Respiratory Medicine (2008) **102**, 1715–1729

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Inspiratory muscle training in adults with chronic obstructive pulmonary disease: An update of a systematic review

E. Lynne Geddes [a,*], Kelly O'Brien [b], W. Darlene Reid [c], Dina Brooks [b], Jean Crowe [a]

[a] *School of Rehabilitation Science, Institute of Applied Health Science, Room 403, McMaster University, 1400 Main Street West, Hamilton, ON, Canada L8S 1C7*
[b] *Department of Physical Therapy, University of Toronto, 500 University Avenue, Room 160, Toronto, ON, Canada M5G 1V7*
[c] *Department of Physical Therapy, University of British Columbia, 617 – 828 W. 10th Avenue, Research Pavilion, VCHRI Vancouver, BC, Canada V5Z 1L8*

Received 17 March 2008; accepted 8 July 2008
Available online 15 August 2008

KEYWORDS
Respiratory muscles;
Inspiratory muscle training;
Breathing exercises;
Lung diseases, obstructive;
Chronic obstructive pulmonary disease;
Pulmonary rehabilitation

Summary
The purpose was to update an original systematic review to determine the effect of inspiratory muscle training (IMT) on inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life for adults with chronic obstructive pulmonary disease (COPD).

The original MEDLINE and CINAHL search to August 2003 was updated to January 2007 and EMBASE was searched from inception to January 2007. Randomized controlled trials, published in English, with adults with stable COPD, comparing IMT to sham IMT or no intervention, low versus high intensity IMT, and different modes of IMT were included.

Nineteen of 274 articles in the original search met the inclusion criteria. The updated search revealed 17 additional articles; 6 met the inclusion criteria, all of which compared targeted, threshold or normocapneic hyperventilation IMT to sham IMT. An update of the sub-group analysis comparing IMT versus sham IMT was performed with 10 studies from original review and 6 from the update.

Sixteen meta-analyses are reported. Results demonstrated significant improvements in inspiratory muscle strength (PI_{max}, PI_{max} % predicted, peak inspiratory flow rate), inspiratory muscle endurance (RMET, inspiratory threshold loading, MVV), exercise capacity (Ve_{max}, Borg Score for Respiratory Effort, 6MWT), Transitional Dyspnea Index (focal score, functional impairment, magnitude of task, magnitude of effort), and the Chronic Respiratory Disease Questionnaire (quality of life).

* Corresponding author. Tel.: +1 905 525 9140x27813; fax: +1 905 524 0069.
E-mail address: geddesl@mcmaster.ca (E.L. Geddes).

0954-6111/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2008.07.005

Results suggest that targeted, threshold or normocapneic hyperventilation IMT significantly increases inspiratory muscle strength and endurance, improves outcomes of exercise capacity and one measure of quality of life, and decreases dyspnea for adults with stable COPD.
© 2008 Elsevier Ltd. All rights reserved.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease of the small airways and lung parenchyma characterized by airflow limitation that is not fully reversible.[1] Because COPD commonly is associated with long-term smoking, it tends to arise in middle age[1] and progresses with aging.[1,2] As a result, the prevalence, morbidity and mortality of COPD increase with age.[2]

Worldwide, the prevalence of moderate ($FEV_1 < 80\%$ predicted) to very severe ($FEV_1 < 30\%$ predicted) COPD is 10%.[3] COPD also is associated with substantial societal burden and mortality. Using disability-adjusted life years (DALYs) as a measure of burden of disease, COPD is projected to increase from the 11th leading cause of DALYs in 2002 to the seventh leading cause in 2030.[4] Similarly, in 2002 COPD was the fifth leading cause of death and is projected to be the fourth leading cause of death in 2030.[4]

Pulmonary rehabilitation is an important component in the management of COPD. It has been shown to improve exercise capacity and health related quality of life, and to reduce breathlessness, anxiety or depression, and the frequency and length of hospitalizations related to COPD.[1,5] Exercise training, a key component of a pulmonary rehabilitation program, may include aerobic exercise such as cycling or walking as well as upper and lower extremity strength training.[1,6,7]

The role of inspiratory muscle training (IMT) for individuals with stable COPD is unclear. The first systematic review on IMT found little evidence to support the use of IMT. However, given limitations in the included studies, Smith and colleagues[8] recommended further research be done. A second systematic review, published in 2002, supported the inclusion of IMT as a part of pulmonary rehabilitation.[9] A third systematic review of randomized control studies compared IMT with sham IMT or no intervention, low versus high intensities of IMT, and different modes of IMT.[10] Results showed improvements in some measures of inspiratory muscle strength and endurance, exercise capacity, and dyspnea with individuals with COPD using targeted or threshold type IMT compared to sham IMT or no intervention.

IMT is not routinely used or recommended.[7,11,12] Neither the American Thoracic Society/European Respiratory Society standards[12] nor the Canadian Thoracic Society Recommendations for the Management of COPD[7] recommend the incorporation of IMT into management plan. The Global Initiative for Chronic Obstructive Lung Disease[1] states that ''respiratory muscle training is beneficial, especially when combined with general exercise training'' (p. 56) based on Level C evidence from non-randomized trials and observational studies.

The purpose of this article is to update the results of the original systematic review conducted by Geddes et al.[10] The objective was to determine the effect of IMT on inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life in adults with COPD.

Methods

Search strategy

A systematic review was conducted using the methods of the Cochrane Collaboration.[13] In the original review, MEDLINE and CINAHL databases, and reference lists from appropriate articles were searched up to August 2003. Authors were contacted for additional data and targeted journals were hand-searched to locate articles for inclusion. In this update, an additional search of the literature was conducted from September 2003 to January 2007 using similar methods to the original review. In addition, EMBASE was searched from inception to January 2007.

Study inclusion

All articles retrieved from the updated search were reviewed independently by two reviewers (KO and DB) to identify the studies that met the inclusion criteria of (i) randomized controlled trial or randomized cross-over trial; (ii) published in English; (iii) with adult participants 18 years of age or older with a diagnosis of stable COPD; and (iv) compared IMT to sham IMT or no intervention, low versus high intensities of IMT, and different modes of IMT. If there was lack of agreement between the reviewers on inclusion, a third reviewer independently read the article and determined study inclusion.

Types of inspiratory muscle training

IMT was defined as any intervention with the goal of training the inspiratory muscles. Types of IMT were classified as non-targeted, targeted, threshold or normocapneic hyperventilation. Sham IMT was defined as using the same type of IMT device at an intensity of ≤ 8.3 cm H_2O for normocapneic individuals or ≤ 11.5 cm H_2O for individuals with moderate hypercapnia.[10] These definitions are further explained in the original review.[10]

Data abstraction

Two reviewers (LG and WDR) independently abstracted the relevant data from each included article onto standardized data abstraction forms. Outcomes assessed for this systematic review included measures of inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life. Data abstraction was confirmed between the two reviewers. If needed, a third reviewer confirmed any discrepancies or uncertainties related to the data abstraction process (KO). Authors were contacted for additional data or information, as necessary.

Methodological quality of the included studies was assessed by two reviewers (LG and WDR) using the Jadad criteria, including randomization, blinding and withdrawals.[14] All studies also were assessed for similarity of groups of participants at baseline and whether an intention-to-treat analysis was conducted. Given the absence of a validated scoring system for assessing the true validity of a trial, a descriptive summary of the methodological quality for all included studies is provided rather than generating an overall quality score.[13]

Data analysis

Where studies were comparable, using similar participants, similar interventions, similar training protocols, and similar outcome measures, meta-analyses were performed using RevMan 4.2.2 computer software.[15] Given that targeted, threshold and normocapneic hyperventilation modes of IMT all include a baseline maximum inspiratory pressure and involve working toward a targeted percentage of the maximal workload, they were considered comparable for this update.

