Review

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Physical therapy in heart failure with preserved ejection fraction: A systematic review

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Abstract

About 50% of patients with heart failure (HF) have preserved ejection fraction (HFpEF) which is especially common in elderly people with highly prevalent co-morbid conditions. HFpEF is usually defined as an ejection fraction equal to or greater than 50%, although some studies have used a limit as low as 40%. The prevalence of this syndrome is expected to increase over the next decades. The associated impact on mortality and hospital readmissions has made of this entity a major public health issue. Despite the fact that mortality and re-hospitalisation rates of HFpEF are similar to the syndrome of HF with reduced ejection fraction (HFrEF), currently there is no available evidence-based therapy as effective as is the case for HFrEF. Exercise intolerance is the principal clinical feature in HFpEF. The pathophysiological mechanisms behind impaired exercise capacity in these patients are complex and not yet fully elucidated. Current guidelines and consensus documents recommend the implementation of exercise training in HFpEF; however, they are based mostly on results from a few small trials evaluating surrogate endpoints such as exercise capacity and quality of life. The aim of this work was to review the current evidence that supports the effect of the different modalities of physical therapies in HFpEF.

Keywords

Heart failure, heart failure with preserved ejection fraction, physical therapy, co-morbidity

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Introduction

Heart failure (HF) is, worldwide, a major cause of morbidity and mortality.[1] Currently, nearly 50% of HF patients have HF with preserved ejection fraction (HFpEF).[2,3] The prevalence of this syndrome has increased over the last decades which, together with the impact that it has on mortality and hospital readmissions, has made of this clinical entity a major public health problem.[2,3] The causal factors postulated for the increased prevalence and the expected increase in incidence, are, among others, population aging and the high prevalence of associated co-morbid conditions such as hypertension, diabetes, atrial fibrillation and obesity.[2,3]

The main clinical features in chronic HF are exertional dyspnoea and reduced aerobic capacity. In HFpEF, the degree of impairment in exercise capacity has shown to be similar to the syndrome of HF with reduced ejection fraction (HFrEF).[4] Even though this exercise impairment is an important determinant of poor prognosis[5] and decreased health-related quality of life (QoL),[4] its pathophysiology is complex and rarely explained by a single mechanism.[6] Moreover, contributing to the concern that HFpEF has as a major public health problem is the fact that the associated morbidity and mortality, the degree of

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impairment in QoL, and the healthcare burden seems to be equal or even higher to HFrEF.[4,7–9] Despite the fact that proven medical therapies for HFrEF have also shown to improve some endpoints in HFpEF, such as diastolic function and exercise capacity,[10–12] they have failed in terms of reduction in mortality.[10] The underlying mechanisms behind this paradoxical result are not well understood,[13–15] although the influence of aged population, aetiology and the burden of associated co-morbidities[2,13–15] seem to play a major role.

In HFrEF, most of the current evidence supports the beneficial role of physical therapies on major clinical outcomes such as HF-related re-hospitalisation and the composite of cardiovascular death and HF-hospitalisation. Likewise, there is a proven effect on other endpoints such as QoL and exercise capacity.[16–18] Based on this evidence, the current guidelines recommend the implementation of regular aerobic exercise for these patients.[19,20]

Conversely, the evidence is not as strong for HFpEF. Indeed, there are only a few small trials showing that physical therapies improve exercise capacity and QoL.[21–28] However, the effect on major clinical outcomes (mortality or re-hospitalisation) is largely unknown. In this systematic review, our aim is to provide up-to-date information on the role of physical therapy for the management of patients with HFpEF.

Methods

A systematic search of PubMed (MEDLINE) was conducted to identify all randomised controlled trials (RCTs) comparing physical therapy protocols versus usual care in HFpEF patients. This included all studies meeting the search criteria up to April 2014. Search terms used were combinations of the terms 'exercise training', 'heart failure', 'preserved ejection fraction', 'physical training', 'inspiratory muscle training', 'functional electrical stimulation', 'mortality', 'morbidity', 'functional capacity' and 'quality of life'. There were no language restrictions.

