaired exercise tolerance in heart failure: role of skeletal muscle morphology and function. Curr Heart Fail Rep 2018;15:323-31.
30. Yamada K, Kinugasa Y, Sota T, et al. Inspiratory muscle weakness is associated with exercise intolerance in patients with heart failure with preserved ejection fraction: apreliminary study. J Card Fail 2016;22:38-47.
31. Zern EK, Ho JE, Panah LG, et al. Exercise intolerance in heart failure with preserved ejection fraction: arterial stiffness and abnormal left ventricular hemodynamic responses during exercise. J Card Fail2021;27:625-34.
32. Desai AS, Mitchell GF, Fang JC, Creager MA. Central aortic stiffnessis increased in patients with heart failure and preserved ejection fraction. J Card Fail 2009;15:658-64.
33. Lewsey SC, Hays AG, Schär M, et al. Nitric oxide-mediated coronary endothelial function is impaired in patients with heart failure with preserved ejection fraction. Circ Heart Fail 2022;15:e009582.
34. Balmain S, Padmanabhan N, Ferrell WR, et al. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. Eur J Heart Fail 2007;9:865-71.
35. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol 2001;38:796-802.
36. Mahfouz RA, Gouda M, Abdelhamid M. Relation of microvascular dysfunction and exercise tolerance in patients with heart failure with preserved ejection fraction. Echocardiography2020;37:1192-8.
37. Corrieri N, Del Torto A, Vignati C, et al. Cardiac output changes during exercise in heart failure patients: focus on mid-exercise. ESC Heart Fail 2021;8:55-62.
38. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
39. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol Ser A 2001;56:M146-56.
40. Xu J, Wan CS, Ktoris K, et al. Sarcopenia is associated with mortality in adults: a systematic review and meta-analysis. Gerontology 2022;68:361-76.

41. Chen R, Xu J, Wang Y, et al. Prevalence of sarcopenia and its association with clinical outcomes in heart failure: an updated meta-analysis and systematic review. Clin Cardiol 2023;46:260-8.
42. Bekfani T, Pellicori P, Morris DA, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: Impact on muscle strength, exercise capacity and quality of life. Int J Cardiol 2016;222:41-6.
43. Haykowsky MJ, Kouba EJ, Brubaker PH, et al. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Cardiol 2014;113:1211-6.
44. Bekfani T, Bekhite Elsaied M, Derlien S, et al. Skeletal muscle function, structure, and metabolism in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Circ Heart Fail 2020;13:e007198.
45. Konishi M, Kagiyama N, Kamiya K, et al. Impact of sarcopenia on prognosis in patients with heart failure with reduced and preserved ejection fraction. Eur J Prev Cardiol 2021;28:1022-9.
46. Bowen TS, Herz C, Rolim NPL, et al. Effects of endurance training on detrimental structural, cellular, and functional alterations in skeletal muscles of heart failure with preserved ejection fraction. J Card Fail 2018;24:603-13.
47. Espino-Gonzalez E, Tickle PG, Benson AP, et al. Abnormal skeletal muscle blood flow, contractile mechanics and fibre morphology in a rat model of obese-HFpEF. J Physiol 2021;599:981-1001.
48. Glezeva N, Baugh JA. Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target. Heart Fail Rev 2014;19:681-94.
49. Seiler M, Bowen TS, Rolim N, et al. Skeletal muscle alterations are exacerbated in heart failure with reduced compared with preserved ejection fraction. Circ Heart Fail 2016;9:e003027.
50. Kitajima Y, Yoshioka K, Suzuki N. The ubiquitin-proteasome system in regulation of the skeletal muscle homeostasis and atrophy: from basic science to disorders. J Physiol Sci 2020;70:40.
51. Bodine SC, Latres E, Baumhueter S, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science 2001;294:1704-8.
52. Cai D, Frantz JD, Tawa NE, et al. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell 2004;119:285-98.
53. Schiaffino S, Mammucari C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. Skelet Muscle 2011;1:4.

54. Chen P, Liu Z, Luo Y, et al. Predictive value of serum myostatin for the severity and clinical outcome of heart failure. Eur J Intern Med 2019;64:33-40.
55. Yoshida T, Delafontaine P. Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy. Cells 2020;9:1970.
56. Sartori R, Milan G, Patron M, et al. Smad2 and 3 transcription factors control muscle mass in adulthood. Am J Physiol Cell Physiol 2009;296:C1248-57.
57. Trendelenburg AU, Meyer A, Rohner D, et al. Myostatin reduces Akt/TORC1/p70S6K signaling, inhibiting myoblast differentiation and myotube size. Am J Physiol Cell Physiol 2009;296:C1258-70.
58. Yang Y, Zheng L, Zheng X, Ge L. Autophagosomal membrane origin and formation. Adv Exp Med Biol 2021;1208:17-42.
59. Tanida I, Ueno T, Kominami E. LC3 and autophagy. Methods Mol Biol 2008;445:77-88.
60. Goto K, Schauer A, Augstein A, et al. Muscular changes in animal models of heart failure with preserved ejection fraction: what comes closest to the patient?. ESC Heart Fail 2021;8:139-50.
61. Bowen TS, Rolim NP, Fischer T, et al. Heart failure with preserved ejection fraction induces molecular, mitochondrial, histological, and functional alterations in rat respiratory and limb skeletal muscle. Eur J Heart Fail 2015;17:263-72.
62. Weiss K, Schär M, Panjrath GS, et al. Fatigability, exercise intolerance, and abnormal skeletal muscle energetics in heart failure. Circ Heart Fail 2017;10:e004129.
63. Kelley RC, Betancourt L, Noriega AM, et al. Skeletal myopathy in a rat model of postmenopausal heart failure with preserved ejection fraction. J Appl Physiol (1985) 2022;132:106-25.
64. Scandalis L, Kitzman DW, Nicklas BJ, et al. Skeletal muscle mitochondrial respiration and exercise intolerance in patients with heart failure with preserved ejection fraction. JAMA Cardiol 2023;8:575-84.
65. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev2019;1:CD003331.
66. Gomes-Neto M, Durães AR, Conceição LSR, et al. Effect of aerobic exercise on peak oxygen consumption, VE/VCO2 slope, and health-related quality of life in patients with heart failure with preserved left ventricular ejection fraction: a systematic review and meta-analysis. Curr Atheroscler Rep 2019;21:45.
67. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail 2015;8:33-40.

