The effect of exercise training and physiotherapy on diastolic function, exercise capacity and quality of life in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis

Authors: Chenchen Zhuang, Xufei Luo, Qiongying Wang, Wenjuan Wang, Runmin Sun, Xiaofang Zhang, Jing Yu

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The effect of exercise training and physiotherapy on diastolic function, exercise capacity and quality of life in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis

Chenchen Zhuang1*, Xufei Luo2*, Qiongying Wang1, Wenjuan Wang1, Runmin Sun1, Xiaofang Zhang1, Jing Yu1

1Hypertension Center, Lanzhou University Second Hospital, Lanzhou, China
2School of Public Health, Lanzhou University, Lanzhou, China
*These authors contributed equally to this work.

Short title: Meta-analysis of exercise and physiotherapy on HFpEF patients
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Correspondence to:
Jing Yu, MD,
Department of Hypertension Center, Lanzhou University Second Hospital,
No. 82 Cuiyingmen, Lanzhou, 730000, China,
phone: +86 138 936 07559
e-mail: ery_jyu@lzu.edu.cn

WHAT’S NEW?
Exercise and physiotherapy is accepted as an important contribution to the rehabilitation of patients with heart failure with preserved ejection fraction (HFpEF). This study aimed to evaluate the effect of endurance training and a combination of endurance and resistance training (combined exercise), functional electrical stimulation (FES) and inspiratory muscle training (IMT) on HFpEF patients, measured by diastolic function, exercise capacity and quality life. This is the first to evaluate the different modalities of physical therapy on HFpEF patients. Our
results showed that FES and IMT improved functional capacity and quality of life (QoL), as well as endurance training. Besides, combined exercise was beneficial to the ratio of peak early to late diastolic mitral inflow velocities and the early diastolic mitral annual velocity. These findings suggest that FES and IMT improve functional capacity and QoL in HFpEF patients, and the outcomes are similar to endurance training. Besides, combined exercise may improve diastolic function.

ABSTRACT

Background: Exercise and physiotherapy is accepted as an important contribution to the rehabilitation of patients with heart failure with preserved ejection fraction (HFpEF). But the previous results are unclear partly because of limited power with small sample sizes.

Aims: We aimed to better understand the effects of 2 exercise training interventions and two modalities of physiotherapies on exercise capacity, quality of life (QoL) and diastolic dysfunction in HFpEF patients.

Methods: Cochrane Library, EMBASE and MEDLINE via PubMed for randomized controlled trials were searched from their inception to May 2021. The effect size was estimated as mean differences (MD) with 95% confidence intervals (CI).

Results: A total of 14 articles on 13 trials were included in this meta-analysis with 673 HFpEF patients. The pooling revealed that peak oxygen uptake was improved by endurance training, functional electrical stimulation (FES) and inspiratory muscle training (IMT). Similar results were observed for 6-minute walk test and QoL. A combination of endurance and resistance training (combined exercise) was beneficial to the ratio of peak early to late diastolic mitral inflow velocities (MD [95% CI]: –2.90 [–4.97, –0.83]; \(P = 0.006\)) and the early diastolic mitral annual velocity (MD [95% CI]: 1.40 [0.68, 2.12]; \(P = 0.006\)). IMT improved ventilation/carbon dioxide ratio slope (MD [95% CI]: –3.36 ml/kg⁻¹/min⁻¹ [–6.17, –0.54]; \(P = 0.019\)).

Conclusions: FES and IMT improve functional capacity and QoL without a change in diastolic function in HFpEF patients, and the outcomes are similar to endurance training. Notably, combined exercise may improve diastolic function.
**Key words:** diastolic function, exercise training, functional electrical stimulation, heart failure with preserved ejection fraction, inspiratory muscle training

**INTRODUCTION**

Heart failure with preserved ejection fraction (HFpEF) comes about nearly half of heart failure (HF) patients in the community, and the mortality and morbidity are high [1]. However, the established neurohormonal-based therapies, used for treating heart failure with reduced ejection fraction (HFrEF), have failed to improve exercise intolerance and provide favorable clinical outcomes for HFpEF [2]. The study of Lelonek [1] reported that although angiotensin receptor neprilysin inhibitors (ARNIs) may benefit from treatment with HFpEF, the relevance of ARNI in HFpEF still has not been clarified.