Studies included in this review were required to have the description of the criteria used for the diagnosis of HFpEF, a reported left ventricular ejection fraction (LVEF), and a clear-cut definition of what is active intervention and primary endpoint. To this end, we qualitatively summarised eight eligible studies in order to extract useful information despite the fact that these studies were heterogeneous in outcomes measures, sample size and type of the intervention (Tables 1–4).[21–28]

Physical therapies in HF

Current guidelines recommend the implementation of exercise training in chronic HF as an evidence-based recommendation (class I, level of evidence A).[19,20] This evidence is based on RCTs performed in HFrEF.[16,17] In the largest RCT, HF-ACTION,[16] the mean LVEF was 25% and patients with HFpEF were excluded. The authors found that exercise training was safe and associated with significant but modest reduction in clinical adverse events. Such benefit measured at three years, translated into a relative risk reduction (RRR) of 11% (adjusted $p = 0.03$) in the primary composite endpoint (all-cause mortality/all-cause hospitalisation), and a 15% RRR (adjusted $p = 0.03$) in the secondary composite endpoint (cardiovascular death/HF hospitalisation). In addition, a significant improvement in QoL was described.[29]

Whether the exercise recommendation in the current guidelines[19,20] and consensus documents[30] may be extrapolated to HFpEF is controversial for the following reasons: (a) these two syndromes shared a different pathophysiology and epidemiology; (b) therapeutic interventions that have been shown efficacious in HFrEF have not been confirmed to be useful for HFpEF; and (c) the evidence measured by the amount of well-designed studies evaluating the safety and efficacy of physical therapies in patients with HFpEF is scarce.

Physical therapies in HFpEF

To date, eight published studies have evaluated the clinical role of physical therapies in HFpEF. The roles of exercise training[21–27] and passive interventions[28] were evaluated in seven and one of them, respectively.

Exercise training

The effect of exercise training in HFpEF has been reviewed and limited to seven small RCTs with a short-term follow up ranged from 12–24 weeks.[21–27] The identification and characteristics of these studies are summarised in Tables 1 and 2.

These studies included a total of 279 patients with HFpEF in which 157 were allocated to exercise training and 122 to the control arm. All patients were classified as symptomatic HF based on the scale of the New York Heart Association (NYHA) functional class (from I–III) and a LVEF $\geq$45%. As depicted in Tables 1 and 2, there is considerable heterogeneity in the inclusion criteria across the studies. The mean age ranged from 63–73 years, and the proportion of females ranged from 29–100%.

All of these studies used different exercise training modalities with different protocols (Table 3). Four of them used continuous endurance training with different levels of intensity and protocols of workload increase.[21,22,25,26] Some used either moderate-

Table 1. Study design and baseline characteristics of randomised controlled trials of physical therapy in heart failure (HF) with preserved ejection fraction (HFpEF) patients.

Study author, country, recruitment date, year of publication	Group (*n*)	Inclusion criteria	Age, years (mean)	Women (%)	Entry NYHA class (%)	Entry LVEF criteria (%)
Alves et al., Israel, single centre, NR, 2012[24]	ET (20)/CT(11)	Presented signs or symptoms of heart failure. and LVEF≥55%	63	29	I (6.5)/II (38.7)/ III (54.8)	≥55%
Edelmann et al., Germany, multicentre (three centres), 2007, 2011[23]	ET (44)/CT(20)	Symptomatic NYHA functional class II/III) outpatients older than 45 years of age were included if they had preserved left ventricular systolic function (LVEF ≥50%), echocardiographically determined diastolic dysfunction (grade≥1), sinus rhythm, and at least 1 of the following cardiovascular risk factors: overweight, diabetes mellitus, hypertension, hyperlipidaemia, smoking.	65	56	II (84)/III (16)	≥50%
Gary, USA, single centre, NR, 2006[21]	ET (15)/CT(13)	Diagnosis of DHF or diastolic dysfunction; an ejection fraction of ≥45% documented within the last year by echocardiography, cardiac catheterisation ventriculography, or radionuclide ventriculography; stable status on cardiac medications for at least 3 months in the period before study enrolment	68	100	II (NR)/III (NR)	≥45%
Karavidas et al., Greece, single centre, NR, 2013.[28]	FES(15)/CT(15)	Symptoms NYHA (class II or III) and signs typical of heart failure; LVEF >50% and LVEDV index <97 ml/m^2; findings of left atrial (LA) dilatation (LA volume index >40 ml/m^2); left ventricular hypertrophy and/or left ventricular diastolic dysfunction (i.e., mitral E/A ratio <1 or >2, mitral E/e' ratio >15 or 8–15 (A pulmonary − A mitral) duration difference >30 ms, etc.); no alterations in medical therapy during the previous 4 weeks, and no myocardial infarction within 3 months before enrolment	69	60	II(70)/III(30)	>50%
Palau et al., Spain, single centre, 2011–2012, 2014[27]	ET (14)/CT(12)	Previous history of symptomatic heart failure NYHA functional class ≥II, normal LVEF (ejection fraction >50% and end-diastolic diameter <60 mm), structural heart disease (left ventricle hypertrophy/left atrial enlargement) and/or diastolic dysfunction estimated by 2D echocardiography and clinical stability.	73	50	II (30)/III (70)	>50%
Kitzman et al., USA, single centre, 1994–1999, 2010[22]	ET (24)/CT(22)	History, symptoms, and signs of HF; a preserved LVEF (≥50%); and no evidence of significant coronary, valvular, or pulmonary disease or any other medical condition that could mimic HF symptoms (anaemia, thyroid dysfunction)	70	75	II (72)/III (28)	>50%
Kitzman et al., USA, single centre, NR, 2013[26]	ET (24)/CT(30)	History, symptoms, and signs of HF; LVEF ≥50%, no segmental wall motion abnormalities, and no significant ischaemic or valvular heart disease, pulmonary disease, anaemia, or other disorder that could explain the patients' symptoms	70	74	II (51)/III (49)	≥50%
Smart, Australia et al, NR, 2004–2005, 2012[25]	ET (16)/CT(14)	Dyspnoeic patients with HFpEF (defined by LVEF>45% and either delayed relaxation or pseudonormal filling)	64	67	I (37)/II (63)	>45%

