

A SYSTEMATIC REVIEW OF EFFECTS OF RESPIRATORY MUSCLE TRAINING FOR INSPIRATORY STRENGTH, DYSPNEA, EXERCISE CAPACITY, AND OUTCOMES IN ASTHMA PATIENTS

KHALID OBAID ALANAZI

Respiratory Therapist, Respiratory Care Services, Intensive Care Unit, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

KHALID HAMDAN ALANAZI

Respiratory Therapist, Respiratory Care Services, Intensive Care Unit, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

ABDULAZIZ AHMED ALHAYTI

Respiratory Therapist, Respiratory Care Services, Intensive Care Unit, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

MOHAMMED SAAD ALDOSARI

Respiratory Therapist, Respiratory Care Services, Intensive Care Unit, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

OSAMA IBRAHIM ALMUJALLI

Respiratory Therapist, Respiratory Care Services, Intensive Care Unit, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

YAZEED MOHAMMED ALKHALIFAH

Respiratory Therapist, Respiratory Care Section, Critical Care Department, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

ABDULLAH HASSAN ASIRI

Respiratory Therapist, Respiratory Care Section, Critical Care Department, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

ALWALEED AHMED AMRI

Respiratory Therapist, Respiratory Care Services, Intensive Care Unit, King Saud University Medical City (KSUMC), Saudi Arabia, Riyadh.

Abstract

Background: Asthma is a highly prevalent chronic respiratory disease associated with airway inflammation, variable expiratory airflow limitation, and respiratory muscle dysfunction. While pharmacological therapy remains the cornerstone of management, non-pharmacological interventions such as respiratory muscle training (RMT) have emerged as potential adjuncts to improve outcomes in asthmatic patients. **Methods:** This systematic review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* guideline. PubMed, Scopus, and Web of Science databases were searched for randomized controlled trials (RCTs) and quasi-experimental studies published between 2000 and 2017. Studies were eligible if they included patients with asthma of any severity undergoing inspiratory muscle training (IMT) or expiratory muscle training (EMT) as stand-alone interventions.

Data extracted included study design, participant demographics, intervention details, and outcomes such as inspiratory and expiratory muscle strength (P_Imax, P_Emax), exercise capacity, dyspnea, lung function, health-related quality of life (HRQoL), and healthcare utilization. **Results:** Six studies met inclusion criteria, comprising five RCTs and one quasi-experimental study. IMT consistently improved inspiratory muscle strength (P_Imax) and reduced exertional dyspnea. Several studies demonstrated reductions in β 2-agonist consumption and emergency department visits, whereas improvements in pulmonary function, expiratory muscle strength, and HRQoL were inconsistent. **Conclusion:** RMT, particularly IMT, appears to be a safe and beneficial adjunct to conventional asthma management. It enhances inspiratory muscle strength and reduces dyspnea, with potential to improve clinical outcomes. High-quality, large-scale trials are warranted to confirm these benefits and define optimal training protocols.

Keywords: Asthma; Respiratory Muscle Training; Inspiratory Muscle Training; Expiratory Muscle Training; Inspiratory Muscle Strength; Dyspnea; Exercise Tolerance; Pulmonary Function; Quality of Life.

INTRODUCTION

Asthma is one of the most prevalent chronic respiratory disorders worldwide and represents a major public health challenge due to its impact on morbidity, quality of life, and healthcare costs (1). Asthma accounts for 1–2% of total healthcare expenditure in developed nations, reflecting its significant economic burden (2). The condition is characterized by chronic airway inflammation, leading to recurrent respiratory symptoms such as wheezing, dyspnea, chest tightness, and cough, which vary in frequency and severity. These symptoms are associated with variable expiratory airflow limitation that may become persistent over time. In addition to airflow restriction, some patients with asthma experience respiratory muscle dysfunction, which can further compromise breathing efficiency and exercise tolerance (3).