68. Sebastian SA, Padda I, Johal G. Supervised exercise training in heart failure with preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Curr Probl Cardiol 2024;49:102426.
69. Fukuta H, Goto T, Wakami K, et al. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Heart Fail Rev 2019;24:535-47.
70. Edelmann F, Gelbrich G, Dungen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780-91.
71. Smart NA, Haluska B, Jeffriess L, et al. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. Congest Heart Fail 2012;18:295-301.
72. Alves AJ, Ribeiro F, Goldhammer E, et al. Exercise training improves diastolic function in heart failure patients. Med Sci Sports Exerc 2012;44:776-85.
73. Kitzman DW, Brubaker PH, Morgan TM et al. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659-67.
74. Hieda M, Sarma S, Hearon C M, et al. One-year committed exercise training reverses abnormal left ventricular myocardial stiffness in patients with stage B heart failure with preserved ejection fraction. Circulation 2021;144:934-46.
75. Marshall KD, Muller BN, Krenz M, et al. Heart failure with preserved ejection fraction: chronic low-intensity interval exercise training preserves myocardial O2 balance and diastolic function. J Appl Physiol (1985) 2013;114:131-47.
76. Olver TD, Edwards JC, Ferguson BS, et al. Chronic interval exercise training prevents BK_{Ca} channel-mediated coronary vascular dysfunction in aortic-banded miniswine. J Appl Physiol (1985) 2018;125:86-96.
77. Ouyang A, Olver TD, Emter CA, Fleenor BS. Chronic exercise training prevents coronary artery stiffening in aortic-banded miniswine: role of perivascular adipose-derived advanced glycation end products. J Appl Physiol (1985) 2019;127:816-27.
78. Liu K, Ju W, Ouyang S, et al. Exercise training ameliorates myocardial phenotypes in heart failure with preserved ejection fraction by changing N6-methyladenosine modification in mice model. Front Cell Dev Biol 2022;10:954769.
79. Fu TC, Yang NI, Wang CH, et al. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. Am J Phys Med Rehabil 2016;95:15-27.

80. Winzer EB, Augstein A, Schauer A, et al. Impact of different training modalities on molecular alterations in skeletal muscle of patients with heart failure with preserved ejection fraction: a substudy of the optimex trial. Circ Heart Fail 2022;15:e009124.
81. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol 2013;62:584-92.
82. Adams V, Alves M, Fischer T, et al. High-intensity interval training attenuates endothelial dysfunction in a Dahl salt-sensitive rat model of heart failure with preserved ejection fraction. J ApplPhysiol (1985) 2015;119:745-52.
83. Li P, Liu Z, Wan K, et al. Effects of regular aerobic exercise on vascular function in overweight or obese older adults: a systematic review and meta-analysis. J Exerc Sci Fit 2023;21:313-25.
84. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36-46.
85. Brubaker PH, Nicklas BJ, Houston DK, et al. A randomized, controlled trial of resistance training added to caloric restriction plus aerobic exercise training in obese heart failure with preserved ejection fraction. Circ Heart Fail 2023;16:e010161.
86. Angadi SS, Mookadam F, Lee CD et al. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. J Appl Physiol (1985) 2015;119:753-8.
87. Donelli da Silveira A, Beust de Lima J, da Silva Piardi D, et al. High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: a randomized clinical trial. Eur J Prev Cardiol 2020;27:1733-43.
88. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2021;325:542-51.
89. Siddiqi TJ, Rashid AM, Javaid SS, et al. High-intensity interval training versus moderate continuous training in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. Curr Probl Cardiol 2023;48:101720.

90. Bode D, Rolim NPL, Guthof T, et al. Effects of different exercise modalities on cardiac dysfunction in heart failure with preserved ejection fraction. ESC Heart Fail 2021;8:1806-18.
91. Palau P, Domínguez E, Núñez E, et al. Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. Eur J Prev Cardiol 2014;21:1465-73.
92. Li H, Tao L, Huang Y, et al. Inspiratory muscle training in patients with heart failure: a systematic review and meta-analysis. Front Cardiovasc Med 2022;9:993846.
93. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.