BMI: body mass index; CT: control group; DHF: diastolic heart failure; DT: deceleration time; E/A: ratio of early to late diastolic mitral inflow waves; E/e': ratio of the mitral inflow E wave to the tissue Doppler e' wave; ET: exercise training group; FES: functional electrical stimulation; LAV: left atrial volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; NR: non reported; NYHA: New York Heart Association.

Table 2. Cardiovascular risk factors and co-morbidities.

Author (reference) year	Hypertension (%)	Atrial fibrillation (%)	Ever smoker (%)	Hyperlipidaemia (%)	Diabetes mellitus (%)	History of CAD (%)	Mean BMI (kg/m^2)	Mean eGFR (ml/min)
Alves et al.[24] 2012	68	3	NR	NR	35	32	31	NR
Edelmann et al.[23] 2011	86	NR	56	47	14	NR	31	NR
Gary[21] 2006	NR	NR	NR	NR	NR	NR	NR	NR
Karavidas et al.[28] 2013	100	40	13	67	47	NR	NR	NR
Palau et al.[27] 2014	96	35	42	89	58	46	31	58.5
Kitzman et al.[22] 2010	68	4	NR	NR	17	NR	30	NR
Kitzman et al.[26] 2013	89	NR	49	NR	24	NR	30	NR
Smart et al.[25] 2012	30	NR	40	NR	16	NR	31.1	NR

AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate (using the Modification of Diet in Renal Disease formula); ES: ever smoker; NR: non reported.

intensity interval training[24] or a combination of moderate-intensity continuous aerobic with strength training.[23] In one recent study, the authors evaluated an inspiratory muscle training modality.[27]

In most of these trials, the control arm received usual medical care with no mention of exercise behaviour; however, only in one study, both groups received an additional educational HF programme.[21]

Efficacy. The main purpose of all of these studies was to evaluate the hypothesis that the different modalities of exercise training would improve any of the following clinical endpoints.

Exercise capacity. Exercise capacity was measured using different instruments such as spirometry-assessed peak oxygen uptake (peak VO_2),[22,23,25–27] 6-minute walked distance (6MWD)[21–23,26] and/or metabolic equivalents (METs).[24,27] Overall, it was observed that all modalities of physical therapies improved exercise capacity in a short-term with a varying degree of improvement among studies (Table 4).