Outcomes were analyzed as continuous variables using a random effects model to determine the weighted mean difference and 95% confidence interval (CI). There were no dichotomous outcomes in this review. A p value less than 0.05 indicated statistical significance for an overall effect and a p value less than 0.1 indicated statistical significance for heterogeneity between studies.[16] In instances of significant heterogeneity, sensitivity analyses were performed whereby studies were systematically removed from the analyses to determine the robustness of the results. Potential reasons for significant heterogeneity were discussed and a rationale determined for whether combining studies made practical sense, as suggested by Lau et al.[16]

Results

Included studies

The search from the initial review revealed 274 articles, of which 19 articles[17–35] met the inclusion criteria. Ten of these studies compared targeted or threshold IMT to sham IMT,[26–35] two studies compared IMT to no intervention,[17,18] one study compared low to high intensity IMT[19] and six studies compared non-targeted IMT to sham IMT.[20–25] The search for this update resulted in an additional 17 articles of which six[36–41] met the inclusion criteria. The two reviewers (KO and DB) achieved total agreement pertaining to study inclusion for this review update. All six of these studies compared targeted, threshold or normocapneic hyperventilation IMT to sham IMT.[36–41] Hence, it was possible to perform an update of those types of IMT versus sham IMT sub-group analysis. This update focuses on the results of the sub-group analysis comparing targeted, threshold or normocapneic hyperventilation IMT versus sham IMT with 16 studies (10 from original review and 6 from the update). None of these 16 studies reported a co-intervention in conjunction with IMT or sham IMT.

Targeted, threshold, or normocapneic hyperventilation IMT versus sham IMT

Characteristics of the 16 included studies are provided in Table 1.[26–41] Two authors were contacted for additional data.

Participant characteristics

Participants in the included studies were adults with moderate to very severe COPD[1,12] as shown by a mean FEV_1 ranging from 24 to 54% predicted[27–33,35–41] or FEV_1/FVC ratio of 0.33–0.39.[26,34] The mean age of participants for all the studies was between 56 and 68 years.[26–41] Participants were predominantly males[26–37,39–41] with the exception of one study that included more females.[38] The mean inspiratory muscle strength of participants at baseline ranged from 42 to 72 cm H_2O for the studies that reported measuring PI_{max} from residual volume[28,30,36,38–41] or from 35.8 to 68.5 H_2O for the studies that reported measuring PI_{max} from functional residual capacity.[26,27,31–34,37]

Methodological quality of included studies

All 16 included studies[26–41] were described as randomized but only three described the randomization process: either a random number table[36,40] or a computer generated random number sequence stratified for sex and severity of airflow obstruction.[37]

Ten of the 16 studies were described as double-blinded in which both the participants and outcome assessors were blind to the intervention and allocation of participants within groups.[29–31,33,34,36,37,39–41] One study was assumed to be double-blinded since the assessors were blinded to the intervention and the allocation of participants within groups, and the participants were unaware of the intervention they received due to the use of sham IMT.[38] Single-blinding occurred in the remaining five studies in which participants were unaware of the intervention they received due to the use of sham IMT.[26–28,32,35]

Fourteen of the 16 included studies reported on participants who withdrew from the study. Five of these 14 studies reported no withdrawals.[28,33,35,39,41] Withdrawal rates in the remaining nine studies ranged from 5.7 to 51.1%.[26,27,29–31,36–38,40] Reasons for withdrawal included: respiratory problems or exacerbations,[27,29,30,38] intercurrent illness,[26,29,37] family or transportation issues,[29,37] death,[36,40] or other reasons, including lack of interest in the program.[29,36,40]

Thirteen of the 16 included studies reported that comparison groups were similar at baseline.[26–29,32,33,35–41] Two studies did not report on group similarity at baseline[31,34] and one study had older participants with lower arterial oxygen in the sham group.[30]

Intention-to-treat analysis was performed in the three studies that reported no withdrawals[28,39,41] and was inferred in nine studies because group participants appeared to be analyzed based on the groups to which they were originally randomized.[26,31–34,36–38,40] In the remaining four studies, a per protocol analysis was conducted whereby

Table 1 Characteristics of studies included in the systematic review: targeted inspiratory resistive IMT or threshold IMT versus sham IMT

Study	Method	Sample size (N = at baseline; W = % withdrawal)	Patient characteristics (mean age in years; % male upon completion of study)	Severity of COPD (FEV_1 % predicted or FEV_1/FVC; mean pCO_2 at baseline)	Mode of IMT and supervision	Monitoring of breathing pattern	Time, intensity and progression of IMT	Frequency and duration of IMT	Intensity of sham IMT (cmH_2O)	Outcomes of interest assessed
Beckerman et al.[36,a]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 42$; $W = 26.1\%$	67 Years; 76% male	FEV_1 42% predicted; pCO_2 NR	Threshold load trainer — POWERbreathe; supervised by RTh during 1st month, daily phone calls and weekly visit by RTh for remaining 11 months of study	NR	15 min per session @ 15% PI_{max} week 1; increased 5–10% each session to achieve 60% PI_{max} by end of week 4, intensity then adjusted monthly to maintain 60% PI_{max}	2× per day, 6 times per week for 12 months	7	Inspiratory muscle strength, exercise capacity, quality of life, pulmonary function tests/spirometry
Belman et al.[26]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$; $W = 15.0\%$	64 Years; 59% male	$FEV_1/FVC = 0.33$; 39 mmHg	Targeted inspiratory resistance trainer; daily log and supervision once per week in lab	Controlled at 12.5 breaths per minute	15 min per session @ the maximum pressure tolerated	2× per day, 7 days per week for 6 weeks	7.5–10	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, pulmonary function tests/spirometry
Harver et al.[27]	RT; IMT versus sham	$N = 23$; $W = 17.4\%$	63 Years; 84% male	FEV_1 38% predicted; pCO_2 NR	PFlex adapted to give targeted visual feedback; not supervised. Biweekly phone calls to home.	Spontaneous breathing pattern	15 min per session @ 5–35 cmH_2O/L s. Participants encouraged to increase to a new training level (PFlex setting) every 7–10 days	2× per day, 7 days per week for 8 weeks	5 cmH_2O/L s	Inspiratory muscle strength, dyspnea, pulmonary function tests/spirometry
Heijdra et al.[28]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$; $W = 0\%$	62 Years; 75% male	FEV_1 36% predicted; 45 mmHg	Targeted inspiratory resistance trainer; PT checked in once per week with participants	3 s inspiration, 4 s expiration monitored by target of incentive spirometry	15 min per session @ 60% PI_{max}; intensity adjusted weekly to maintain PI_{max} of 60%	2× per day, 7 days per week for 10 weeks	5.7 (10% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance, pulmonary function tests/spirometry

Hill et al.[37,a]	RT; IMT versus sham	$N = 35$; $W = 5.7\%$	68 Years; 67% male	FEV_1 37% predicted; pCO_2 NR	Threshold load trainer; supervised	Spontaneous breathing pattern	21 min per session with 7 cycles of 2 min at max load tolerable followed by 1 min rest;	1× per day, 3 days per week for 8 weeks	6.7 (10% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, quality of life pulmonary function tests/spirometry
Kim et al.[29]	RT; IMT versus sham	$N = 112$; $W = 40.2\%$	65 Years; 76% male	FEV_1 40% predicted; 42 mmHg	Threshold load trainer; diary and nurse called participants at home to monitor progress, provide coaching, encourage adherence	Noseclips	15–30 min per session @ 30% PI_{max}; Intensity increased monthly to sustain 30% PI_{max}	1× per day, 7 days per week for 24 weeks	"Barely perceptible and too light to influence strength" (p. 358)	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, dyspnea
Koppers et al.[38,a]	RT; IMT versus sham	$N = 39$; $W = 7.7\%$	56 Years; 47% male	FEV_1 54% predicted; pCO_2 NR	Normocapnic hyperpnea tube breathing[b]; supervised	Noseclips and instructed to take deep breaths with metronome to max of 20 breaths per min	15 min per session @ 60% MVV	2× per day, 7 days per week for 5 weeks	3.6 (±5% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, quality of life, pulmonary function tests/spirometry
Larson et al.[30]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 45$; $W = 51.1\%$	63 Years; 91% male	FEV_1 32% predicted; 41 mmHg	Threshold load trainer; daily log and telephone call once per week	NR	15 min (week 1), 30 min (week 2–8) @ 30% PI_{max}, progression of intensity: NR	1× per day, 7 days per week for 8 weeks	8 (15% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, quality of life
Lisboa et al.[31]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$; $W = $ NR	62 Years; 65% male	FEV_1 38% predicted; 41 mmHg	Threshold load trainer; not supervised	NR	30 min per session @ 30% PI_{max}; intensity adjusted every week to ensure PI_{max} remained at target level	1× per day, 6 days per week for 10 weeks	5 (10% PI_{max} at baseline)	Inspiratory muscle strength, exercise capacity, dyspnea, pulmonary function tests/spirometry
Patessio et al.[32]	RT; IMT versus sham	$N = 16$; $W = $ NR	63 Years; 100% male	FEV_1 52% predicted; 42 mmHg	Targeted inspiratory resistance trainer (resistance trainer with visual feedback); not supervised	Spontaneous breathing pattern	15 min per session @ 50% PI_{max}, progression of intensity NR	4× per day, 7 days per week for 8 weeks	No inspiratory resistance	Inspiratory muscle strength, inspiratory muscle endurance, pulmonary function tests/spirometry