Cardiac dysfunction appears in diastolic dysfunction in echocardiography, exercise intolerance may be objectively measured by peak oxygen uptake (peak VO₂), and poor quality of life (QoL) completes the typical clinical image of HFpEF [3]. Exercise training appears to be a promising strategy to improve peak VO₂ and QoL in HFpEF patients [4, 5]. However, previous meta-analyses hold inconsistent opinions on diastolic function in HFpEF patients experiencing exercise training [6–8] due partly to failed to assess the different modalities of exercise training. HFpEF is more common in elderly patients, and these patients have poor adherence to exercise training [9]. It is time to carry out physiotherapy to relieve the symptoms of HFpEF. At present, physiotherapy mainly includes inspiratory muscle training (IMT) and functional electrical stimulation (FES), which are effective interventions to improve exercise intolerance in HFrEF [10, 11]. HF has been commonly associated with inspiratory muscle weakness [12]. IMT, the diaphragm-based muscles with inspiratory function, improves inspiratory muscle weakness, cardiorespiratory fitness and QoL similarly to exercise training leading a better adaptation to posterior exercise training [13]. The other physiotherapy involves a neuromuscular stimulation FES, which delivers in a specific recruitment pattern for performing a muscular movement necessary for exercise [14]. FES has shown potential beneficial effects in HF patients, including
increased muscle mass and improved QoL [15, 16]. IMT and FES may serve HF patients excluded from exercise training, being interesting treatment options for clinicians. Accordingly, both IMT and FES may have potential benefits to HFpEF patients, which may not only be limited in HFpEF patients unable to undergo exercise training but also may be expanded in the general HFpEF population. However, there has so far been no published meta-analysis to evaluate the impact of IMT and FES on exercise tolerance in HFpEF patients. In this meta-analysis, we aimed to evaluate the effects of different modalities of exercise training [endurance, and a combination of endurance and resistance training (combined exercise)] and physiotherapies (FES and IMT) on exercise capacity, QoL and diastolic function in HFpEF patients.

**METHODS**

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [17]. The protocol was prospectively registered with Open Science Framework (https://osf.io/sufc8).

**Search strategy**

Studies on the effect of physical therapy in HFpEF patients published until May 20, 2021 were searched by Cochrane Library, EMBASE and MEDLINE via PubMed. We used a mix of medical subject heading (MeSH) and keywords including exercise training, aerobic exercise, endurance training, inspiratory muscle training, functional electrical stimulation, and heart failure with preserved ejection fraction.

**Study selection**

Studies were considered eligible if they (a) were published as randomized controlled trials (RCTs); (b) included patients (aged ≥18 years) with HFpEF; (c) included patients undergoing physical therapy; (d) included comparison of physical therapy with standard medical care or placebo control group. Articles that failed to meet the inclusion criteria were removed,
including reviews, animal studies, non-RCTs, non-English language, and intervention durations with less than 4 weeks.

**Main outcomes**

Primary outcomes of this study were exercise capacity measured by peak VO\textsubscript{2} and 6-minute walk test (6MWT), QoL measured by Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score. Secondary outcomes were evaluated by ventilation/carbon dioxide ratio slope (VE/VCO\textsubscript{2}) slope and diastolic function measured by peak early to late diastolic mitral inflow velocities (E/A), the ratio of early diastolic mitral inflow to annular velocities (E/e’), and the early diastolic mitral annular velocity (e’).

**Data extraction**

Two reviewers (CCZ and XFL) extracted the following data independently: study characteristics (authors, year of publication and country), participant characteristics (age and sample size of different groups), study methods/design and period of exercise intervention.

**Risk of Bias**

We evaluated the risk of bias for inclusion in this meta-analysis by the Physiotherapy Evidence Database (PEDro) scale [18]. When a disagreement occurred, a third reviewer was consulted.

**Statistical analysis**

For each outcome, the effect size in our study was assessed by the baseline to follow-up change. We used weighted mean difference (MD) and 95% confidence intervals (CI) for the same scale of the outcomes. When the \( I^2 \) statistic was lower than 30% and \( P < 0.10 \), a fixed-effect model was used; otherwise, a random effect model was used. All analyses were used by STATA version 14.0 (StataCorp, College Station, TX, USA). Furthermore, meta-regression analyses were also performed with STATA software using the restricted maximum likelihood method. Two dependent variables (peak VO\textsubscript{2} and QoL) was tested against several independent variables.
including age, sex and exercise period. A value of $P<0.01$ was considered significant.

