Review Article

Inspiratory Muscle Training in Patients with Heart Failure: Meta-Analysis of Randomized Trials

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Abstract

Patients with chronic heart failure (CHF) may have lower inspiratory muscle strength and endurance, which may contribute to exercise intolerance. Inspiratory muscle training (IMT) can have beneficial effects on these patients. Thus, the aim of this study was to systematically review the effects of IMT compared to control groups (placebo-IMT or another intervention) in patients with CHF. A search of databases (MEDLINE, Cochrane CENTRAL and PEDro) and references of published studies, from 1960 to 2011, was conducted. Randomized trials comparing IMT to control groups in the treatment of patients with CHF were included. The GRADE approach was used to determine the quality of evidence for each outcome. Of 119 articles identified, 7 studies were included. IMT increased the distance walked in the six-minute walk test [69 m (95% CI: 7.21 to 130.79)] (very low evidence) and maximal static inspiratory pressure [23.36 cmH20 (95% CI: 11.71 to 35.02)] (low evidence) compared to control groups. However, IMT provides a significant improvement in peak oxygen consumption only in the studies that performed IMT for 12 weeks against no inspiratory load in patients with inspiratory muscle weakness [3.02 ml/kg/min-1 (95% CI: 0.43 to 5.61)]. IMT improves functional capacity and inspiratory muscle strength thereby deserving consideration as an additional intervention in patients with CHF. Larger and better-designed studies, however, are needed to clarify the potential benefit of IMT in this patient population.

Introduction

There are multiple reasons for the profound reduction of aerobic capacity in patients with chronic heart failure (CHF) and they involve the cardiovascular, skeletal muscle

Keywords

Breathing exercises; heart failure; meta-analysis; review.

and respiratory systems. Patients with CHF may present abnormalities in respiratory muscle function, such as reduced endurance and strength, diaphragm fiber I atrophy[1] and increased deoxygenation during exercises[2]. Moreover, the physical activity of most patients with CHF is limited by fatigue and dyspnea, and it has been suggested that respiratory muscle weakness and deconditioning may be involved in the increased effort required to breathe during exercise hyperpnea[3,4]. In addition, these abnormalities may have important implications for exercise capacity, quality of life as well as in their poor prognosis[5,6].

Although the vast majority of research into CHF has focused on pharmacological or electrical therapies[7], programs involving inspiratory muscle training (IMT) are increasingly propagated as a potential strategy for further improving outcomes in CHF patients[6]. IMT can reduce symptoms such as dyspnea and inspiratory muscle fatigue, through effects on the respiratory and cardiovascular systems. Despite this, IMT is not widely used as a non-pharmacological treatment in patients with CHF and inspiratory muscle weakness, perhaps because few data are available regarding its effect on functional capacity[6,8].

Randomized controlled trials (RCTs) have focused on the effects of IMT on inspiratory muscle strength and endurance, which leads to improvement in peak oxygen consumption, quality of life and dyspnea[8-14]. However, the sample sizes of studies comparing these benefits to those obtained with a control group in these patients have been small.

Systematic review with meta-analysis of RCTs can provide more reliable estimates of treatment effectiveness than individual trials because they have greater statistical power. Therefore, we report a meta-analysis of RCTs comparing IMT to control groups (placebo-IMT or another intervention) in patients with CHF. Accordingly, the aim of the study was to estimate the effects of IMT on functional capacity evaluated by peak oxygen consumption (peak VO_2) and the 6-minute walk test (6-MWT) and maximal static inspiratory pressure (PImax) by gathering all available evidence.

Methods

Eligibility criteria

We included RCTs assessing IMT in the treatment of CHF patients with New York Heart Association (NYHA) functional

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class I, II or III. We included studies that compared IMT to control groups [placebo-IMT (the same regimen as the IMT group, except that the treatment was performed with a lower inspiratory load or with no inspiratory load) or any other intervention] and that evaluated the following outcomes: peak VO_2, distance walked in the 6-MWT and/or PImax. Exclusion criteria were the following: (1) inclusion of subjects other than CHF patients; (2) lack of a reliable definition of what was considered CHF; (3) absence of IMT with inspiratory load; (4) follow-up shorter than 6 weeks; (5) lack of control group data description.

Search strategy and study selection

We independently searched, in duplicate, the following electronic databases (from 1960 to July 2011): MEDLINE (accessed by PubMed), Physiotherapy Evidence Database (PEDro) and the Cochrane Central Register of Controlled Trials (Cochrane CENTRAL)[15]. In addition, we searched the bibliographies of published studies[6,16]. The search was performed in July 2011 and comprised the following terms: "breathing exercises", "inspiratory muscle training", "respiratory muscle training", "heart failure", "congestive heart failure", "heart ventricles", "congestive cardiomyopathy", "ventricular dysfunction" combined with a high sensitivity combination of words used in the search for randomized clinical trials[17]. There were no language or publication status restrictions. The complete search strategy used for the MEDLINE database is shown in Appendix[18]. Details for the other strategies used are available on request.

Titles and abstracts of all articles identified by the search strategy were independently evaluated by two investigators (G.S. and J.B.F.), in duplicate. All abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full-text articles and made their selection in accordance with the eligibility criteria. Disagreements between reviewers were solved by consensus.

Data extraction

Using standardized forms, the same two reviewers independently conducted data extraction with regard to the methodological characteristics of the studies, interventions and outcomes; disagreements were also solved by consensus. The main outcome extracted was peak VO_2 in ml/kg/min^{-1}. Other outcomes of interest were distance walked in the 6-MWT in meters (m) and PImax in cmH_2O.