Improvement in peak VO_2 (ranging from 11.3–28.3%) was reported in five studies. The magnitude of improvement in cardiorespiratory fitness according to exercise training intensity was difficult to summarise due to the heterogeneity of exercise interventions (not only in modality but also in intensity). Among the evaluated studies, the modality of exercise training with greater improvement in peak VO_2 was respiratory training.[27] Moderate continuous endurance training[25] and moderate continuous endurance training combined with resistance training[23] showed beneficial effects but the magnitude of the effect reported was lower than respiratory training (Table 4).[27] Likewise, in a recent meta-analysis of five small and heterogeneous studies of subjects with preserved ejection fraction and diastolic dysfunction, Taylor et al.[31] reported that aerobic and resistance exercise training modalities, as compared to usual care, improved exercise capacity (mean increase of peak VO_2 in the exercise training over the control group = 3.0 ml/kg/min, 95% confidence interval (CI): 2.4–3.6, $p < 0.0001$). Worthy of mention is the fact that some studies of this meta-analysis included a wide range of patients with diastolic dysfunction, even patients with no mention of signs or symptoms of HF.[32,33]

Four RCTs reported that low intensity endurance training[21] showed the largest increment in the 6MWD, followed by respiratory training[27] and moderate continuous endurance training,[22,23,26] respectively.

Finally, only two studies reported the results in METs changes. Respiratory training[27] and moderate-high intensity interval endurance training[24] showed improvement in METs.

QoL. Six studies assessed QoL by two validated questionnaires.[21–23,25–27] All of them used the Minnesota Living With Heart Failure Questionnaire (MLHFQ) and three studies[22,23,26] also used the 36-Item Short Form Health Survey (SF-36) as general health tool measure. Physical therapy was associated with a significant improvement in MLHFQ scores in three studies[21,22,27] and in SF-36 scores in two studies (Table 4).[23,26] No significant changes in MLHFQ scores were observed in three studies.[23,25,26] In the meta-analysis of Taylor et al.,[31] a significant improvement of QoL was also reported; in fact, there was a mean reduction of MLHFQ with exercise of −7.3 points (95% CI: −11.4 to −3.3, $p < 0.0001$) as compared to control.

Echocardiographic parameters. Echocardiographic parameters were analysed in six studies. Echocardiographic evidence of diastolic dysfunction was diversely diagnosed among different trials (Table 1).

Table 3. Physical training modalities, endpoints and adverse events.

Author (reference) year	Mode length of program, weeks	Intensity	Frequency, sessions/ week	Comparator	Peak VO_2 at baseline (ml/kg/min) METs 6MWD (meters)	Endpoints	Adverse events
Alves et al.[24] 2012	Interval endurance training (cycling/treadmill) 24	Intervals of 3 to 5′ at 70–75% MHR with 1′ recovery 45–55% MHR	3	UC	NR 3.9 NR	LVEF/exercise capacity/diastolic function	No serious adverse events
Edelmann et al.[23] 2011	Continuous endurance training (cycling) + resistance training 12	HR 50–70% of peak VO_2 + 60–65% 1RM	2–3	UC	16.1 NR 545	Exercise capacity (primary) QoL/Diastolic function/LVEF/ Prognostic biomarkers	No serious adverse events
Gary[21] 2006	Continuous endurance training (walking) 12	4–50% THR	3	UC + heart failure educational programme	NR NR 256	Exercise capacity (6MWD)/QoL	No serious adverse events
Karavidas et al.[28] 2013	Functional electrical stimulation 6	Start at 25 Hz (adjusted to achieve a muscle contraction)	5	UC	NR NR 324	Endothelial function(primary) Exercise capacity/QoL/emotional status/diastolic function/prognostic biomarkers	NR
Palau et al.[27] 2014	Respiratory training 12	30% Maximal inspiratory pressure (weekly measured)	7	UC (+weekly visits for measure of maximal inspiratory training)	10 2.95 294	Exercise capacity (primary) QoL/diastolic function/prognostic biomarkers/ventilatory efficiency	No serious adverse events
Kitzman et al.[22] 2010	Continuous endurance training (cycling/walking) 16	40–70% HRR	3	UC (+telephone calls every 2 weeks)	13.8 NR 455	Exercise capacity (primary) QoL/Diastolic function/LVEF/ biomarkers/ventilatory efficiency	2 HF-hospitalisation in control group
Kitzman et al.[26] 2013	Continuous endurance training (cycling/walking + isolated arm ergometry) 16	40–70% HRR	3	UC (+telephone calls every 2 weeks)	14.2 NR 447	Endothelial function, arterial distensibility, peak VO_2 (primary) QoL/diastolic function/LVEF/ ventilatory efficiency	1 HF-hospitalisation in exercise group
Smart et al.[25] 2012	Continuous endurance training (cycling) 16	HR 60–70% peak VO_2	3	UC	12.2 NR NR	Exercise capacity/QoL/diastolic function/LVEF/ventilatory efficiency	No serious adverse events

1RM: one-repetition maximum; 6MWD: 6-minute walked distance; HF: heart failure; HR: heart rate; HRR: heart rate reserve; LVEF: left ventricular ejection fraction; METs: metabolic equivalents; MHR: maximal heart rate; NR: non reported; QoL: quality of life; THR: target heart rate; UC: usual care; VO_2: oxygen uptake.