(continued on next page)

Table 1 (*continued*)

Study	Method	Sample size (N = at baseline; W = % withdrawal)	Patient characteristics (mean age in years; % male upon completion of study)	Severity of COPD (FEV_1 % predicted or FEV_1/FVC; mean pCO_2 at baseline)	Mode of IMT and supervision	Monitoring of breathing pattern	Time, intensity and progression of IMT	Frequency and duration of IMT	Intensity of sham IMT (cmH_2O)	Outcomes of interest assessed
Sánchez-Riera et al.[33]	RT; IMT versus sham	$N = 20$; $W = 0\%$	67 Years; 90% male	FEV_1 40% predicted; pCO_2 NR	Targeted inspiratory resistance trainer; not supervised	Controlled at 8 breaths per min with metronome	15 min per session @ 30% PI_{max}; modified every 6 weeks to maintain 30% PI_{max} (target load began at 6 cmH_20 and increased every 2 min by 2 cmH_20)	2× per day, 6 days per week for 24 weeks	No inspiratory resistance	Inspiratory muscle strength; inspiratory muscle endurance; exercise capacity; quality of life; dyspnea
Villafranca et al.[34]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$; W = NR	62 Years; 65% male	$FEV_1/FVC = 0.39$; pCO_2 NR	Threshold load trainer; not supervised	NR	15 min per session @ 30% PI_{max}; intensity adjusted each week to ensure PI_{max} remained at target level	2× per day, 6 days per week for 10 weeks	6.8 (10% PI_{max} at baseline)	Inspiratory muscle strength; inspiratory muscle endurance
Ramírez-Sarmiento et al.[35]	RT; IMT versus sham	$N = 14$; $W = 0\%$	66 Years; 100% male	FEV_1 24% predicted; 45 mmHg	Threshold load trainer; supervised by personnel	NR	30 min per session @ 60% maximum sustained inspiratory pressure (SIP). Intensity adjusted dependent on participant tolerance	1× per day, 5 days per week for 5 weeks	No inspiratory resistance	Inspiratory muscle strength; inspiratory muscle endurance; exercise capacity; pulmonary function tests/spirometry

Weiner and Weiner[39,a]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 28$; $W = 0\%$	63 Years; 57% male	FEV_1 37% predicted; pCO_2 NR	Threshold load trainer — POWERbreathe; not supervised	NR	1 h per session @ 15% PI_{max} week 1; increased 5–10% each session to achieve 60% PI_{max} by end of week 4, intensity then adjusted weekly to maintain 60% PI_{max}	1× per day, 6 days per week for 8 weeks	7	Inspiratory muscle strength
Weiner et al.[40,a,c]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 32$ (at 3 months: time of randomization); $W = 34\%$	65 Years; 82% male (at baseline 0 months)	FEV_1 46% predicted; pCO_2 NR	Threshold load trainer; daily phone calls and once weekly visits by RTh	NR	30 min per session @ 60% PI_{max} adjusted monthly to the new PI_{max} achieved.	1× per day, 3 days per week for 12 months	7	Inspiratory muscle strength, inspiratory muscle endurance, dyspnea, pulmonary function tests/spirometry
Weiner et al.[41,a,d]	RT; high versus low IMT (redefined as IMT versus sham for this review). Note: this study also included EMT and EMT + IMT groups not reported here	$N = 16$; $W = 0\%$	62 Years; 81% males	FEV_1 44% predicted; pCO_2 NR	Threshold load trainer; not supervised	NR	30 min per session @ 15% PI_{max} week 1; increased 5–10% each session to achieve 60% PI_{max} by end of week 4, intensity then adjusted weekly to maintain 60% PI_{max}	1× per day, 6 days per week for 3 months	7	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, dyspnea, pulmonary function tests/spirometry

IMT — inspiratory muscle training; EMT — expiratory muscle training; N — number; % — percent; W — % withdrawal; FEV_1 — forced expiratory volume in 1 s; FVC — forced vital capacity; pCO_2 — arterial partial pressure of carbon dioxide; mmHg — millimeters of mercury; cmH_2O — centimeters of water; RT — randomized trial; @ - at; X — times; NR - not reported; PI_{max} - maximum inspiratory pressure; MVV — maximum voluntary ventilation; min — minutes; s — second; PT — physical therapist; and RTh — respiratory therapist.

[a] New studies included in this systematic review update.

[b] Given targeted, threshold and normocapneic hyperventilation modes of IMT include a baseline maximum inspiratory pressure and involve working toward a targeted workload, they were considered comparable for this update.

[c] Based on 3–15 month data which was the duration of the IMT versus sham intervention in this study.

[d] Only data from Specific IMT (SIMT) and sham groups are reported as they were the groups applicable to this review.

participants who were non-adherent to the intervention were excluded from the analysis.[27,29,30,35]

Meta-analyses

The addition of six new studies enabled an update of the sub-group analysis that compared targeted/threshold/normocapneic hyperventilation IMT to sham IMT. This resulted in 16 meta-analyses, of which nine were updated with new studies from this update incorporated in the meta-analyses, five were entirely new (i.e. there were previously insufficient studies to perform the meta-analyses with only studies from the original review) and two were meta-analyses that only included studies from the original review (Table 2). The results and discussion focus on these analyses.

Of the 16 meta-analyses performed, statistical heterogeneity was present in 11 of the meta-analyses. Heterogeneity may be attributed to variation between studies related to the type of participants, frequency, intensity, mode and duration of the intervention and sham IMT, whether or not the intervention was supervised, and differences in the way outcomes were measured. In instances where there was statistical heterogeneity, a random effects model was used and sensitivity analyses performed. Sensitivity analyses for each of the 11 outcomes resulted in the same conclusions for overall effect compared with the meta-analyses that included all possible studies (with heterogeneity). Further, meta-analyses that included all possible studies often yielded a more conservative estimate. Hence, meta-analyses are reported with all possible included studies in this review.

Inspiratory muscle strength

Three meta-analyses using measures of inspiratory muscle strength (maximum inspiratory pressure [PI_{max}], PI_{max} % predicted, peak inspiratory flow rate) were conducted (Table 2.1). This sub-group analysis was not stratified based on level of preservation of inspiratory muscle strength. Two of these were updates of meta-analyses included in the original review and showed a significant improvement in PI_{max} of 11.6 cm H_2O (95% CI: 8.7, 14.4; $p < 0.0001$; $n = 330$) and in PI_{max} % predicted of 23.2% (95% CI: 11.3, 35.1; $p = 0.0001$; $n = 67$) favouring participants in the IMT group compared with the sham IMT group. A new meta-analysis was conducted for peak inspiratory flow rate, and similarly demonstrated a significant effect favouring IMT with an increase of 12.6 L/min (95% CI: 9.7, 15.6; $p < 0.0001$: $n = 45$) in the IMT group compared with the sham IMT group.

Inspiratory muscle endurance

Three meta-analyses using measures of inspiratory muscle endurance (respiratory muscle endurance time [RMET], inspiratory threshold loading, maximum voluntary ventilation [MVV]), were conducted (Table 2.2). Two of the meta-analyses (RMET, maximal inspiratory threshold load) were updates of those in the original review. Results showed a significant improvement in RMET of 4.4 min (95% CI 0.7, 8.2; $p = 0.02$; $n = 147$) and in maximal inspiratory threshold load of 1.4 kPa (95% CI: 0.8, 1.9; $p < 0.0001$; $n = 143$) favouring participants in the IMT group compared with the sham IMT group. The meta-analysis conducted for MVV also demonstrated a significant effect favouring IMT with an increase of 6.6 L/min (95% CI: 1.8, 11.3; $p = 0.007$; $n = 36$) in the IMT group compared with the sham IMT group.