Assessment of risk of bias

Study quality assessment included adequate sequence generation, allocation concealment, blinding, blinding of outcome assessors, use of intention-to-treat analysis and description of losses and exclusions. Studies without a clear description of an adequate sequence generation were considered not to have fulfilled these criteria. A lack of description of how the allocation list was concealed (which could include terms like "central", "web-based" or "telephone randomization", or a clear statement that the

allocation list was concealed) was judged to characterize absence of allocation concealment. Use of intention-to-treat analysis was considered as confirmation on study assessment that the number of participants randomized and the number analyzed were identical, except for patients lost to follow-up or who withdrew consent for study participation. Studies without this characteristic were considered not to have fulfilled this criterion. Quality assessment was independently performed by the same two reviewers (G.S. and J.B.F.).

Data analysis

Pooled-effect estimates were obtained by comparing the least square mean percentage change from baseline to study end for each group, and were expressed as the weighted mean difference between groups[19]. Calculations were performed using a random effects method. p value ≤ 0.05 was considered statistically significant. Statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency I^2 test, in which values above 25% and 50% were considered indicative of moderate and high heterogeneity, respectively[20]. All analyses were conducted using Review Manager version 5.1 (Cochrane Collaboration)[21].

We explored heterogeneity between studies using two strategies: 1) we re-ran the meta-analyses removing one paper at a time to check whether some individual study explained heterogeneity; 2) we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of intervention based on pre-specified relevant clinical information which influences IMT effects on outcomes [duration of the intervention, intervention performed by control group, inspiratory load and if the studies included patients with weakness of inspiratory muscles (PImax < 70% of predicted)].

Summary of evidence: GRADE-criteria

We presented the overall quality of the evidence using the GRADE approach as recommended by the Cochrane Handbook for Systematic Reviews of Interventions[19]. For each specific outcome, the quality of the evidence was based on 5 factors: (1) limitations of the study design; (2) consistency of results; (3) directness; (4) precision and (5) potential for publication bias. The quality was reduced by one level for each of the factors not met. The GRADE approach resulted in 4 levels of quality of evidence: high, moderate, low and very low[22]. GRADE profiler software (version 3.6) was used[23].

Results

Description of studies

The search strategy yielded 119 abstracts, from which 14 studies were considered as potentially relevant and retrieved for detailed analysis. Seven of these studies met the eligibility criteria and were included in the systematic review (n = 182). However, only six studies, with 150 patients with CHF, were included in the meta-analysis.

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Figure 1 shows the flow diagram of the studies included in this review and Table 1 summarizes the characteristics of these studies. Five trials[8-11,14] compared IMT to placebo-IMT, with minimum inspiratory load or with no training effects (total n = 118, of which 61 were on IMT), one trial[12] compared IMT to another intervention [education program (total n = 32, of which 15 were on IMT)] and one study[24] compared IMT plus aerobic exercise training (AE) to AE alone (total n = 24, of which 12 were on IMT). This last study was not included in the meta-analysis and in the sensitivity analysis because it was associated with another intervention (AE) with the IMT, which is different from the other studies included.

Risk of bias

Of the included studies in the systematic review, 71.4% presented an adequate sequence generation, 14.3% reported allocation concealment, 14.3% had blinded patients and investigators, 57.1% had blinded assessment of outcomes, 85.7% described losses to follow-up and exclusions, and none of the studies used the intention-to-treat principle for statistical analyses (Table 2).