Table 4. Efficacy of different physical therapies.

Author (reference), year	Exercise capacity	QoL	Echocardiographic parameters	Biomarkers	Others surrogate endpoints
Alves et al.[24] 2012	↑ METs by 8% ($p = 0.046$)	NR	↑ LVEF by 2,3% ($p = 0.01$) ↑ E/A ratio by 13% ($p < 0.001$) ↓ DT by 6% ($p < 0.001$)	NR	NR
Edelmann et al.[23] 2011	↑ Peak VO_2 by16% ($p < 0.001$) ↑ 6MWD by 4.4% ($p = 0.001$)	↑QoL (SF-36) by 22% ($p < 0.001$) No significant changes in MLHFQ	↓ E/e' ratio by 19% ($p < 0.001$) LAV by 13.3% ($p < 0.001$) No changes in other echocardiographic parameters	↓Procollagen type I by 2.5% ($p = 0.049$) No significant changes in NT-proBNP levels	NR
Gary[21] 2006	↑ 6MWD by 24.2% ($p = 0.002$)	↑ QoL (MLHFQ) by 42% ($p = 0.002$)	NR	NR	NR
Karavidas et al.[28] 2013	↑ 6MWD by 23.5% ($p = 0.001$)	↑ QoL: MLHFQ by 62.5% and KCCQ by 38.2% ($p = 0.017$ and $p = 0.006$)	No significant changes in echocardiographic parameters	No significant changes in BNP levels	↑ brachial artery FMD by 56.6% ($p = 0.002$) ↑ BDI and SDS scales by 45.8% and 23.3% ($p = 0.015$ and 0.019)
Palau et al.[27] 2014	↑ Peak VO_2 by 28.3% ($p < 0.001$) ↑ 6MWD by 12.7% ($p < 0.001$) ↑ METs by 23.7% ($p < 0.001$)	↑ QoL (MLWHFQ) by 26.8% ($p = 0.037$)	No significant changes in echocardiographic parameters	No significant changes in NT-proBNP levels No significant changes in CA125 levels	↓ VE/VCO_2 slope by 16.1% ($p = 0.007$)
Kitzman et al.[22] 2010	↑ Peak VO_2 by 16.7% ($p < 0.001$) ↑ 6MWD by 11% ($p < 0.002$)	↑ physical QoL (MLHFQ) by 31.3% ($p = 0.03$) No significant changes in SF-36	No significant changes in echocardiographic parameters	No significant changes in BNP levels or norepinephrine	No significant changes in CES-D score. No significant changes in VE/VCO2 slope
Kitzman et al.[26] 2013	↑ Peak VO_2 by 11.3%($p < 0.001$) ↑ 6MWD by 8.7% ($p < 0.009$)	↑ physical and emotional QoL(SF-36) by 31.3 and 31.7% ($p = 0.03$ and 0.04) No significant changes in MLHFQ	No significant changes in echocardiographic parameters	NR	No significant changes in endothelial function or arterial FMD No significant changes in VE/VCO_2 slope
Smart et al.[25] 2012	↑ Peak VO_2 by 24.6% ($p = 0.02$)	No significant changes in QoL (MLHFQ)	No significant changes in echocardiographic parameters	NR	↓ VE/VCO_2 slope by 12.7% ($p = 0.02$) No significant changes in Hare-Davis scale.

6MWD: 6-minute walked distance; BDI: Beck Depression Inventory; BNP: brain natriuretic peptide; CA125: carbohydrate antigen 125; CES-D: Center for Epidemiological Studies Depression survey; CET: continuous endurance training; CT: control group; DT: deceleration time; E/A: ratio of early to late diastolic mitral inflow waves; E/e': ratio of the mitral inflow E wave to the tissue Doppler e' wave; ET: exercise training group; FES: functional electrical stimulation; FMD: flow-mediated arterial dilation; Hare-Davis: depression scale for cardiac patient; HFpEF: heart failure preserved ejection fraction; IET: interval endurance training; KCCQ: Kansas City Cardiomyopathy Questionnaire; LAV: left atrial volume; METs: metabolic equivalents; MIP: maximal inspiratory pressure; MLHFQ: Minnesota Living with Heart Failure Questionnaire score NR: non reported; NT-proBNP: N-terminal pro brain natriuretic peptide; QoL: quality of life; RT: respiratory training; RST: resistance/strength training; SDS: Zung self-rating depression scale; SF-36: 36-Item Short Form Health Survey; UC: usual care; VE/VCO_2 slope: slope of ventilation (VE) relative to CO_2 production (VCO_2); VO_2: oxygen uptake.