This mechanical disadvantage of the diaphragm can cause dyspnea and greater strain for the inspiratory muscles, particularly during exercise when dynamic hyperinflation may develop (3). Furthermore, some research has demonstrated that steroid-induced myopathy or muscular weakening might result from large dosages of systemic corticosteroids given to asthmatic patients (4). Additionally, people with mild stable asthma have been shown to have thoraco-abdominal asynchrony with moderate exercise. Because it is non-invasive and volitional, the evaluation of maximum respiratory pressures is frequently used in clinical practice to detect respiratory muscle weakness. When the readings fall between 65% and 80% of the anticipated range, the maximal inspiratory pressure (P_Imax) and maximal expiratory pressures (P_Emax) are deemed lowered (5).

When managing asthma over the long term, respiratory muscle dysfunction must be taken into account. Comprehensive programs incorporating education, breathing exercises, and exercise training have been emphasized as adjuvant therapy to asthma pharmaceutical treatment (6), in accordance with the chronic care paradigm and multidisciplinary approach. Nevertheless, these regimens have not consistently incorporated respiratory muscle training (RMT). RMT has demonstrated efficacy in

treating patients with various respiratory deficits and chronic obstructive pulmonary disease (COPD) (7). RMT's usefulness in treating asthmatics is yet unknown, though. Our goal in this study was to examine how respiratory muscle training affects asthmatic patients.

METHODOLOGY

This systematic review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* guidelines (8).

Search Strategy

A comprehensive search of the electronic databases PubMed, Scopus, and Web of Science was performed to identify relevant studies published between 2000 and 2025. Weekly automated updates from these databases were also screened for newly indexed articles. In addition, the reference lists of retrieved studies, prior systematic reviews, and key journals in the field were manually searched to capture any eligible publications not identified through the electronic search. The following search terms and their combinations were applied: *asthma, bronchoconstriction, bronchial spasm, breathing exercises, inspiratory muscle training (IMT), respiratory muscle training (RMT), expiratory muscle training (EMT), maximal voluntary ventilation, maximal respiratory pressures, dry powder inhalers, rescue medication, metered dose inhalers, respiratory function test, dyspnea, adverse effects, and exercise tolerance*.

Eligibility Criteria

We included randomized controlled trials (RCTs) and quasi-experimental studies involving patients with asthma of any severity. Eligible interventions were defined as inspiratory or expiratory muscle training programs applying an external load to increase inspiratory muscle strength (IMS) or endurance, provided as a stand-alone intervention. Studies combining IMT or EMT with other interventions were excluded unless the effect of respiratory muscle training could be isolated.

Study Selection

Four independent reviewers screened titles and abstracts for relevance after removal of duplicates. Full texts of potentially eligible studies were then assessed against the inclusion criteria. Discrepancies were resolved by consensus, with arbitration from a senior reviewer when required.

Data Extraction

Data were extracted using a standardized form and included: citation details, study design, country, sample size, asthma severity, participant characteristics, intervention type, comparator, outcome measures, and main findings. The primary outcomes were inspiratory and expiratory muscle strength, measured as maximal inspiratory pressure (P_Imax) and maximal expiratory pressure (P_Emax). Secondary outcomes included exercise capacity, asthma symptoms, dyspnea, β_2 -agonist consumption, lung function,

health-related quality of life (HRQoL), and healthcare utilization (emergency department visits).