Exercise capacity

Five meta-analyses using measures of exercise tolerance were performed, three of which demonstrated a significant effect favouring IMT compared to sham (Table 2.3). Results showed a significant improvement in maximum exercise minute ventilation (Ve_{max}) of 4.9 L/min in the IMT group compared with the sham IMT group (95% CI: −8.2, −1.7; $p = 0.003$; $n = 40$). Updated meta-analyses' results demonstrated a significant improvement in the Borg Score for Respiratory Effort by 1.8 points (95% CI: −2.4, −1.2; $p < 0.0001$; $n = 109$) and significant improvement in 6-minute walk test (6MWT) distance of 32.1 m (95% CI: 11.6, 52.7; $p = 0.002$; $n = 103$) in the IMT group compared with the sham IMT group. Results for maximal oxygen consumption (VO_{2max}) and work rate maximum were both updated in this review but remained not significant for an overall effect (Table 2.3).

Dyspnea

Four meta-analyses of the Transitional Dyspnea Index (TDI) and its subscales were performed (Table 2.4). Meta-analysis of the TDI − Focal Score was updated in this review and remained significant demonstrating an improvement of 2.6 points (95% CI: 0.9, 4.2; $p = 0.002$; $n = 96$) with IMT compared with sham. Three new meta-analyses were performed for the other TDI subscales and demonstrated a significant improvement in the Functional Impairment score: 0.7 points (95% CI: 0.1, 1.3; $p = 0.02$; $n = 56$); Magnitude of Task score: 0.7 points (95% CI: 0.5, 1.0; $p < 0.0001$; $n = 56$;) and Magnitude of Effort score: 0.5 points (95% CI: 0.2, 0.7; $p < 0.0001$; $n = 56$) in the IMT group compared with the sham IMT group.

Quality of life

No meta-analysis for quality of life was possible in the original review. In this update, both Hill et al.[37] and Koppers et al.[38] showed data for the Chronic Respiratory Disease Questionnaire (CRQ) as an outcome measure. Meta-analysis demonstrated a significant improvement in the CRQ total score of 0.3 points (95% CI: 0.2, 0.5; $p < 0.0001$; $n = 69$) in the IMT group compared with the sham IMT group (Table 2.5).

Discussion

For this update, six additional studies were incorporated in the review, all of which compared targeted, threshold, or normocapneic hyperventilation IMT to sham IMT.[36–41] Hence, the update of this systematic review focused on the sub-group analysis comparing those types of IMT versus sham IMT. Five of the six new studies were incorporated into meta-analyses. Of the 16 meta-analyses performed, 14 demonstrated significant effect favouring the IMT intervention compared with sham. Results demonstrated significant improvements in three measures of inspiratory muscle strength (PI_{max}, PI_{max} % predicted, peak inspiratory

Table 2 Meta-analyses results comparing targeted inspiratory resistive IMT or threshold IMT versus sham IMT

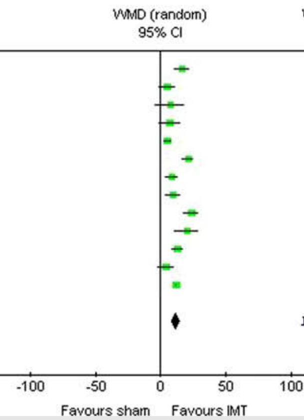
(1) Inspiratory muscle strength

PI_{max} (cmH_20)[a,c]

Review: Inspiratory Muscle Training in Adults with COPD: A Systematic Review
Comparison: 01 Targeted Inspiratory Resistive IMT or Threshold IMT Versus Sham
Outcome: 01 Maximum Inspiratory Pressure (Pimax) (cmH20)

Study or sub-category	N	IMT Mean (SD)	N	Sham Mean (SD)	Weight %	WMD (random) 95% CI
Belman 1988	8	21.30(5.76)	9	5.00(7.14)	7.40	16.30 [10.16, 22.44]
Larson 1988	10	12.00(8.06)	11	7.00(6.60)	7.24	5.00 [-1.34, 11.34]
Harver 1989	10	11.00(13.31)	9	3.90(12.28)	3.96	7.10 [-4.41, 18.61]
Patessio 1989	8	13.00(6.52)	8	6.00(9.83)	5.84	7.00 [-1.17, 15.17]
Kim 1993	40	18.00(5.70)	26	13.00(6.38)	10.03	5.00 [1.98, 8.02]
Heijdra 1996	10	22.50(5.53)	10	1.50(4.87)	8.75	21.00 [16.43, 25.57]
Lisboa 1997	10	17.40(5.42)	10	9.00(5.04)	8.74	8.40 [3.81, 12.99]
Villafranca 1998	10	22.50(5.80)	10	13.00(7.24)	7.73	9.50 [3.75, 15.25]
Sanchez 2001	10	21.60(6.70)	10	-1.80(6.96)	7.53	23.40 [17.41, 29.39]
Ramirez-Sarmiento 02	7	22.00(11.76)	7	2.00(5.08)	5.00	20.00 [10.51, 29.49]
Hill 2006	16	18.00(6.07)	17	5.20(6.46)	9.01	12.80 [8.52, 17.08]
Koppers 2006	18	7.00(9.50)	18	3.00(8.91)	7.50	4.00 [-2.02, 10.02]
Weiner 2006	14	12.43(0.72)	14	0.86(0.75)	11.27	11.57 [11.03, 12.11]
Total (95% CI)	171		159		100.00	11.58 [8.75, 14.42]

Test for heterogeneity: Chi² = 69.36, df = 12 (P < 0.00001), I² = 82.7%
Test for overall effect: Z = 8.00 (P < 0.00001)

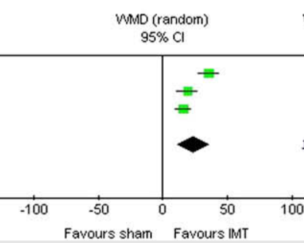


PI_{max} (% predicted)[a,c]

Review: Inspiratory Muscle Training in Adults with COPD: A Systematic Review
Comparison: 01 Targeted Inspiratory Resistive IMT or Threshold IMT Versus Sham
Outcome: 18 Maximum Inspiratory Pressure (% predicted)

Study or sub-category	N	IMT Mean (SD)	N	Sham Mean (SD)	Weight %	WMD (random) 95% CI
Heijdra 1996	10	38.70(9.82)	10	3.30(8.41)	32.70	35.40 [27.39, 43.41]
Ramirez-Sarmiento 02	7	21.00(10.43)	7	2.00(3.74)	32.47	19.00 [10.79, 27.21]
Hill 2006	16	21.90(9.19)	17	6.30(8.80)	34.83	15.60 [9.45, 21.75]
Total (95% CI)	33		34		100.00	23.18 [11.29, 35.07]

Test for heterogeneity: Chi² = 15.42, df = 2 (P = 0.0004), I² = 87.0%
Test for overall effect: Z = 3.82 (P = 0.0001)

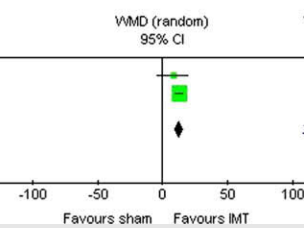


Peak inspiratory flow rate (L/min)[b]

Review: Inspiratory Muscle Training in Adults with COPD: A Systematic Review
Comparison: 01 Targeted Inspiratory Resistive IMT or Threshold IMT Versus Sham
Outcome: 17 Peak Inspiratory Flow Rate (L/min)

Study or sub-category	N	IMT Mean (SD)	N	Sham Mean (SD)	Weight %	WMD (random) 95% CI
Belman 1988	8	12.30(13.80)	9	4.00(11.90)	5.80	8.30 [-4.02, 20.62]
Weiner 2006	14	14.80(4.38)	14	1.90(3.86)	94.20	12.90 [9.84, 15.96]
Total (95% CI)	22		23		100.00	12.63 [9.67, 15.60]

Test for heterogeneity: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%
Test for overall effect: Z = 8.34 (P < 0.00001)



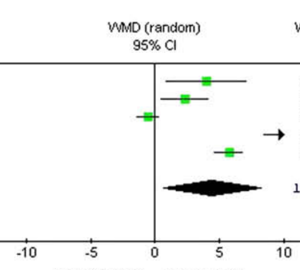
(2) Inspiratory muscle endurance

Respiratory muscle endurance time (minutes)[a,c]