There were no changes in any echocardiographic parameters in four studies.[22,25–27] Two studies reported significant improvement in different echocardiographic parameters after exercise training (Table 4).[23,24] For instance, Edelmann et al.[23] found that 12 weeks of combined aerobic and resistance training was associated with a significant reduction of left atrial volume index and resting E/e' ratio. Moreover, in a smaller study, Alves et al.[24] reported that 24 weeks of interval endurance training improved not only diastolic function (reduction in resting E/A ratio and deceleration time) but also resting left ventricular systolic function (Table 3).

Biomarkers. Measurement of different prognostic biomarkers was carried out in three studies.[22,23,27] Changes in brain natriuretic peptides were evaluated in the three studies with no significant reduction in any of them after exercise training. Only Edelmann et al.[23] reported a significant decrease of procollagen type I biomarker after 12 weeks of combined aerobic and resistance training (Table 3).

Other surrogate endpoints. Other surrogate endpoints, such as endothelial function or ventilatory efficiency,[34] were assessed in some studies (Table 3). Kitzman et al., after 16 weeks of continuous endurance training, did not find differences between the two groups on endothelial and arterial stiffness.[26] Changes in ventilatory efficiency were evaluated in four studies. In two, continuous endurance[26] and respiratory training[27] were associated with a significant improvement in the pattern of ventilatory efficiency. However, no significant differences were found in other two studies (Table 4).[22,26]

Major clinical outcomes. None of the studies were designed to analyse the effect of exercise training on major clinical outcomes. No deaths in the seven RCTs were reported. However, Kitzman et al.,[22] reported two hospitalisations in the control group (one of them for acute pulmonary oedema) during the follow-up. This same group reported one HF-related hospitalisation in the exercise training group in another study.[26]

Safety, compliance and logistic feasibility. No serious adverse events related to the interventions were reported in any study. Two studies reported minor adverse events during or immediately after exercise. In one study,[23] 11 patients in the training group (25%) manifested some complaints: palpitations ($n=2$), transient dyspnoea ($n=3$) and mild musculoskeletal discomfort during exercise ($n=9$). Only one patient left the trial after one week of exercise sessions without requiring hospitalisation. In another study, Kitzman et al., reported an isolated case of transient hypoglycaemia during an exercise session.[26] Overall, the trials performed up-to-date have corroborated the safety of the different modalities of exercise training (Table 3).

Data on compliance and adherence to exercise training varied among the seven studies. Adherence to exercise training sessions was not reported in all studies. In four studies, the degree of adherence ranged from 64–100%.[21–23,26]

Regarding logistic feasibility, exercise training was centre-based and supervised in five studies[22–26] and home-based in two of them.[21,27]

Other physical therapies in HFpEF

To date, only one trial has analysed the effects of passive intervention, such as functional electrical stimulation (FES), on HFpEF.[28] This RCT evaluated the effects of a supervised six-week FES programme over a selected population of 30 HFpEF patients in terms of exercise capacity, QoL, diastolic function, biomarkers and endothelial function (Tables 1–4). The authors found that short-term FES improved functional capacity, QoL and endothelial function with no changes in levels of biomarkers nor in diastolic function. No results regarding safety or compliance were reported.

Discussion

The present review summarised data from eight prospective RCTs that examined the effects of different modalities of physical therapies in HFpEF patients. Findings from these trials suggest that most of these physical therapy protocols can be safely implemented in patients with HFpEF. In terms of efficacy, exercise training seems to improve functional capacity and QoL. Evidence is not convincing regarding changes in echo parameters, biomarkers and other surrogate endpoints. Data regarding other physical therapies are even scarcer. Unfortunately, the effect of physical therapies on major clinical outcomes such as mortality or hospitalisation is unknown.