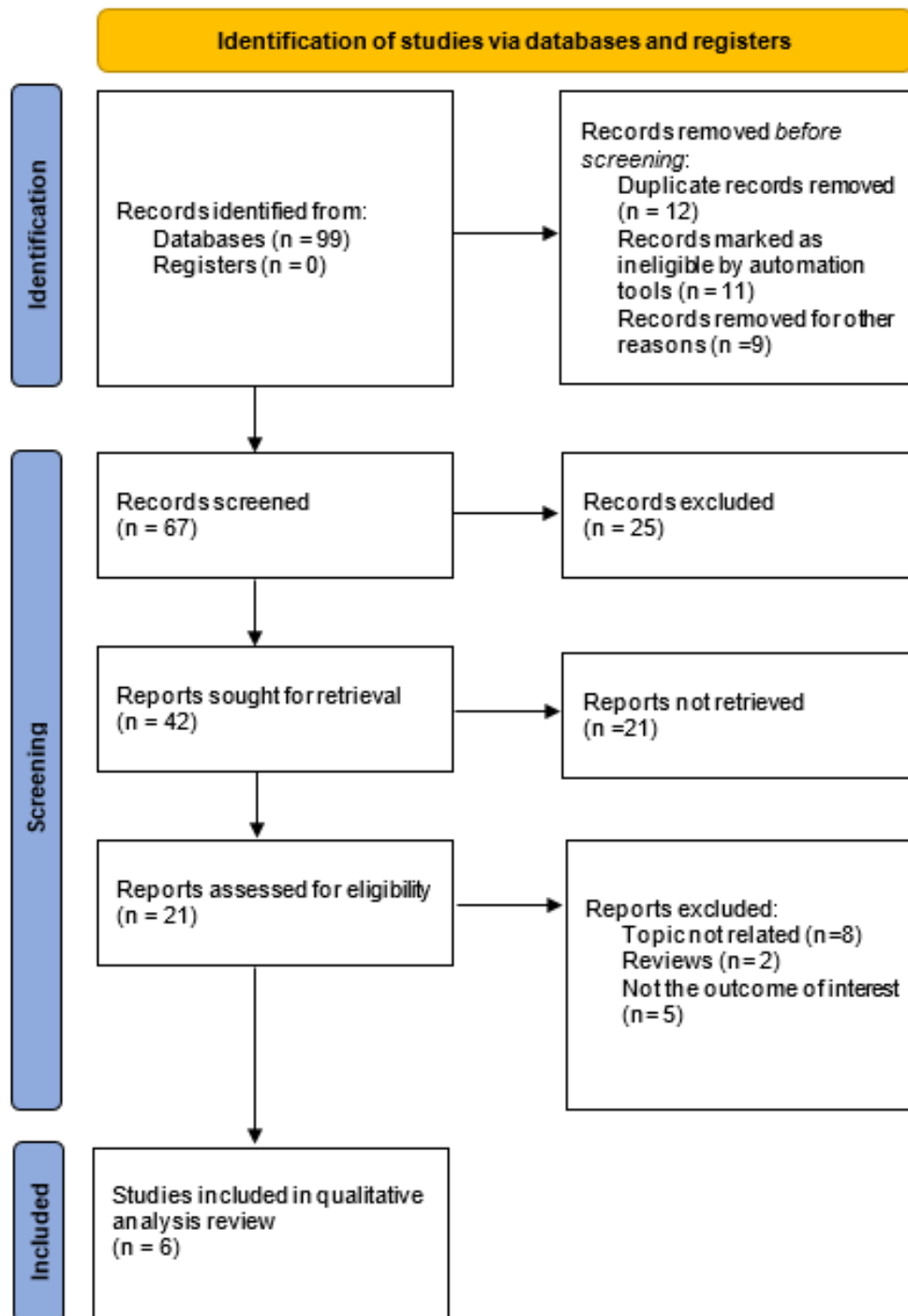


Fig 1: PRISMA consort chart

RESULT AND DISCUSSION

This systematic review included six studies, comprising five randomized controlled trials (RCTs) and one quasi-experimental study, all investigating the effects of respiratory muscle training (RMT) interventions in patients with asthma. The interventions primarily focused on inspiratory muscle training (IMT), with one study combining IMT and expiratory muscle training (EMT). Collectively, the studies assessed a range of outcomes, including inspiratory muscle strength (P_Imax), expiratory muscle strength (P_Emax), exercise capacity, exertional dyspnea, health-related quality of life (HRQoL), lung function, and healthcare utilization. Outcome measures used were (Exercise capacity, inspiratory muscle strength (IMS), Exertional dyspnea, Emergency department visits, and asthma symptoms, consumption of β_2 -agonist, IMS and lung function (Table 1).