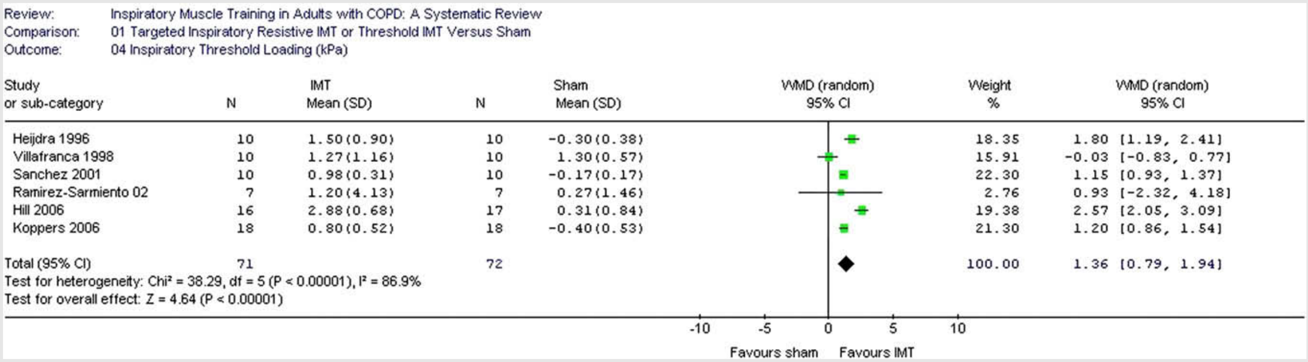
Review: Inspiratory Muscle Training in Adults with COPD: A Systematic Review
Comparison: 01 Targeted Inspiratory Resistive IMT or Threshold IMT Versus Sham
Outcome: 03 Respiratory Muscle Endurance Time (RMET) (min)

Study or sub-category	N	IMT Mean (SD)	N	Sham Mean (SD)	Weight %	WMD (random) 95% CI
Larson 1988	9	5.40(4.46)	10	1.40(2.00)	18.54	4.00 [0.83, 7.17]
Patessio 1989	8	2.90(1.83)	8	0.60(1.99)	20.25	2.30 [0.43, 4.17]
Kim 1993	39	1.90(1.05)	23	2.42(2.05)	21.06	-0.52 [-1.42, 0.38]
Ramirez-Sarmiento 02	7	11.00(3.21)	7	-0.10(1.69)	19.24	11.10 [8.41, 13.79]
Koppers 2006	18	4.98(1.94)	18	-0.76(1.46)	20.92	5.74 [4.62, 6.86]
Total (95% CI)	81		66		100.00	4.43 [0.66, 8.21]

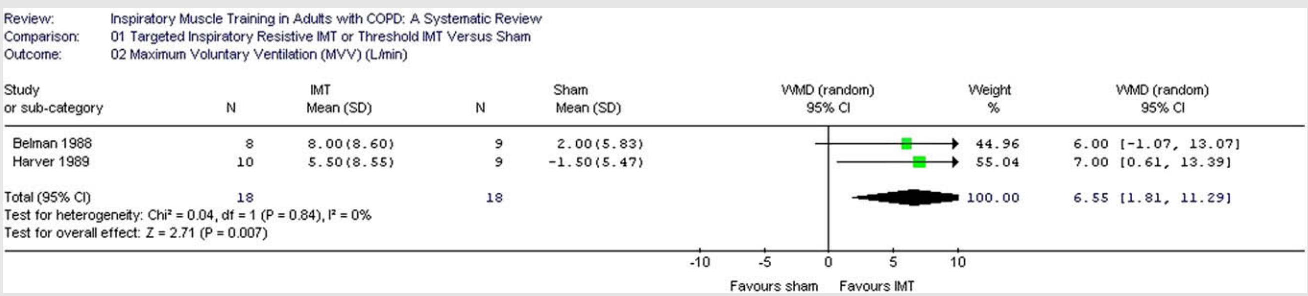
Test for heterogeneity: Chi² = 115.50, df = 4 (P < 0.00001), I² = 96.5%
Test for overall effect: Z = 2.30 (P = 0.02)



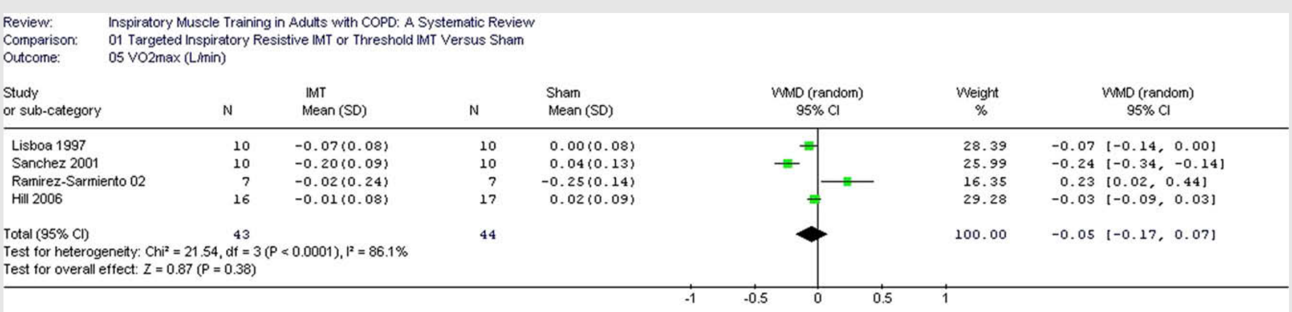
Inspiratory threshold loading (kPa)[a,c]



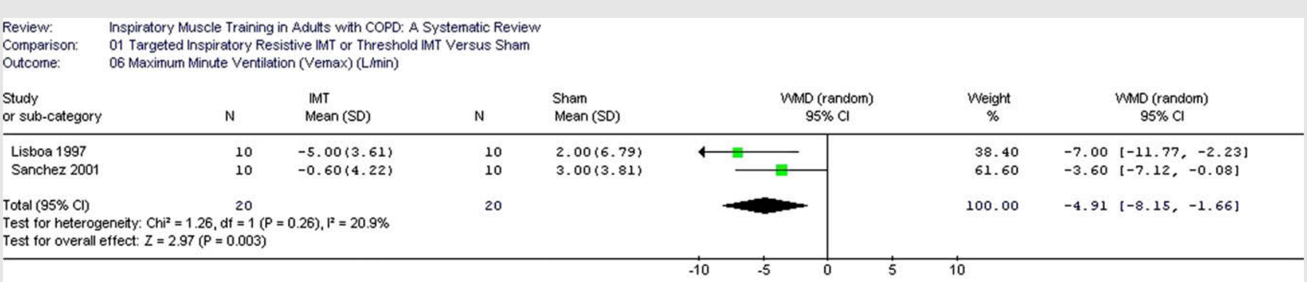
Maximum voluntary ventilation (MVV) (L/min)



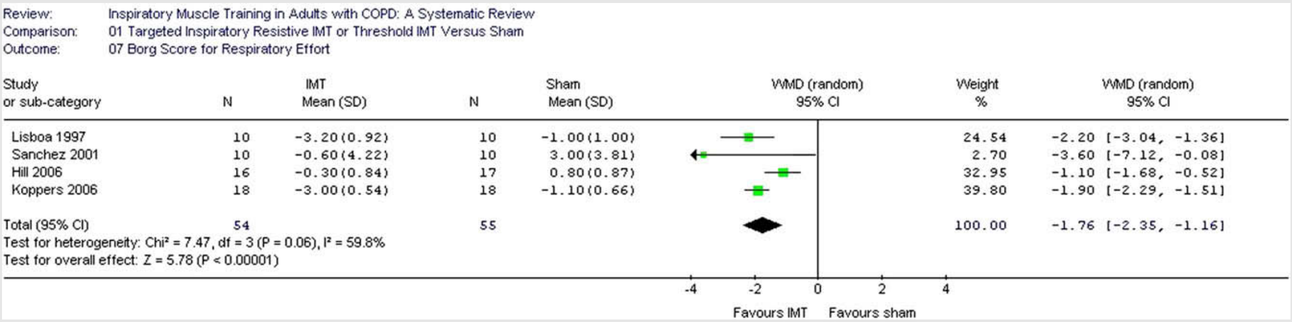
(3) Exercise capacity
Maximal oxygen consumption — VO_{2max} (L/min)[a,c]