These findings contrast with the robust information available on exercise-based rehabilitation for HFrEF (30 trials with more than 4000 HFrEF patients),[17] where physical therapy has commonly shown positive results by improving not only major clinical events, QoL and exercise capacity[17,18] but also echo parameters,[35,36] biomarkers[37] and other surrogate endpoints[34,38] of HF severity. The basis for this discrepancy is not well understood; potentially epidemiological differences including aetiology and the burden of associated co-morbidities may be crucial issues.[39,40] For instance, the importance of prevalent

conditions in HFpEF that may operate as important confounders such as coronary artery disease (ranging from 36–42% among different studies), renal dysfunction and chronic obstructive pulmonary disease remains to be clarified.

Because of the limited information available on HFpEF, these results must be considered preliminary. Thus, a number of flaws and pitfalls must be considered before extracting definitive conclusions.

Few trials, few patients. The available evidence stemmed on the information supplied by only eight trials, where the number of participants ranged from 26–64.

Heterogeneous interventions. Each trial has employed a different exercise training modality with a singular intensity and duration protocol. For instance, four studies evaluated continuous endurance training with different intensity levels,[21,22,25,26] one trial assessed combined continuous aerobic with strength training[23] whereas only one analysed interval training[24] or inspiratory muscle training.[27]

Heterogeneous criteria for defining HFpEF. Appropriate diagnosis of HFpEF remains a matter of debate. Overall, diagnostic criteria for defining HFpEF requires the simultaneous and obligatory presence of four conditions to be satisfied: (a) typical signs and symptoms of HF; (b) typical symptoms of HF; (c) normal LVEF with left ventricle not dilated; and (d) relevant evidence of structural heart disease, such as left ventricular hypertrophy, left atrial enlargement, and/or diastolic dysfunction.[20] Only two studies[27,28] fulfilled all four criteria. The most frequently overlooked condition for the diagnosis of HFpEF[19,20] was the evidence of left ventricle not dilated. In fact, only two trials[27,28] required this condition as inclusion criteria. The other overlooked condition was related to failure of achieving the criteria for diastolic dysfunction. Only five HFpEF trials[21,23,25,27,28] required this diagnosis as an enrolment criterion. Finally, two studies did not meet the recommended criterion for LVEF in HFpEF, with a generally accepted LVEF cutpoint at >50% (Table 1).[21,25] Furthermore, it is remarkable that none of the current studies have selected a natriuretic peptide level as an inclusion criterion. We believe this is an important flaw with potential repercussions on correct patient selection.

Heterogeneous population. In contrast to the evidence presented in population-based studies,[2] patients included in this systematic review are younger and have a lower prevalence of co-morbidities (when it was reported) (Table 2). Moreover, the baseline distribution of clinical variables such us severity of symptoms (NYHA class) or parameters of exercise capacity (peak VO_2, 6MWD and METs) varied among these trials (Table 1). As an example, only two studies included predominantly patients with NYHA functional class III and severely reduced aerobic capacity.[21,27]

Endpoints. We should point out that data on efficacy was only based on intermediate endpoints such as exercise capacity, QoL, diastolic dysfunction or endothelial dysfunction. Besides, every study has used different diagnostic methods for assessing functional capacity[30,41] (peak VO_2, 6MWD or METs) and/or echocardiographic evidence of diastolic dysfunction[42,43] Moreover, none of the trials reviewed were designed to evaluate the efficacy of these techniques on major clinical outcomes.

Future directions

We believe that this research avenue should be further developed by including larger RCTs, testing different physical therapy modalities, and including patients with more advanced disease, and thus be more representative of the real-world population. At the same time, more trials with a follow-up planned to evaluate long-term effects, especially regarding major clinical and safety endpoints are needed. Equally important is also the cost-effectiveness evaluation.

Along these lines, we believe that the results from ongoing larger multi-centre Ex-DHF ($n = 320$) and OptimEx-CLIN ($n = 180$) trials[44,45] will provide more evidence about the long-term efficacy, safety and logistic feasibility of exercise training in HFpEF.

Conclusions

The eight trials included in this systematic review provided evidence that exercise training and, perhaps, other physical therapies are a safe approach for the treatment of HFpEF. The evidence here presented also suggests a significant short-term improvement in functional capacity and quality of life associated with the intervention. However, large studies are warranted aiming at determining the effect of exercise training on long-term adverse clinical outcomes, and on cost-effectiveness parameters.

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Conflict of interest

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