RESULTS

Included studies

The flow chart is shown in Figure 1, screening identified 129 potential reports. After removal of duplicates, 152 records remained. 117 studies were excluded after scanning titles and abstracts. Then 21 were excluded because they did not report HFpEF. Ultimately, 11 RCTs on exercise training [5, 19–28] and 3 RCTs on physiotherapies were included in this meta-analysis [14, 29, 30].

Characteristics of studies

The basic characteristics of each study were summarized in Table S1. The present meta-analysis included 673 HFpEF patients. The mean age of participants ranged 60.5–75 years, and the proportion of men ranged 0%–64%.

Quality assessment

The quality of included RCTs is presented in Supplementary material, Table S2. In none of the studies was there objective evidence of imbalance in baseline characteristics between the intervention and control groups. The moderate risk of bias was due to inadequate blinding of participants and therapists, allocation concealment and intention-to-treat methodologies.

Functional capacity indicator

Our meta-analysis could be performed for two functional capacity indicators: 6MWT and peak VO$_2$. Eight trials with 411 patients reported on 6MWT (Figure 2A). The heterogeneity was small ($I^2 = 0.0\%$; $P = 0.560$, fixed-effect). 6MWT was increased by endurance training (MD [95% CI]: 38.79 m [19.97, 57.61]; $P <0.001$) and FES (MD [95% CI]: 52.77 m [30.61, 74.93]; $P <0.001$). However, there was no change after IMT (MD [95% CI]: 84.00 m [–31.73, 199.73]; $P = 0.155$) and combined exercise (MD [95% CI]: 7.00 m [–37.61, 51.61]; $P = 0.758$).
Thirteen trials with 411 patients reported on peak VO\textsubscript{2} (Figure 2B). The heterogeneity was small ($I^2 = 0.0\%$; $P = 0.739$, fixed-effect). Peak VO\textsubscript{2} was improved by endurance training (MD [95\% CI]: $1.89$ ml/kg\textsuperscript{-1}/min\textsuperscript{-1} [1.32, 2.46]; $P < 0.001$), FES (MD [95\% CI]: $2.28$ ml/kg\textsuperscript{-1}/min\textsuperscript{-1} [0.92, 3.65]; $P = 0.001$), IMT (MD [95\% CI]: $2.72$ ml/kg\textsuperscript{-1}/min\textsuperscript{-1} [1.44, 3.99]; $P < 0.001$) and combined exercise (MD [95\% CI]: $3.30$ ml/kg\textsuperscript{-1}/min\textsuperscript{-1} [0.44, 6.16]; $P = 0.024$). Meta-regression analysis showed no significant effect of age (coefficient, 0.007; $P = 0.989$), sex (coefficient, 0.010; $P = 0.826$) and exercise period (coefficient, $-0.736$; $P = 0.036$).

**Quality of life**

Thirteen trials with 560 patients reported on the MLHFQ total score (Figure 3). The heterogeneity was small ($I^2 = 28.5\%$; $P = 0.158$, fixed-effect). The MLHFQ total score was improved by endurance training (MD [95\% CI]: $-9.13$ [–12.98, –5.28]; $P < 0.001$), FES (MD [95\% CI]: $-14.74$ [–22.44, –7.08]; $P < 0.001$) and IMT (MD [95\% CI]: $-11.49$ [–20.08, –2.91]; $P = 0.009$). However, no difference was found on combined exercise (MD [95\% CI]: $-6.00$ [–15.99, 3.99]; $P = 0.239$). Meta-regression analysis showed no significant effect of exercise period (coefficient, 1.116; $P = 0.574$), age (coefficient, $-0.689$; $P = 0.800$) and sex (coefficient, $-0.523$; $P = 0.852$).

**Diastolic function**

Eight trials with 416 patients reported on E/A (Figure 4A). The heterogeneity was small ($I^2 = 0\%$; $P = 0.606$, fixed-effect). E/A was no change by endurance training (MD [95\% CI]: $0.03$ [–0.03, 0.09]; $P = 0.307$), combined exercise (MD [95\% CI]: $-0.03$ [–0.17, 0.11]; $P = 0.678$), and FES (MD [95\% CI]: $-0.12$ [–0.29, 0.05]; $P = 0.162$).