Effects of interventions

Peak oxygen consumption

Three studies[8,10,11] assessed peak VO_2 (n = 72). We observed that IMT provides a non-significant improvement in peak VO_2 compared to control groups [1.98 ml/kg/min^{-1} (95% CI: -0.67 to 4.62, p = 0.09; I^2: 59%)] (Figure 2). Based on the GRADE approach, the quality of the evidence for this outcome was considered very low (based on the limitations in design, imprecision and inconsistency of the results) (Table 3). Statistical heterogeneity can be explained by Dall'Ago et al.[8] which showed a higher improvement in this outcome compared to other studies. Removing this paper from meta-analysis, there is an absence of heterogeneity (0.45 ml/kg/min^{-1}; 95% CI: -2.01 to 2.91), I^2: 0%. In this meta-analysis, two studies[8,11] performed IMT for 12 weeks, included only patients with inspiratory muscle weakness, and had control groups that performed placebo-IMT with no inspiratory load. In contrast, Martínez et al.[10] conducted training only for 6 weeks, included patients without inspiratory weakness and the control group performed placebo-IMT at 10% of PImax. In sensitivity analyses, analyzing only the first two studies[8,11], we observed that IMT promoted a clinically significant improvement in peak VO_2 by 3.02 ml/kg/min^{-1} (95% CI: 0.43 to 5.61, I^2: 39%) compared to control groups (Figure 2).
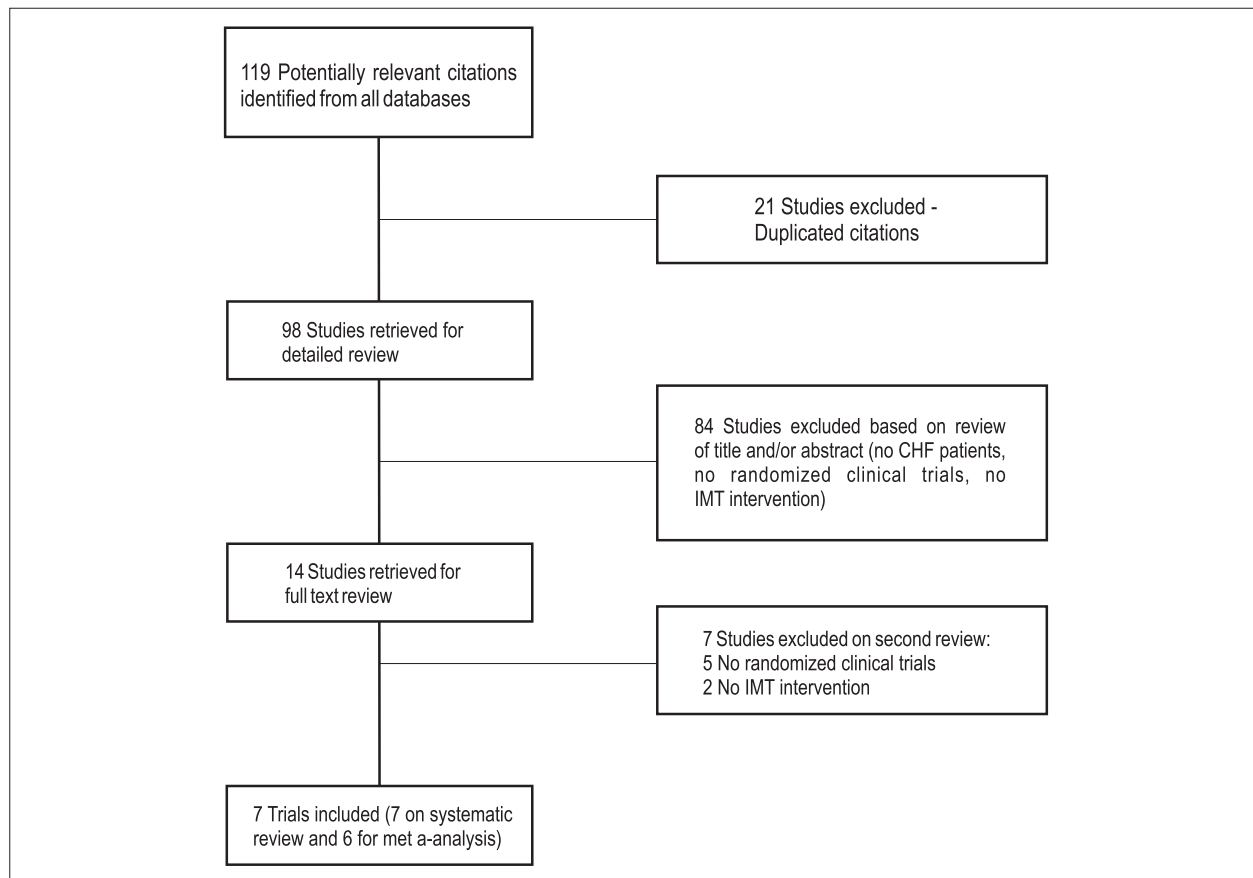

Figure 1 - *Flow diagram of included studies.*
CHF - chronic heart failure; IMT - inspiratory muscle training.

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Table 1 - **Characteristics of studies included in this review**

Study, year	Methods	Patients (n)	Age y [mean ± SD or mean (range)]	Male gender (n)	NYHA I - II - III (n)	Features
IMT vs. P-IMT						
Johnson et al., 1998[9]	Training group: Load: 30% PImax. Control group: Load: 15% PImax.	8 / 8	70 ± 4.6 / 63.4 ± 4.5	15*	0 - 12 - 6*	IMT: Threshold load 30% PImax adjusted for each increment of PImax. P-IMT: Threshold load 15% PImax not adjusted. - Both groups: trainers for 15 min twice daily for at least 8 weeks.
Weiner et al., 1999[11]	Training group: Load: 15% of their PImax for 1 week and the resistance then increased to 60% Control group: with no inspiratory load.	10 / 10	66.2 ± 14.5 / 63.8 ± 12.6	18*	2.3 ± 0.6 / 2.4 ± 0.6	IMT: Threshold load 15% to 60% PImax. Week 1 = 15% PImax; week 2 = +5% PImax for each session until 60% PImax is reached (should be reached until the end of the first month); month 2 and 3 = Threshold load 60% of PImax adjusted weekly. P-IMT: The same device although without load. - Both groups trained 90 min daily, 6 days per week, for 12 weeks.
Martinez et al., 2001[10]	Training group: Load: 30% PImax. Control group: Load: 10% PImax.	11 / 9	60 ± 14 / 57 ± 13	16*	0 - 5 - 6 / 0 - 2 - 7	IMT: Workload valve load 30% PImax adjusted weekly according to PImax. P-IMT: Workload valve load 10% PImax adjusted weekly. - Both groups: 15 min twice daily, 6 days per week for 6 weeks; PImax measured weekly.
Dall'Ago et al., 2006[8]	Training group: Load: 30% PImax adjusted weekly to maintain 30% PImax. Control group: with no inspiratory load.	16 / 16	54 ± 3 / 58 ± 2	11 / 10	4 - 6 - 6 / 4 - 5 - 7	IMT: Threshold load 30% PImax; adjusted weekly in order to maintain 30% PImax. P-IMT: Threshold no load. - Both groups trained 30 min daily, 7 days per week, for 12 weeks.
Bosnak-Guclu et al., 2011[14]	Training group: Load: 40% PImax adjusted weekly to maintain 40% PImax. Control group: Load: 15% PImax.	16/14	69.5 ± 7.9 / 65.7 ± 10.5	12 / 12	0 - 11- 5 / 0 - 9 - 5	IMT: Threshold load 40% PImax; training loads were adjusted weekly to maintain 40% of the PImax. P-IMT: Threshold load 15% PImax not adjusted. - Both groups: 30 min-per day, 7 days per week, for 6 weeks.
IMT vs. Another intervention						
Padula et al., 2009[12]	Training group: 30% PImax. Control group: Education program	15 / 17	76 (51 – 89) / 73 (32 – 95)	5 / 7	5 - 7 / 9 - 6	IMT: Threshold device training load 30% PImax adjusted. Individuals trained 10 to 20 min daily, 7 days/week, for 12 weeks. Education program: received, home visit for 12 weeks, a booklet designed and covering information such as: basic anatomy and physiology of the heart, diet, medication regimen, sleep, rest, and activity patterns, and what and when to report to the doctor.
Winkelmann, 2009[24]	Training group: IMT (30% PImax) + aerobic exercise Control group: Aerobic exercise	12 / 12	54 ± 12 / 59 ± 9	7 / 4	Not reported	IMT: Threshold load 30% PImax; adjusted weekly to maintain 30% PImax. Individuals trained 30 minutes daily, 7 times per week, for 12 weeks. Aerobic exercise: Supervised exercise program performed 3 times per week, for 12 weeks.

