Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies

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CRD summary
This review concluded that exercise training for patients with heart failure, with a preserved ejection fraction, could improve exercise capacity and health-related quality of life, and it appeared to be safe. Given the lack of high-quality data, these conclusions seem overly strong. The recommendation for further research seems appropriate.

Authors' objectives
To assess the effects of exercise training for patients with heart failure, with a preserved ejection fraction.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, MEDLINE In Process, CINAHL, PsycINFO, ISRCTN Register, ClinicalTrials.gov, and Web of Science were searched, without language and date restrictions; search terms were reported and the MEDLINE strategy was given in an appendix. The reference lists of included studies were searched.

Study selection
Comparative studies of adults (over 18 years old) with heart failure with a preserved ejection fraction, or diastolic heart failure of any aetiology, who received exercise training alone or as part of a comprehensive rehabilitation programme, were eligible for inclusion. Eligible outcomes were mortality, hospitalisations, health-related quality of life (assessed by a validated tool), exercise capacity, diastolic function, left ventricular function, and adverse events. Studies of patients with various conditions were included if the results for those with heart failure with a preserved ejection fraction were reported separately.

Across the included studies, the mean age ranged from 55 to 70 years; 52% of participants were male. The minimal ejection fraction for entry into a study was 45% or 50%. Most studies were of supervised interventions, with various regimens; the exercise programmes lasted from 12 to 24 weeks. The comparators varied across studies, but none included exercise training.

Two independent reviewers selected studies for the review; disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed, using the Cochrane risk of bias tool, by one reviewer. This assessment was checked by a second reviewer.

Data extraction
The mean changes from baseline in the measures of exercise capacity and health-related quality of life, along with either 95% confidence intervals or standard deviations, and the incidences of death, hospital admission, and serious adverse events, were extracted by one reviewer and checked by a second. Study authors were contacted for missing information.

Methods of synthesis
The pooled mean differences, with 95% confidence intervals, were calculated using a fixed-effect meta-analysis, unless substantial heterogeneity was observed ($I^2 \geq 50\%$), in which case a random-effects model was used. Heterogeneity was investigated using $X^2$ and $I^2$. An assessment of publication bias was planned, but too few studies were identified.

Results of the review
Five studies met the inclusion criteria, with 228 participants (range 26 to 67); three were randomised controlled trials (152 participants), one was a non-randomised controlled trial (50 participants), and one was a before-and-after study (26 participants). Of the five studies, only one reported concealed allocation, none showed imbalances in baseline
characteristics, two reported blinding outcome assessors, and four reported an intention-to-treat analysis. Where reported, loss to follow-up ranged from 4% to 31%. Follow-up ranged from 12 to 24 weeks.

Compared with controls, exercise training significantly increased the mean peak oxygen uptake (MD 3.0mL/kg per minute, 95% CI 2.4 to 3.6; four studies; $I^2$=31%), health-related quality of life (MD −7.3 Minnesota Living with Heart Failure score, 95% CI −11.4 to −3.3; four studies; $I^2$=34%).

There was no statistically significant impact of exercise training on left ventricular end-diastolic volume (two studies), change in left ventricular ejection fraction (three studies), left ventricular volume index (one study), the ratio between early and late ventricular filling velocity (three studies), and the ratio between early diastolic peak left ventricular inflow velocity and the early diastolic peak lateral mitral annular velocity (three studies).

There were no deaths across the studies, and only one heart failure-related hospital admission, in a control patient. One study reported 11 minor adverse events, with exercise training, and one study reported no adverse events, with exercise training; the other three studies did not report whether adverse events occurred or not.

Authors’ conclusions
Exercise training for patients with heart failure, with a preserved ejection fraction, could improve exercise capacity and health-related quality of life, and was safe. Its impact on diastolic function remained unclear.

CRD commentary
The review addressed a clear research question, with reproducible inclusion criteria. An extensive search was conducted for published studies and ongoing trials, without language restrictions; no specific search for unpublished studies was reported. Appropriate methods were used to reduce error and bias. Appropriate criteria were used to assess the quality of the included randomised controlled trials, and the results were published in full; other study designs were included, but criteria specific to these designs were not assessed.

All of the included studies were subject to bias, and they were small, with up to 31% of participants being lost to follow-up. The results of a statistical test for heterogeneity, rather than the clinical comparability of the studies, was used to determine the choice of model, resulting in a mixture of fixed-effect and random-effects analyses. Given the small number of studies included in all of the analyses, the use of a random-effects model is questionable, as there were insufficient studies to inform the distribution of effects within the model. In addition, the substantial clinical heterogeneity across the studies makes the value of pooling the studies, even with a fixed-effect model, uncertain.

Given the lack of high-quality data, the conclusions of the review seem overly strong; the authors did not define what they considered to be clinically relevant improvement. The recommendation for further research seems appropriate.

Implications of the review for practice and research
Practice: The authors stated that their results supported the guidelines that recommended exercise-based interventions for patients with heart failure and a preserved ejection fraction. But the impact of exercise training on diastolic function and peripheral haemodynamics, and the long-term outcomes, remained unclear.

Research: The authors stated that adequately powered trials, with objectively defined patients with heart failure with a preserved ejection fraction, were required. These trials should provide data on the long-term effects, prognostic relevance, and cost-effectiveness. They reported that a relevant randomised controlled trial was in process.

Funding
Funded by the National Institute for Health Research, UK.

Bibliographic details

PubMedID
22664368
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.