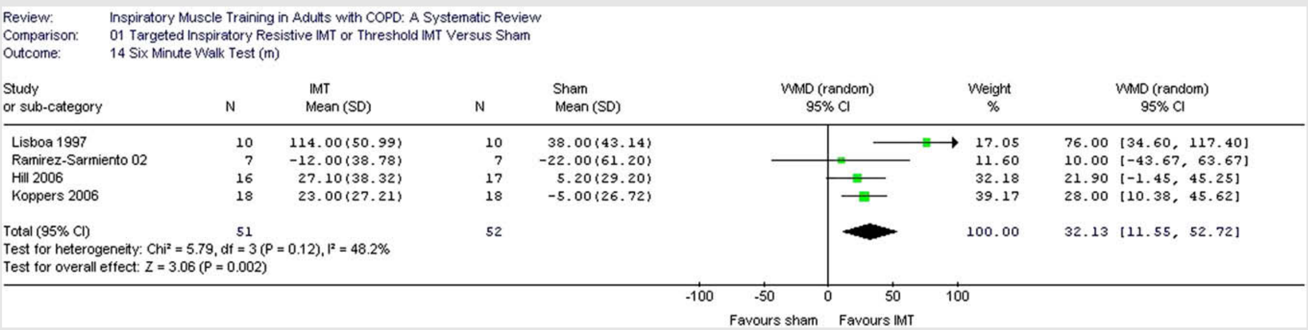
Maximum minute ventilation (Ve_{max}) (L/min)



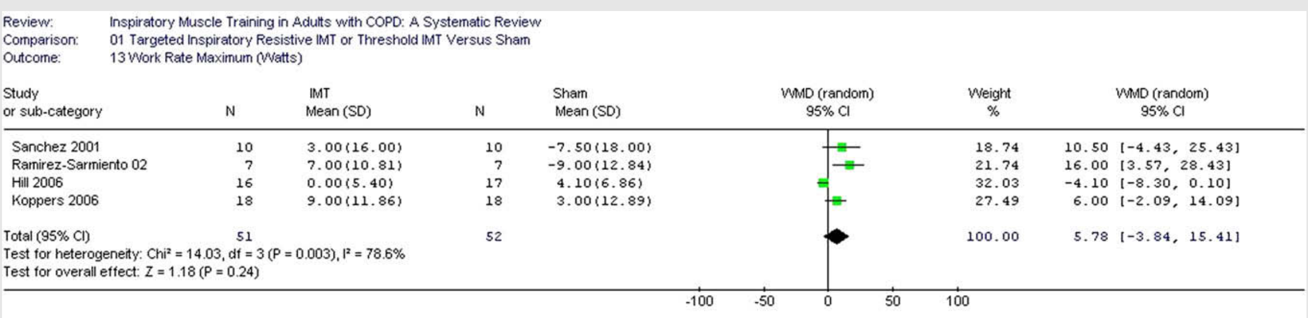
Borg scale for respiratory effort (modified Borg scale)[a,c]



6-minute walk test (metres)[a]

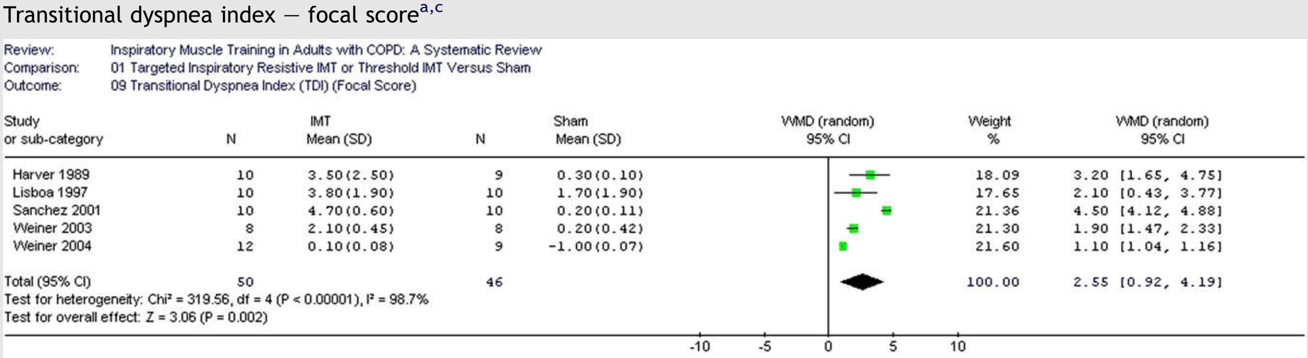


Work rate maximum (Watts)[a,c]

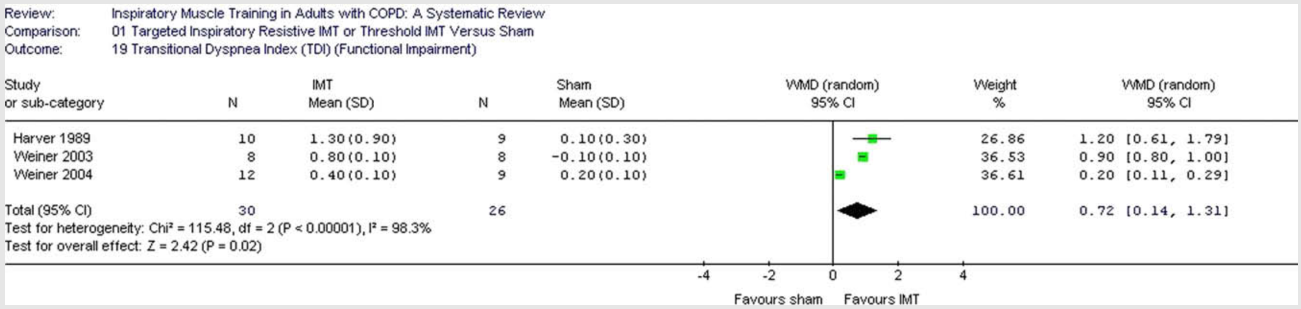


(4) Dyspnea

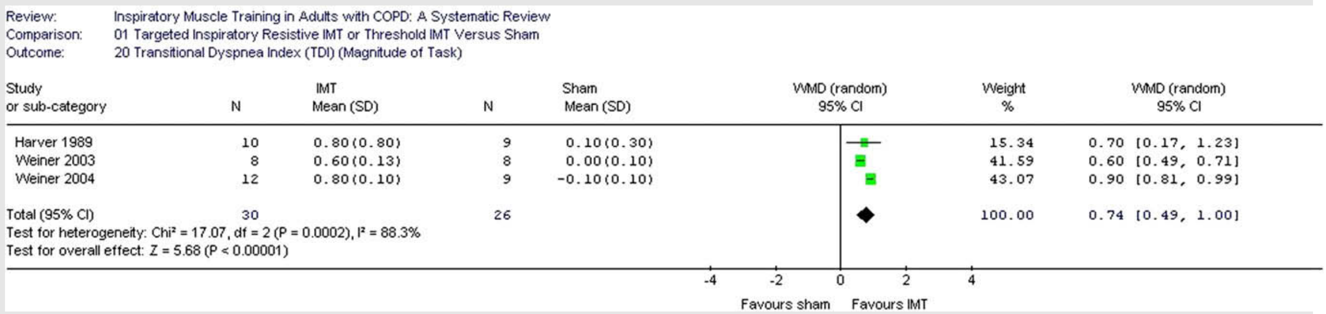
Transitional dyspnea index — focal score[a,c]