Ten trials with 416 patients reported on E/e’ (Figure 4B). There was a statistical heterogeneity ($I^2 = 43.1\%$; $P = 0.071$, random-effect). E/e’ was improved by combined exercise with one included study (MD [95\% CI]: $-2.90$ [–4.97, –0.83]; $P = 0.006$). There was no change in E/e’ by endurance training (MD [95\% CI]: $-0.03$ [–2.83, 2.78]; $P = 0.983$), FES (MD [95\% CI]: $-2.16$ [–4.41, 0.09]; $P = 0.060$) and IMT (MD [95\% CI]: $-1.10$ [–4.56, 2.36]; $P = 0.533$).
Four trials with 215 patients reported on e’ (Figure 4C). There was a statistical heterogeneity ($I^2 = 81.3\%; P = 0.001$, random-effect). e’ was improved by combined exercise with one included study (MD [95% CI]: 1.40 [0.68, 2.12]; $P < 0.001$). There was no change in e’ by endurance training (MD [95% CI]: –2.90 [–4.97, –0.83]; $P = 0.140$) and IMT (MD [95% CI]: 0.30 [–1.28, 1.88]; $P = 0.709$).

**Exercise physiology parameter**
Eleven trials with 502 patients reported on VE/VCO$_2$ slope (Figure 2C). There was a statistical heterogeneity ($I^2 = 39.9\%; P = 0.083$, random-effect). VE/VCO$_2$ slope was improved by IMT (MD [95% CI]: –3.36 [–6.17, –0.54]; $P = 0.019$). No significant difference was found after endurance training (MD [95% CI]: –1.04 [–2.73, 0.64]; $P = 0.226$), FES (MD [95% CI]: 0.35 [–2.67, 3.37]; $P = 0.819$), and combined exercise (MD [95% CI]: –1.90 [–4.44, 0.64]; $P = 0.142$). Smart et al. [22] may be the source of heterogeneity due to the small sample.

**DISCUSSION**
The present meta-analysis summarized data that evaluated the effects of two exercise interventions and two physiotherapy modalities in HFpEF patients. FES and IMT improved exercise performance and QoL, and the outcomes were similar to endurance training. Notably, combined exercise has a potential therapy to improve diastolic function in HFpEF patients.

The previous studies have focused on overall exercise training rather than the different types of exercise training. The meta-analysis of Gomes-Neto et al. [31] only conducted endurance training and failed to represent other exercise modalities. Some meta-analyses [8, 32] showed that exercise training improved exercise capacity and QoL in HFpEF patients, but a methodological limitation was the combination of endurance training and combined exercise. The previous meta-analyses held inconsistent opinions on diastolic function in HFpEF patients during exercise training [6–8, 32]. Thus, the present meta-analysis compensated for the weakness of the previous studies.

The present meta-analysis observed that peak VO$_2$, 6MWT and QoL were improved by exercise
training, as well as FES and IMT. The peak VO$_2$ may affect oxygen delivery and/or utilization via cardiac, vascular and skeletal muscle function [33]. Therefore, active skeletal muscle is the major reason to induce the augment of peak VO$_2$ in HFpEF patients, including oxidative enzyme activity and capillary density [25].

Left ventricular (LV) diastolic dysfunction plays a fundamental, pivotal role in the pathophysiological hallmark of HFpEF [34]. In assessing patients for diastolic dysfunction and possible HFpEF, application of the 2009 consensus guideline on diastolic function yielded a sensitivity of 47% to rule out HFpEF, whereas other proposed classification schemes actually yielded higher sensitivities of between 72% and 77% to rule out of HFpEF [35, 36]. Notably, echocardiography for impaired diastolic dysfunction has been sine qua non of diagnosis in HFpEF [37]. Earlier occurring LV diastolic pressure relates best with E/A, E/e’, and e’ [38]. With respect to the estimation of LV filling pressures, early work suggested that E/e’ could be used to reliably estimate of LV filling pressure in HFpEF, and even in atrial fibrillation. E-wave is smaller, leading to the diastolic dysfunction filling pattern where E/A <1, occurring with hypertension, hypertrophic cardiomyopathy, ischemia, and myocardial infarction. Reduced e’ velocity is resulted by a variety of comorbidities to impaired myocardial relaxation and restoration forces. Edelmann et al. [19] reported that combined exercise improved diastolic function. Our findings showed that combined exercise improved E/e’ and e’, suggesting an improvement in left ventricular filling pressures. However, endurance training failed to improve diastolic function. Smart et al. [22] suggested that 16-week endurance training may not be sufficient to elicit alteration in myocardial properties. Fujimoto et al. [39] reported that 1-year endurance training had little effect on left ventricular compliance in HFpEF patients. In response to exercise training, cardiac relaxation may be compounded by abnormalities in skeletal muscle oxygen use, which augments cardiac output, and flow into a small, stiff and slowly relaxing heart [40].