Trials did not report separate mean ± SD age, number of male subjects or functional class for IMT versus control group. / IMT versus control group. IMT - inspiratory muscle training; P-IMT - placebo-inspiratory muscle training; NYHA - New York Heart Association; PImax - maximal inspiratory pressure.

Table 2 - Risk of bias of included studies

	Adequate sequence generation	Allocation concealment	Blinding of patients and investigators	Blinding of outcome assessors	Description of losses and exclusions	Intention-to-treat analysis
Johnson et al., 1998[9]	Yes	No	No	No	Yes	No
Weiner et al., 1999[11]	Yes	No	No	Yes	Yes	No
Martinez et al., 2001[10]	Yes	No	No	No	No	No
Dall'Ago et al., 2006[8]	No	No	No	Yes	Yes	No
Padula et al., 2009[12]	Yes	Yes	No	No	Yes	No
Winkelmann, 2009[24]	No	No	No	Yes	Yes	No
Bosnak-Guclu et al., 2011[14]	Yes	No	Yes	Yes	Yes	No

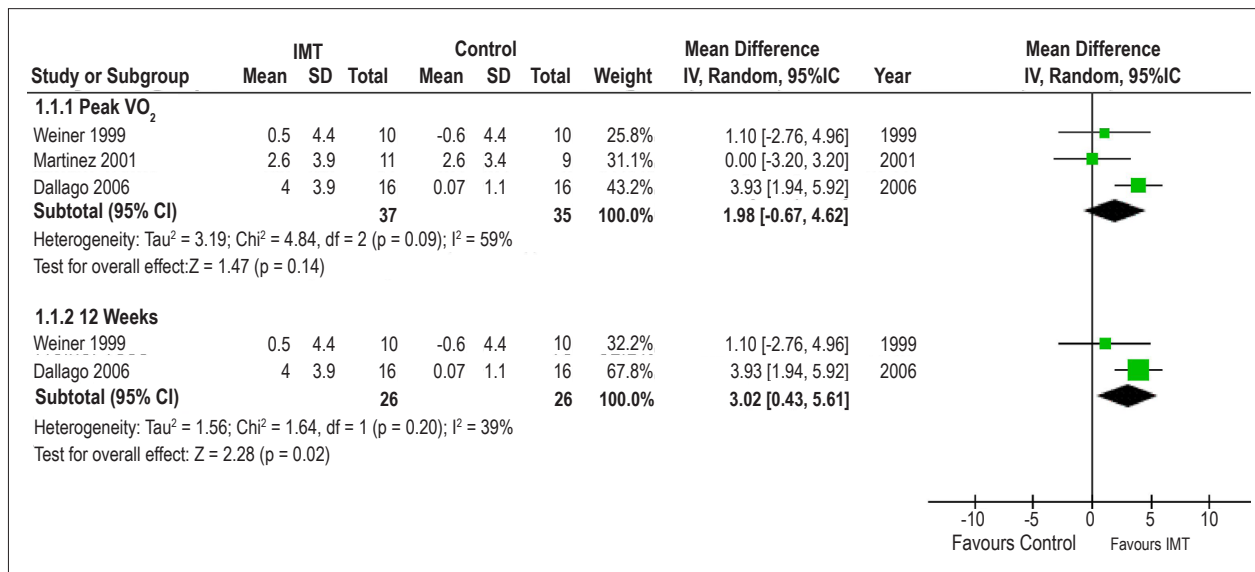| Study or Subgroup	IMT Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95%IC	Year
1.1.1 Peak VO₂									
Weiner 1999	0.5	4.4	10	-0.6	4.4	10	25.8%	1.10 [-2.76, 4.96]	1999
Martinez 2001	2.6	3.9	11	2.6	3.4	9	31.1%	0.00 [-3.20, 3.20]	2001
Dallago 2006	4	3.9	16	0.07	1.1	16	43.2%	3.93 [1.94, 5.92]	2006
Subtotal (95% CI)			37			35	100.0%	1.98 [-0.67, 4.62]	
Heterogeneity: Tau² = 3.19; Chi² = 4.84, df = 2 (p = 0.09); I² = 59%									
Test for overall effect: Z = 1.47 (p = 0.14)									
1.1.2 12 Weeks									
Weiner 1999	0.5	4.4	10	-0.6	4.4	10	32.2%	1.10 [-2.76, 4.96]	1999
Dallago 2006	4	3.9	16	0.07	1.1	16	67.8%	3.93 [1.94, 5.92]	2006
Subtotal (95% CI)			26			26	100.0%	3.02 [0.43, 5.61]	
Heterogeneity: Tau² = 1.56; Chi² = 1.64, df = 1 (p = 0.20); I² = 39%									
Test for overall effect: Z = 2.28 (p = 0.02)									

Figure 2 - *Peak VO₂ for treatment with inspiratory muscle training versus control groups.*
IMT - inspiratory muscle training; CI - confidence interval; SD - standard deviation. 1.1.1 – Peak VO₂ for all studies; 1.1.2 – Peak VO₂ for studies that performed IMT for 12 weeks.