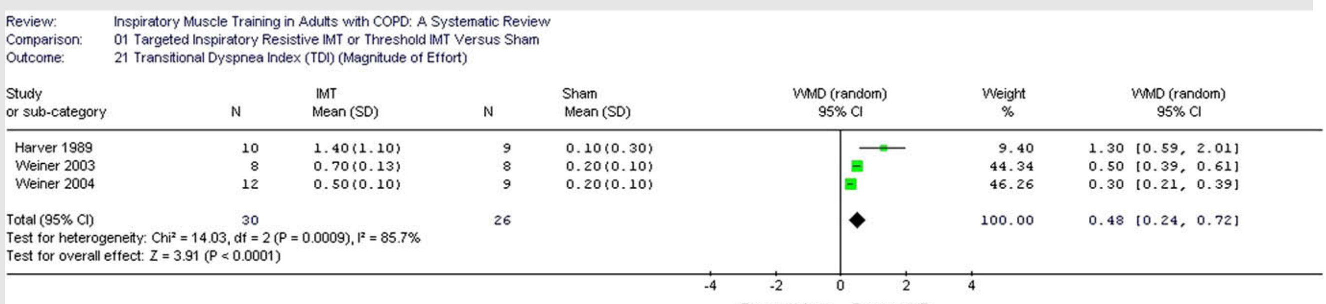
Transitional dyspnea index — functional impairment[b,c]



Transitional dyspnea index — magnitude of task[b,c]

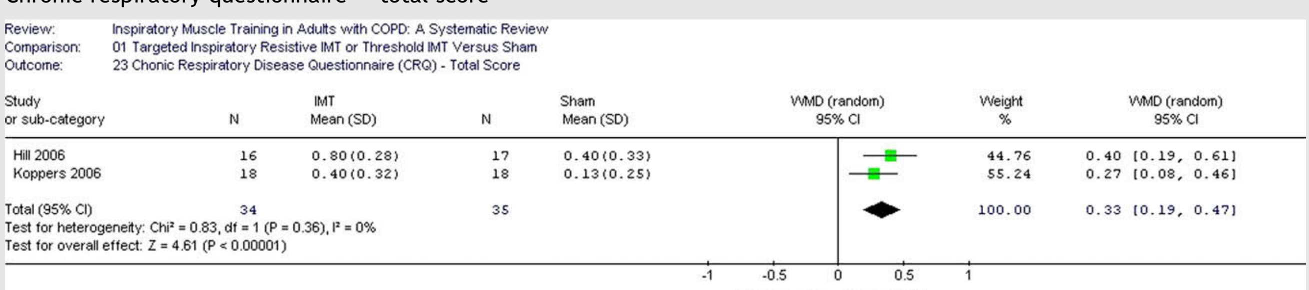


Transitional dyspnea index — magnitude of effort[b,c]



(5) Quality of life

Chronic respiratory questionnaire — total score[b]



[a] Updated meta-analysis from the original review performed for this update.
[b] New meta-analysis performed for this update.
[c] Statistically significant for heterogeneity.

flow rate), three measures of inspiratory muscle endurance (RMET, inspiratory threshold loading, MVV), three measures of exercise capacity (Ve_{max}, Borg Score for Respiratory Effort, 6MWT), four TDI subscales' scores (focal score, functional impairment, magnitude of task and magnitude of effort), and the CRQ. No significant difference in effect was found for meta-analyses of VO_{2max} or exercise work rate maximum.

Nine of the 16 meta-analyses were updates of those performed in the original review, six of which confirmed findings from the original review, and three that demonstrated changes in the overall effect on outcomes. The two meta-analyses for inspiratory muscle strength (PI_{max}, PI_{max} %) in this update reported similar significant improvements favouring IMT as seen in the original review. Four other updated findings for outcomes of inspiratory muscle endurance (inspiratory threshold loading), exercise capacity (VO_{2max}, Borg Score for Respiratory Effort) and dypnea (TDI-Focal Score) also were similar to those in the original review, with all but VO_{2max} showing significant improvements favouring IMT.

The three updated meta-analyses that changed in overall effect on outcomes included RMET, work rate maximum and 6MWT. Meta-analyses results for RMET in this update changed from no overall effect of IMT in the original review (WMD: 4.11 min; 95% CI: −0.6, 8.8) to demonstrating a significant improvement with IMT compared to sham in this updated review (WMD: 4.4 min; 95% CI: 0.7, 8.2). Updated meta-analysis results for work rate maximum changed from a significant effect of IMT in the original review (WMD: 13.8 W; 95% CI: 4.2, 23.3) to demonstrating no significant overall effect with IMT compared to sham in this updated review (WMD: 5.8 W; 95% CI: −3.8, 15.4). Finally, most notably, when studies by Hill[37] and Koppers[38] were added, updated meta-analysis for the 6MWT distance changed from no significant overall effect in the original review to demonstrating a significant increase of 32 m (95% CI: 11.6, 52.7) in 6MWT distance among those in the IMT group compared with the sham IMT group.

These results provide evidence supporting the use of IMT in persons with COPD. As with the original review, the type of IMT used is important. This update focused on targeted, threshold and normocapneic hyperventilation types of IMT as they ensure or facilitate the attainment of a training intensity during the training session. This is in contrast to non-targeted inspiratory resistive trainers that do not provide a target or means of controlling the breathing pattern to ensure a sufficient, consistent training intensity.

While these results demonstrate statistical significance for some outcomes of inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life, the clinical importance of these findings for persons with COPD is less clear. For example, a change score in the CRQ of 0.5 is considered to be a clinically significant small change, while a change of 1.0 is medium importance and of 1.5 is great importance.[42] The difference between the IMT and sham groups in this meta-analysis was 0.3 points favouring IMT, which is less than the clinically important change.

The clinically important difference for 6MWT is reported to be 54 m.[43] The updated meta-analysis found an effect size of 32 m which is below the clinically important difference. However, the Redeilmeier study[43] found a difference of 54 m for those who walked an average of 350 m. In this systematic review, the average 6MWT distance was higher for participants in both of the included studies. In Hill et al.,[37] the baseline mean distance on the 6MWT was 446 m increasing to 473 post-training in the IMT group. Koppers[38] reported a baseline 6MWT mean distance of 512 m improving to 535 m post-training in the IMT group. Given participants in this review walked further at baseline, further research is needed to determine whether the change in outcome was clinically important for the 6MWT.

The clinically important difference in the TDI − Focal Score is considered to be 1.0.[44] The updated meta-analysis found an effect size of 2.6 which is 2.6 times more than the clinically important difference, suggesting a clinically important improvement in dyspnea for those in the IMT group compared with the sham IMT group.

Some patients with severe COPD may not be able to generate a sufficient flow rate to ensure optimal deposition of particles using certain inhalation devices.[39] Following 8 weeks of training with IMT, Weiner and Weiner[39] reported that all patients exceeded the optimal flow rate of 60 L/min required to use one particular device. A positive correlation was found between peak inspiratory flow rate and PI_{max}.[39] The significant effect in the updated meta-analyses for PI_{max} and peak inspiratory flow rate implies that IMT might facilitate the use of certain inhalation devices for some patients with COPD.

Results of the review should be interpreted cautiously for a variety of reasons. The sub-group analysis of this update is based on a small number of trials ($n = 16$) that included a small number of participants (range: 14–112 participants). Further, individual studies were fraught with withdrawal rates ranging from 0 to 51%. Thus, the overall findings among those who continued to use IMT might not reflect the general use of IMT among adults with COPD.

The ability to perform meta-analyses remained limited due to the breadth of outcome measures used in the trials. While incorporation of five of the six new studies into the meta-analyses strengthened the review, most meta-analyses included only 2–6 studies with the exception of the meta-analysis for PI_{max} that included 13 studies. The meta-analysis for PI_{max} did not separate studies into those whose participants presented with poorer inspiratory muscle strength at baseline and those whose participants presented with relatively preserved inspiratory muscle strength at baseline. Doing so may be a consideration for future research, where a standardized protocol is used and reported for measuring PI_{max} and an appropriate or valid categorization of inspiratory muscle strength is identified.

Two studies included in this update followed participants for 12 months[36,40] compared with the 24 week maximum duration of studies included in original review. This enabled the ability to explore the longer-term outcomes associated with IMT for persons with COPD. Similar to the original review, individual studies in the update continued to include mostly men, as such, findings should be interpreted cautiously with respect to women living with COPD. Finally, this review specifically focused on the effect of targeted, threshold, or normocapneic hyperventilation IMT versus sham IMT. Results exploring the effect of IMT (either alone or combined with exercise and/or pulmonary rehabilitation) compared with other rehabilitation interventions is published elsewhere.[45]

Conclusions

Results of this systematic review update suggest that targeted inspiratory resistive, threshold or normocapneic hyperventilation IMT significantly increases inspiratory muscle strength and endurance, improves outcomes of exercise capacity, one measure of quality of life and decreases dyspnea for adults with stable COPD. However, the clinical importance of these findings remains unclear. Further research is needed to explore the impact that different training protocols (frequency, intensity and duration of IMT, supervision) may have on outcomes and to determine the extent to which changes in outcomes associated with IMT translate into clinically important improvements for adults with COPD.