The hemodynamic changes that occur during exercise constitute the primary stimulus for diastolic function [41]. Endurance training sustained elevations in cardiac output with reduced peripheral vascular resistance by increased mitochondrial biogenesis and capillary density, aid
in the body’s transport and use oxygen to generate energy [42], while resistance intense bouts of increased peripheral vascular resistance and only slightly evaluated cardiac output by training add muscle bulk to peripheral muscles and increases bone mass, then leading to an increased in muscle strength and power [43]. Thus, the difference of diastolic function between combined exercise and endurance training may be induced by resistance training.

FES and IMT had no substantial changes in the E/e’, E/A and e’, despite the improvement in exercise capacity and QoL [14, 30]. Extra-cardiac effects not directly related to improvement in cardiac function may play a critical role in the beneficial effect of physiotherapy. Our result showed that IMT significantly improved VE/VCO₂ slope alone. Various studies of HF patients have shown that selective respiratory muscle training improved submaximal and maximal exercise capacity during daily living activities [13]. The development of diaphragmatic fatigue is a delay, leading to a reduction in the recruitment of accessory respiratory muscles, and an improved ventilatory efficiency [44]. Although FES fails to improve VE/VCO₂ slope, the beneficial effects of FES on functional capacity and QoL is similar to those in IMT. FES and IMT interventions improve the recruitment of accessory respiratory muscles and ventilatory efficiency by delayed diaphragmatic fatigue, which increase muscle strength, muscle mass and aerobic-oxidative capacity [10, 29]. Both IMT and FES interventions are a simple, low-cost, and harmless intervention for patients with HFpEF, and may serve as “bridge therapies” to exercise training.

Physical therapy may be a safe approach for the treatment of HFpEF. However, there is a demanding challenge for exercise training will be translating these programs to HFpEF patients with relevant comorbidity (i.e. frailty), after cardiac surgery or with advanced age. Notably, FES and IMT seem to be alternative treatments for patients who are unable to perform exercise training. In fact, many patients with HFpEF, unable to exercise training, pay more attention to medication treatments. Thus, the greatest challenge is to implement the existing knowledge regarding training benefits in HFpEF as a standard in clinical practice and to increase the participation rates of patients with a clear indication for physiotherapy-based cardiac rehabilitation in existing programs.
**Strengths and limitations**

This study is the first to evaluate the different modalities of exercise training and physiotherapy on exercise capacity, QoL and diastolic function in HFpEF patients. However, several limitations should be addressed. Firstly, the major limitation of this analysis is the small sample sizes in most the RCTs. There are only two studies that reported combined exercise, and they share one set of date using different results [19, 20]. New large-scale RCTs are needed to confirm the findings of this meta-analysis. Secondly, few studies compared exercise training and physiotherapy on exercise capacity, QoL and diastolic function. Accordingly, it is not possible to state which intervention modality is outstanding to apply in HFpEF patients. Thirdly, heterogeneity scores suggested the majority of analyses were justified, but this of e’ may display heterogeneity at levels too high to justify this analysis. Finally, more standardized, high qualitative, larger scale and longer intervention period trials are needed for further research in order to estimate the most effective training modality.

**CONCLUSIONS**

Our meta-analysis suggests that FES and IMT, as well as endurance training, have a positive effect on functional capacity and QoL without a significant change in diastolic function. Notably, combined exercise may improve diastolic function and peak VO₂. Further trials are required to determine which training modalities are effective forms of training to improve aerobic capacity in HFpEF patients.

**REFERENCES**


Figure 1. Flow chart of the study selection procedure
Figure 2. Effects of exercise on exercise performance: 6-minute walk test (6MWT); Change in peak oxygen consumption (peak VO₂), ventilation/carbon dioxide ratio slope (VE/VCO₂ slope)
**Figure 3.** Effects of exercise on Minnesota Living With Heart Failure Questionnaire (MLHFQ) total score
Figure 4. A. Effects of exercise on diastolic function: the ratio of peak early to late diastolic mitral inflow velocities (E/A). B. Change in the ratio of early diastolic mitral inflow to annular velocities (E/E’). C. The early diastolic mitral annular velocity (e’).