Table 3 - Quality of evidence using the GRADE approach

Outcome measure	N of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Effect (95% CI)	Quality of Evidence
Peak VO₂	3	serious[1]	serious[2]	no serious indirectness	serious[3]	1.98 (-0.67 to 4.62)	Very Low
6-MWT	3	serious[1]	serious[2]	no serious indirectness	serious[3]	69 (7.21 to 130.79)	Very Low
PImax	6	serious[1]	serious[2]	no serious indirectness	no serious imprecision	23.36 (11.71 to 35.02)	Low

Peak VO₂ - peak oxygen consumption; 6-MWT - 6-minute walk test; PImax - maximal static inspiratory pressure. 1 – Limitations in design; 2 – moderate heterogeneity; 3 – large confidence interval.

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Winkelmann et al.[24] observed an improvement in peak VO_2 comparing before and after treatment measurements in the IMT plus AE group (15.1 ± 4.2 to 19.7 ± 4.1, p < 0.001) and in the AE group (16.1 ± 4.6 to 19.2 to 4.2, p < 0.001). As noted, 40% mean increment in peak VO_2 in the IMT plus AE group was significantly larger than the 21% mean increment observed in the AE group.

Distance walked in the 6-MWT

Three studies[8,10,14] assessed distance walked in the 6-MWT (n = 82). We observed that IMT provides a significant improvement in distance walked in the 6-MWT compared to control groups [69 m (95% CI: 7.21 to 130.79; I^2: 78%)] (Figure 3). According to GRADE, there was very low quality evidence for this outcome based on the limitations in design imprecision and inconsistency of the results (Table 3).

Statistical heterogeneity is also explained by Dall'Ago et al.[8], who showed a higher improvement in this outcome compared to other studies. This study presented different clinical characteristics from the other two studies[10,14]: 1) IMT performed for 12 weeks, 2) control groups received placebo-IMT with no inspiratory load, and 3) included only patients with weakness of inspiratory muscles. In sensitivity analyses, analyzing only the other two studies[10,14] that performed IMT for 6 weeks, the control groups received placebo-IMT with inspiratory load (10% and 15% of PImax, respectively). We observed an absence of heterogeneity (I^2: 0%), but also smaller effect size in this outcome (43.59 m; 95% CI: 12.77 to 74.41) (Figure 3).

In the study by Winkelmann et al.[24] both groups presented similar improvement in the distance walked in the 6-MWT (IMT plus AE = 420 ± 90 m before and 500 ± 72 m after; AE = 433 ± 108 m before and 489 ± 81 m after).

Maximal static inspiratory pressure

All articles[8-12,14] included in this meta-analysis evaluated PImax (n = 150). There was a significant improvement in PImax when comparing IMT versus all control groups [23.36 cmH_2O (95% CI: 11.71 to 35.02; I^2: 64%)] (Figure 4). Based on the GRADE approach, the quality of evidence for this outcome was low, based on the limitations in design and inconsistency of the results (Table 3).

Statistical heterogeneity can be explained by Dall'Ago et al.[8] and Weiner et al.[11] These studies included only patients with inspiratory muscle weakness and control groups that received placebo-IMT with no inspiratory load. Removing these articles there is an absence of heterogeneity (I^2: 0%). Sensitivity analysis was performed for duration of intervention. We observed that IMT performed for 6 or 8 weeks improved PImax by 14.56 cmH_2O (95% CI: 6.38 to 22.73, I^2: 0%), but studies that performed IMT for 12 weeks led to a higher improvement in PImax compared to control groups (35.17 cmH_2O; 95% CI: 10.96 to 59.38) (Figure 4). Furthermore, Weiner et al.[11] was the only study that used high-intensity IMT (15% to 60% PImax). The other studies performed IMT with 30%[8-10,12] or 40%[14] of PImax. When this study was omitted individually from the meta-analyses to assess possible individual influences on results, heterogeneity and weighted mean difference remained unchanged.

Winkelmann et al.[24] show that the IMT plus AE (57 ± 12 to 120 ± 12) and AE group (56 ± 13 to 95 ± 14) presented significant improvements in PImax. Likewise, the 110% mean increment in PImax at 12 weeks in the IMT plus AE group was significantly larger than the 72% mean increment observed in the AE group.

