Inspiratory muscle training in patients with heart failure: meta-analysis of randomized trials

CRD summary
The authors concluded that inspiratory muscle training improved functional capacity and inspiratory muscle strength, so deserves consideration as an additional intervention in patients with chronic heart failure. Limitations of the evidence suggest that these conclusions may be overly strong.

Authors' objectives
To compare the effects of inspiratory muscle training with placebo or another intervention in patients with chronic heart failure.

Searching
MEDLINE, Physiotherapy Evidence Database and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1960 to July, 2011. No language or publication status restrictions were imposed. Search terms were reported. Bibliographies of published studies were searched to locate further studies.

Study selection
Randomised controlled trials that compared the effects of inspiratory muscle training with placebo or another intervention were included. Eligible study populations were chronic heart failure patients with New York Association functional class I, II or III. The primary outcome of interest was peak oxygen consumption (VO$_2$ in ml/kg/min$^{-1}$); other outcomes of interest included distance walked in the 6-minute walk test (6-MWT) in metres (m), and maximal static inspiratory pressure (Plmax) in centimetres of water (cmH$_2$O). To be included, all trials had to have a follow-up period of six weeks or more.

Mean age of participants ranged from 54 to 76 years. Most studies compared inspiratory muscle training to placebo, with minimum or no inspiratory load. One trial's control group received another intervention (an education program). Another trial compared inspiratory muscle training plus aerobic exercise to aerobic exercise alone. Proportions of male participants, intensity of interventions, and proportions of patients in each functional class varied across the included trials. Intervention duration ranged from six to 12 weeks.

Two reviewers independently selected studies for inclusion; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed the risk of bias in trials according to the following criteria: adequate sequence generation, allocation concealment, blinding of participants, investigators and outcome assessors, use of intention-to-treat analysis, and description of drop-outs. The GRADE approach was used to evaluate the overall strength of evidence for each outcome.

Data extraction
Data on the outcomes (least square mean percentage change from baseline to study end for each trial arm) were extracted to calculate mean differences and 95% confidence intervals. Two reviewers independently extracted the data; any disagreements were resolved by consensus.

Methods of synthesis
Mean differences and 95% confidence intervals from individual studies were pooled per outcome, using inverse variance random-effects models. The summary pooled estimates were weighted mean differences. Between-study heterogeneity was assessed using the Cochran's Q test and I$^2$ (values above 25% indicated moderate heterogeneity, and values above 50% indicated high heterogeneity). Any heterogeneity was explored by re-running meta-analyses and removing a different trial every time, or by performing sensitivity analyses on the trials most likely to yield valid estimates of the intervention (based on pre-specified information related to intervention and participant characteristics, Database of Abstracts of Reviews of Effects (DARE) Produced by the Centre for Reviews and Dissemination Copyright © 2020 University of York
which might influence the effect of inspiratory muscle training on outcomes).

**Results of the review**

Seven randomised controlled trials were included in the review (174 participants), and six of these were included in the meta-analysis (150 participants). Five of the seven trials reported adequate sequence generation, one reported allocation concealment, one reported blinding of participants and investigators, four reported blinding of outcome assessors and six adequately described dropouts. None of the trials reported intention-to-treat analyses. Overall strength of the evidence was rated as very low for the peak VO\textsubscript{2} and 6-MWT outcomes and low for the Plmax outcome.

**Peak oxygen consumption (three trials):** Inspiratory muscle training provided a statistically non-significant improvement in peak VO\textsubscript{2} compared with controls (WMD=1.98 ml/kg/min\textsuperscript{-1}, 95% CI -0.67 to 4.62). Statistical heterogeneity for this meta-analysis was high (I\textsuperscript{2}=59%). Removal of one trial resulted in the eradication of statistical heterogeneity (I\textsuperscript{2}=0%), and a weaker improvement in peak VO\textsubscript{2} with inspiratory muscle training. Further sensitivity analysis was conducted in the two trials of 12 weeks duration that compared inspiratory muscle control training to placebo control groups with no inspiratory load in patients with inspiratory muscle weakness. In this analysis, inspiratory muscle training resulted in a clinically significant improvement in peak VO\textsubscript{2} compared with controls (WMD 3.02 ml/kg/min\textsuperscript{-1}, 95% CI 0.43 to 5.61), although moderate heterogeneity was shown (I\textsuperscript{2}=39%).

**Distance walked in the 6-MWT (three trials):** A statistically significant improvement in distance walked was observed with inspiratory muscle training, compared with controls (WMD 69m, 95% CI 7.21 to 130.79); high heterogeneity was shown (I\textsuperscript{2}=78%). A sensitivity analysis, only including the two trials that performed the intervention for six weeks with placebo controls that had an inspiratory load of 10% and 15% was performed. This resulted in a smaller, but still statistically significant improvement with the inspiratory muscle training (WMD 43.59m, 95% CI 12.77 to 74.41; I\textsuperscript{2}=0%).

**Maximal static inspiratory pressure (six trials):** A statistically significant improvement in Plmax was observed for inspiratory muscle training, compared with controls (WMD 23.36cmH\textsubscript{2}O, 95% CI 11.71 to 35.02); high heterogeneity was shown (I\textsuperscript{2}=64%). Removal of two trials with particular population characteristics eradicated the heterogeneity (I\textsuperscript{2}=0%) and did not substantially change the pooled result. Subgroup analyses according to the duration of the intervention (six to eight weeks, 12 weeks) also resulted in statistically significant improvements with inspiratory muscle training over controls, although the effect was stronger with interventions of longer durations. No heterogeneity was shown in the analysis of six to eight week interventions, but it was high among the 12 week interventions (I\textsuperscript{2}=76%). Results from the meta-analyses (and the single trial not included in the meta-analyses) were fully reported in the review.

**Authors’ conclusions**

Inspiratory muscle training improved functional capacity and inspiratory muscle strength, so deserved consideration as an additional intervention in patients with chronic heart failure.

**CRD commentary**

The review question and inclusion criteria were clearly defined. Relevant databases were accessed and no language restrictions were imposed, but the limited search for unpublished literature may mean that relevant studies were missed. Efforts were made throughout the review process to minimise any reviewer error or bias, and a suitable quality assessment tool was used. Results showed that the quality of studies was mixed, and the overall strength of evidence for the outcomes was low or very low. Study details were presented.

The statistical methods of synthesis may not have been appropriate, given the heterogeneity between the small number of trials that were included. Sample sizes were small and confidence intervals for the pooled results were wide, which indicated a high degree of imprecision. The authors stated that the low or very low strength of the evidence means that any estimate of effect was very uncertain, and that further research was likely to have a major impact and change the estimate. They also acknowledged that many of the included trials were limited by their methodology and were not sufficiently powered.

Given these limitations it appears as though the authors’ conclusions may be overly strong.

**Implications of the review for practice and research**

Practice: The authors stated that inspiratory muscle training deserved consideration as an additional intervention in patients with chronic heart failure.

Research: The authors stated that larger randomised controlled trials, with more rigorous methodology and longer periods of intervention, were required to further investigate the benefit of inspiratory muscle training in people with chronic heart failure.

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