Conflict of interest statement

There were no known perceived or real conflict of interests for any of the co-authors.

Acknowledgements

This study was supported by the Ontario Respiratory Care Society (Ontario Lung Association) and the Canadian Respiratory Health Professionals (Canadian Lung Association). Kelly O'Brien is supported by a Fellowship from the Canadian Institutes for Health Research. Dr. Dina Brooks was supported by a New Investigator Award during this project. None of the study sponsors had any involvement in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

References

1. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease website. Available from: <http://www.goldcopd.com/Guidelineitem.asp?l1 = 2&l2 = 1&intId = 989>; 2007 [accessed 08.02.07].
2. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765–73.
3. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**:741–50.
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 3(11):e442. doi: 10. 1371/journal.pmed.0030442.
5. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *[Systematic Review] Cochrane Airways Group Cochrane Database of Systematic Reviews* 2007;**1**.
6. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;**173**:1390–413.
7. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can Respir J* 2007;**14**(Suppl. B):5B–32B.
8. Smith K, Cook D, Guyatt GH, Madhavan J, Oxman AD. Respiratory muscle training in chronic airflow limitation: a meta-analysis. *Am Rev Respir Dis* 1992;**145**:533–9.
9. Lötters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J* 2002;**20**:570–6.
10. Geddes EL, Reid WD, Crowe J, O'Brien K, Brooks D. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: a systematic review. *Respir Med* 2005;**99**:1440–58.
11. Crowe J, Geddes EL, Brooks D, Reid WD. Inspiratory muscle training for individuals with cervical spinal cord injury or chronic obstructive pulmonary disease: a survey of Canadian physical therapists. *Physiother Can* 2006;**58**:271–9.
12. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERJ position paper. *Eur Respir J* 2004; **23**:932–46.
13. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions 4.2.6 [updated September 2006]*: The Cochrane Library. Chichester, UK: John Wiley and Sons, Ltd; 2006. Issue 4.
14. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, McQuay HJ. Assessing the quality of randomized controlled trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
15. *Review Manager (RevMan) [Computer Program]. Version 4.2 for Windows*. Oxford, England: The Cochrane Collaboration; 2002.
16. Lau J, Ioannidis JPA, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997;**127**:820–6.
17. Reid WD, Warren CPW. Ventilatory muscle strength and endurance training in elderly subjects and patients with chronic airflow limitation: a pilot study. *Physiother Can* 1984; **36**(6):305–11.
18. Hsiao SF, Wu YT, Wu HD, Wang TG. Comparison of effectiveness of pressure threshold and targeted resistive muscle training in patients with chronic obstructive pulmonary disease. *J Formos Med Assoc* 2003;**102**:240–5.
19. Preusser BA, Winningham ML, Clanton TL. High vs low-intensity inspiratory muscle interval training in patients with COPD. *Chest* 1994;**106**(1):110–7.
20. Bjerre-Jepsen K, Secher NH, Kok-Jensen A. Inspiratory resistance training in severe chronic obstructive pulmonary disease. *Eur J Respir Dis* 1981;**62**:405–11.
21. Falk P, Eriksen AM, Kølliker K, Andersen JB. Relieving dyspnea with an inexpensive and simple method in patients with severe chronic airflow limitation. *Eur J Respir Dis* 1985;**66**(3): 181–6.
22. Guyatt G, Keller J, Singer J, Halcrow S, Newhouse M. Controlled trial of respiratory muscle training in chronic airflow limitation. *Thorax* 1992;**47**(8):598–602.
23. Jones DT, Thomson RJ, Sears MR. Physical exercise and resistive breathing training in severe chronic airways obstruction – are they effective? *Eur J Respir Dis* 1985;**67**:159–66.
24. McKeon JL, Turner J, Kelly C, Dent A, Zimmerman PV. The effect of inspiratory resistive training on exercise capacity in optimally treated patients with severe chronic airflow limitation. *Aust N Z J Med* 1986;**16**(5):648–52.
25. Richardson J, Dunn L, Pardy R. Inspiratory resistive endurance training in patients with chronic obstructive pulmonary disease: a pilot study. *Physiother Can* 1989;**41**(2):85–92.
26. Belman MJ, Shadmehr R. Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease. *J Appl Physiol* 1998;**65**(6):2726–35.
27. Harver A, Mahler DA, Daubenspeck JA. Targeted inspiratory muscle training improves respiratory muscle function and

reduces dyspnea in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1989;**111**(2):117–24.
28. Heijdra YF, Dekhuijzen PNR, van Herwaarden CLA, HThM Folgering. Nocturnal saturation improves by target-flow inspiratory muscle training in patients with COPD. *Am J Respir Crit Care Med* 1996;**153**:260–5.
29. Kim MJ, Larson JL, Covey MK, Vitalo CA, Alex CG, Patel M. Inspiratory muscle training in patients with chronic obstructive pulmonary disease. *Nurse Res* 1993;**42**(6):356–62.
30. Larson JL, Kim MJ, Sharp JT, Larson DA. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;**138**(3):689–96.
31. Lisboa C, Villafranca C, Leiva A, Cruz E, Pertuzé J, Borzone G. Inspiratory muscle training in chronic airflow limitation: effect on exercise performance. *Eur Respir J* 1997;**10**(3):537–42.
32. Patessio A, Rampulla C, Fracchia C, Ioli F, Majani U, De Marchi A, et al. Relationship between the perception of breathlessness and inspiratory resistive loading: report on a clinical trial. *Eur Respir J Suppl* 1989;**7**:587s–91s.
33. Sánchez Riera H, Montemayor Rubio T, Ortega Ruiz F, Cejudo Ramos P, Castillo Otero DD, Hernandez TE, et al. Inspiratory muscle training in patients with COPD: effect on dyspnea, exercise performance, and quality of life. *Chest* 2001;**120**(3): 748–56.
34. Villafranca C, Borzone G, Leiva A, Lisboa C. Effect of inspiratory muscle training with an intermediate load on inspiratory power output in COPD. *Eur Respir J* 1998;**11**(1):28–33.
35. Ramírez-Sarmiento A, Orozco-Levi M, Gűell R, Barreiro E, Hernandez N, Mota S, et al. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptations and physiologic outcomes. *Am J Respir Crit Care Med* 2002;**166**:1491–7.
36. Beckerman M, Magadle R, Weiner M, Weiner P. The effects of 1 year of specific inspiratory muscle training in patients with COPD. *Chest* 2005;**128**(5):3177–82.
37. Hill K, Jenkins SC, Philippe DL, Cecins N, Shepherd KL, Green DJ, et al. High-intensity inspiratory muscle training in COPD. *Eur Respir J* 2006;**27**:1119–28.
38. Koppers RJH, Vos PJE, Boot CRL, Folgering HTh M. Exercise performance improves in patients with COPD due to respiratory muscle endurance training. *Chest* 2006;**129**:886–92.
39. Weiner P, Weiner M. Inspiratory muscle training may increase peak inspiratory flow in chronic obstructive pulmonary disease. *Respiration* 2006;**73**:151–6.
40. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Maintenance of inspiratory muscle training in COPD patients: one year follow-up. *Eur Respir J* 2004;**23**:61–5.
41. Weiner P, Magadle M, Beckerman M, Weiner M, Berar-Yanay N. Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD. *Chest* 2003;**124**: 1357–64.
42. Finch E, Brooks D, Stratford PW, Mayo NE. *Physical rehabilitation outcome measures: a guide to enhanced clinical decision making*. Toronto: Canadian Physiotherapy Association; 2002.
43. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk Test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;**155**:1278–82.
44. Mahler DA, Witek TJ. The MCID of the transition dyspnea index is a total score of one unit. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2004;**2**(1):99–103.
45. O'Brien K, Geddes L, Reid WD, Brooks D, Crowe J. Inspiratory muscle training compared with other rehabilitation interventions in chronic obstructive pulmonary disease: a systematic review update. *JCRP* 2008;**28**:128–41.