Discussion

Summary of evidence

In this systematic review, we found that IMT was associated with significant improvement in functional capacity and inspiratory muscle strength in patients with CHF. However,
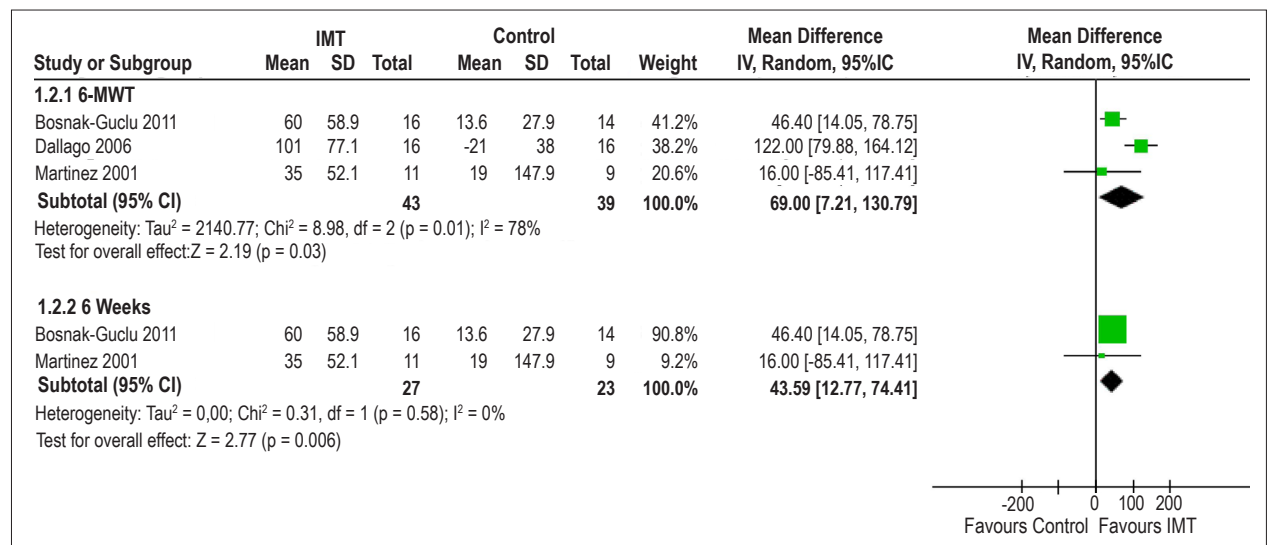
Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95%IC	Mean Difference IV, Random, 95%IC
1.2.1 6-MWT									
Bosnak-Guclu 2011	60	58.9	16	13.6	27.9	14	41.2%	46.40 [14.05, 78.75]	
Dallago 2006	101	77.1	16	-21	38	16	38.2%	122.00 [79.88, 164.12]	
Martinez 2001	35	52.1	11	19	147.9	9	20.6%	16.00 [-85.41, 117.41]	
Subtotal (95% CI)			**43**			**39**	**100.0%**	**69.00 [7.21, 130.79]**	
Heterogeneity: Tau² = 2140.77; Chi² = 8.98, df = 2 (p = 0.01); I² = 78%									
Test for overall effect:Z = 2.19 (p = 0.03)									
1.2.2 6 Weeks									
Bosnak-Guclu 2011	60	58.9	16	13.6	27.9	14	90.8%	46.40 [14.05, 78.75]	
Martinez 2001	35	52.1	11	19	147.9	9	9.2%	16.00 [-85.41, 117.41]	
Subtotal (95% CI)			**27**			**23**	**100.0%**	**43.59 [12.77, 74.41]**	
Heterogeneity: Tau² = 0,00; Chi² = 0.31, df = 1 (p = 0.58); I² = 0%									
Test for overall effect: Z = 2.77 (p = 0.006)									

-200   0   100   200
Favours Control Favours IMT

Figure 3 - *Distance walked in the 6-MWT for treatment with inspiratory muscle training versus control groups.*
IMT - inspiratory muscle training; CI - confidence interval; SD - standard deviation. 1.2.1 - Distance walked in the 6-MWT for all studies; 1.2.2 – Distance walked in the 6-MWT for studies that performed IMT for 6 weeks.
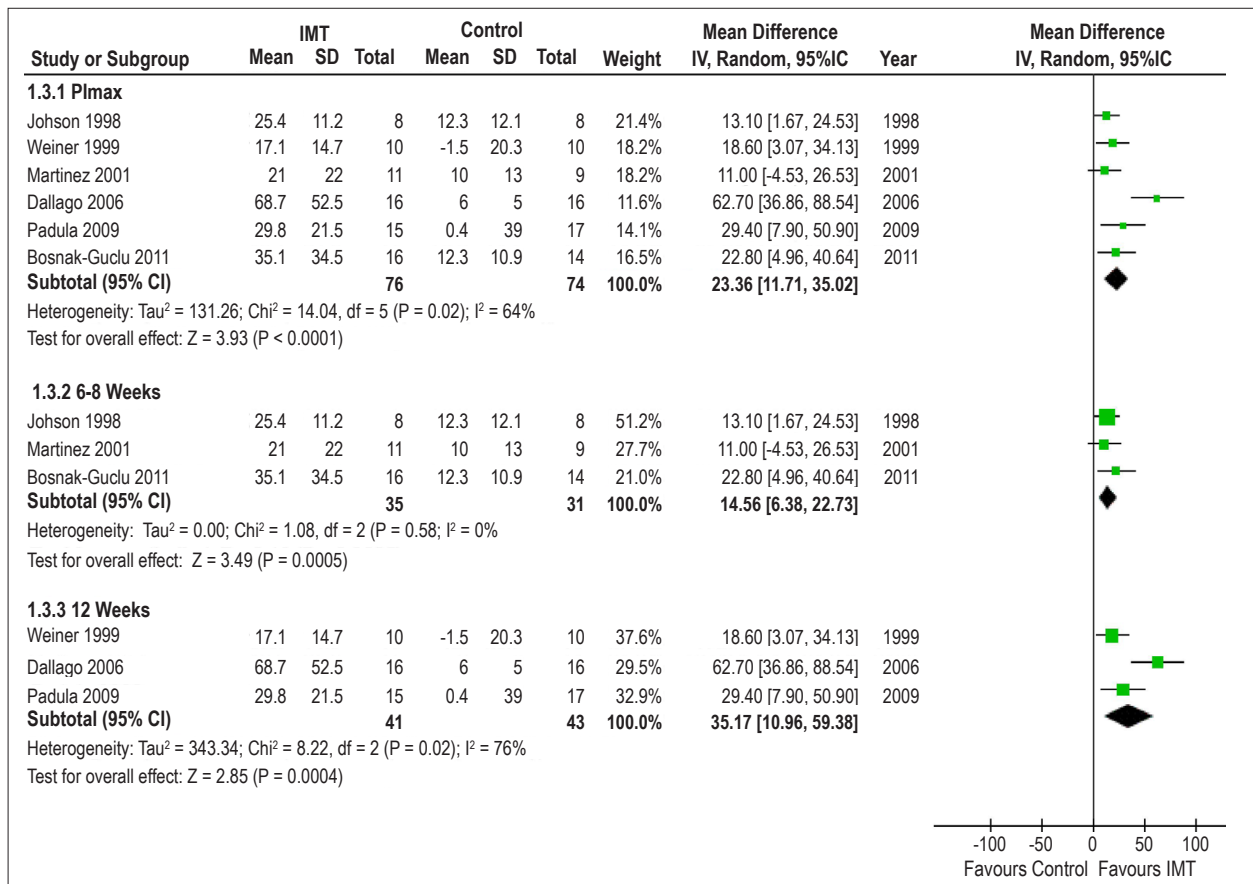
Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95%IC	Year	Mean Difference IV, Random, 95%IC
1.3.1 PImax										
Johson 1998	25.4	11.2	8	12.3	12.1	8	21.4%	13.10 [1.67, 24.53]	1998	
Weiner 1999	17.1	14.7	10	-1.5	20.3	10	18.2%	18.60 [3.07, 34.13]	1999	
Martinez 2001	21	22	11	10	13	9	18.2%	11.00 [-4.53, 26.53]	2001	
Dallago 2006	68.7	52.5	16	6	5	16	11.6%	62.70 [36.86, 88.54]	2006	
Padula 2009	29.8	21.5	15	0.4	39	17	14.1%	29.40 [7.90, 50.90]	2009	
Bosnak-Guclu 2011	35.1	34.5	16	12.3	10.9	14	16.5%	22.80 [4.96, 40.64]	2011	
Subtotal (95% CI)			76			74	100.0%	**23.36 [11.71, 35.02]**		
Heterogeneity: Tau^2 = 131.26; Chi^2 = 14.04, df = 5 (P = 0.02); I^2 = 64%										
Test for overall effect: Z = 3.93 (P < 0.0001)										
1.3.2 6-8 Weeks										
Johson 1998	25.4	11.2	8	12.3	12.1	8	51.2%	13.10 [1.67, 24.53]	1998	
Martinez 2001	21	22	11	10	13	9	27.7%	11.00 [-4.53, 26.53]	2001	
Bosnak-Guclu 2011	35.1	34.5	16	12.3	10.9	14	21.0%	22.80 [4.96, 40.64]	2011	
Subtotal (95% CI)			35			31	100.0%	**14.56 [6.38, 22.73]**		
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.08, df = 2 (P = 0.58; I^2 = 0%										
Test for overall effect: Z = 3.49 (P = 0.0005)										
1.3.3 12 Weeks										
Weiner 1999	17.1	14.7	10	-1.5	20.3	10	37.6%	18.60 [3.07, 34.13]	1999	
Dallago 2006	68.7	52.5	16	6	5	16	29.5%	62.70 [36.86, 88.54]	2006	
Padula 2009	29.8	21.5	15	0.4	39	17	32.9%	29.40 [7.90, 50.90]	2009	
Subtotal (95% CI)			41			43	100.0%	**35.17 [10.96, 59.38]**		
Heterogeneity: Tau^2 = 343.34; Chi^2 = 8.22, df = 2 (P = 0.02); I^2 = 76%										
Test for overall effect: Z = 2.85 (P = 0.0004)										

-100 -50 0 50 100
Favours Control Favours IMT

Figure 4 - *Maximal inspiratory pressure for treatment with inspiratory muscle training versus control groups.*
PImax - maximal inspiratory pressure; IMT - inspiratory muscle training; CI - confidence interval; SD - standard deviation. 1.3.1 - PImax for all studies; 1.3.2 - PImax for studies that performed IMT for 6-8 weeks; 1.3.3 - PImax for studies that performed IMT for 12 weeks.

IMT provides a significant improvement in peak VO$_2$ only in the studies that performed IMT for 12 weeks against no inspiratory load in patients with inspiratory muscle weakness.

The improvement of peak VO$_2$ by IMT performed for 12 weeks can be attributed to delay in the development of diaphragmatic fatigue in patients with CHF, leading to a reduction in the recruitment of accessory respiratory muscles, increasing ventilatory efficiency, and/or reducing the blood flow required by the respiratory muscles during exercise, consequently reducing sympathetic activation and improving systemic vasodilation, perfusion of the peripheral muscles, and increasing functional capacity[25,26]. In a group of CHF patients, Chiappa et al.[27] demonstrated that IMT was able to improve blood flow to both resting and exercising limb muscles in the setting of respiratory muscle fatigue, suggesting that the inspiratory muscle metaboreflex had been partially attenuated[28]. In our study, we demonstrated that duration of intervention and inspiratory muscle weakness are partly responsible for the positive changes observed in patients.

As to distance walked in the 6-MWT, we observed a clinically significant increase[29] for patients in the IMT group. Furthermore, we observed that the study that included patients with inspiratory muscle weakness, who performed IMT for 12 weeks, and had a control group that received placebo-IMT with no inspiratory load[8] showed greater gains in this variable. This may be due to the greater degree of impairment in the patients included in this trial and the longer duration of the intervention and it compares the IMT group to the control group that received placebo-IMT with no inspiratory load. Laoutaris et al.[13] demonstrated that there is an inverse correlation between change in dyspnea and walking distance, probably linked to improved exercise capacity.

In this meta-analysis, we found a different result concerning functional capacity. We observed a significant increase in distance walked in the 6-MWT which was not observed in relation to peak VO$_2$. This can be explained by the fact that maximal and submaximal tests have physiological determinants and potential for improvement different post-intervention. Thus, different test paradigms may not respond equally to a given intervention[30]. Furthermore, in the analysis of peak VO$_2$, there was a small number of patients and, according to GRADE, the quality of evidence presented by this outcome was very low, due to the limitations in design, imprecision and inconsistency of the results. We believe that further research may increase confidence and change the estimates of effect.

In addition, we observed that IMT significantly improved PImax compared to control groups. Several studies have observed that PImax is reduced in patients with CHF. Mancini et al.[31] were the first to demonstrate the beneficial effects of selective respiratory muscle training in improving respiratory muscle strength and overall aerobic capacity in CHF. The improvement in inspiratory muscle function may have achieved respiratory unloading with restoration of the imbalance between the ability of the inspiratory muscles to sustain activity and inspiratory loads. There is evidence that respiratory muscle weakness observed in CHF patients is reversible. Furthermore, this variable correlates significantly with peak VO_2, suggesting that respiratory muscle weakness contributes to impaired exercise capacity in CHF[28].

Another aspect to note is with regard to load analyzed in articles that ranged from 30% to 60% PImax. In a non-randomized trial, Laoutaris et al.[32] compared high intensity versus low intensity IMT in patients with CHF. The high-intensity training regimen involved repetitive efforts at 60% PImax until exhaustion, whereas the low intensity group trained at 15% of PImax with only six inspiratory efforts. Patients in both groups trained three times a week for 10 weeks. While there was a statistically significant increase in PImax in both groups after training compared with baseline, the gains were greater in the high-intensity training group. However, in this systematic review, Weiner et al.[11] was the only RCT that used high-intensity IMT (15% to 60% PImax) and when this study was omitted individually from the meta-analyses to assess possible individual influences on results, heterogeneity and weighted mean difference were unchanged.

Strengths and limitations of the review

Our study has several methodological strengths, which are: 1. The focused review questions, 2. A comprehensive and systematic literature search and 3. The collaboration of a multidisciplinary team of health researchers and methodologists that used explicit and reproducible eligibility criteria. Furthermore, we employed meta-analysis to quantitatively express the results obtained and evaluated the quality of evidence for each outcome analyzed.

We found that many of these RCTs were methodologically limited by a degree of attrition bias. Only one study clearly described the blinding (patients and therapists)[14], and the confidentiality of the allocation concealment[12], and four trials reported that the outcome evaluation was blind[8,11,14,24]. Moreover, one study[10] also failed to describe the losses and exclusions that occurred during the treatment period. Therefore, sensitivity analyses were impaired by the methodological quality presented by the included studies and by the small number of studies and participants. Furthermore, the included studies do not have sufficient power, since even performing meta-analysis, the 95% confidence intervals remained wide, suggesting that further studies should be performed with a larger number of patients and longer follow-up periods.

According to the GRADE approach, all outcomes presented low or very low quality of evidence. This indicates that any estimate of effect is very uncertain and further research is very likely to have a major impact on our confidence to estimate effect and is likely to change the estimate[22], suggesting that new studies should be carried out with a larger number of patients.

We decided to perform a systematic review with meta-analysis since this type of study can provide more reliable estimates of treatment effectiveness than individual trials because they have greater statistical power. Because of statistical heterogeneity found in the meta-analysis, we performed a detailed exploration of possible sources of heterogeneity between studies, including a detailed description of sensitivity analysis and subgroups analysis. The steps used to deal with the moderate and high heterogeneity of the studies were: 1) to perform the meta-analyses removing each paper at a time to check whether some individual study explained heterogeneity; 2) performed sensitivity analyses based on pre-specified relevant clinical information which influences IMT effects on outcomes [duration of the intervention, intervention performed by control group and if the studies included patients with weakness of inspiratory muscles (PImax < 70% of predicted)]. Using these analyses, we observe that IMT for patients with weakness of the inspiratory muscles and undergoing IMT for 12 weeks increases the gains in all outcomes evaluated. Thus, the inspiratory load does not seem to influence the results observed.

Conclusions

This systematic review with meta-analysis suggests that treatment with inspiratory muscle training improves functional capacity and inspiratory muscle strength thereby deserving consideration as an additional intervention in patients with CHF. However, the methodological quality of the articles included and the small sample sizes suggest that new RCTs are needed on this subject. Studies must be planned with greater methodological strictness, a larger number of patients and longer periods of intervention.

Review Article

#1	Heart next failure OR cardiac next insufficienc* OR dilated next cardiomyo* OR heart ventricle OR heart failure congestive OR ventricular dysfunction OR cardiomyopathy congestive OR heart failure
#2	Respiratory muscle training OR Inspiratory muscle training OR Breathing exercises
#3	Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]
#4	#1 AND #2 AND #3

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