This comprehensive review shown that an IMT program is a useful intervention for enhancing IMS in individuals with asthma. It also raises the possibility that this intervention may positively impact IMS, the need for rescue medicine, and exertional dyspnea while having no negative side effects. The data are conflicting on the effects of IMT for exercise capacity, hospital admissions, and HRQoL. It did not increase expiratory muscular strength or lung function.

The present systematic review includes additional outcomes, such as exercise capacity, health related QoL, and respiratory muscle endurance, than the review published in 2013 (9). Higher P_Imax and P_Emax were seen in the expiratory muscle training (EMT) group compared to the control group in a systematic evaluation of COPD patients, and these effects were more pronounced when IMT and EMT were combined. Moreover, there was a correlation found between increased exacerbations, hospital admissions, and death with weakening of the expiratory muscles (10). Thus, we think that more research is necessary to examine the potential advantages of EMT in conjunction with IMT for asthma.

When compared to no intervention or instructional programs, IMT can cause an increase in P_Imax in individuals with asthma. The majority of research conducted on chronic respiratory disorders used sham-IMT with training loads $\leq 15\%$ P_Imax, which did not result in changes to strength (6). Therefore, we think that the control group's inspiratory muscular strength was likely increased by a load of 20% P_Imax (11).

The primary conclusions of the TURNER et al. study is that asthmatic patients undergoing six weeks of IMT get a decreased oxygen consumption and the experience of dyspnea during exercise; enhanced IMS and demonstrated reduction of exercise-induced inspiratory muscle fatigue; and raised T_{lim} during constant-power exercise.

Consistent with the findings of TURNER et al. study, impaired IMS prior to exercise has been demonstrated to exacerbate exertional dyspnea in asthmatic individuals (12) and may also decrease exercise tolerance in these individuals (9). Additionally, IMT has been demonstrated to decrease the perception of exercise dyspnea in healthy individuals (13) and during pressurized threshold inspiratory loading in asthmatics (12). One important indicator of dyspnea during bronchoconstriction is the increased inspiratory muscle effort

linked to increased airway resistance and dynamic hyperinflation (14) It might be caused by a variety of things, such as the recruitment of extra accessory respiratory muscles, a decrease in IMS because to their shorter operational duration, and an increase in inspiratory activity during expiration (15).

According to the TURNER et al. research, the decrease in dyspnea perception that they observed was probably caused by an IMS improvement following IMT rather than by modifications to lung function. Furthermore, literature indicates a negative correlation between changes in IMS and the severity of dyspnea during an inspiratory loading test after IMT (16).

To be more precise, after inspiratory muscle training, a lower proportion of maximum force-generating capacity would be needed to provide the necessary pressure for a given volume change. This would lower the central motor demand and, consequently, the perception of effort (17).

Aerobic training (18) and the injection of bronchodilators (19) have been demonstrated to diminish exertional dyspnea, one of the symptoms of asthma that is linked to poor exercise tolerance (20). TURNER et al. study conclude that, among recreationally active persons with moderate asthma, IMT can lessen the sense of dyspnea and increase exercise tolerance. This discovery raises the possibility of IMT serving as a supplemental intervention for this population.

It should be highlighted, nonetheless, that for the tiny percentage of asthmatics who have a poor perception of dyspnea, a decrease in that perception might be harmful as it could lead to an under estimation of the severity of asthmatic exacerbations.

Asthma sufferers may have decreased exercise tolerance in correlation with expiratory flow restriction and dynamic hyperinflation during exercise (19). TURNER et al. study participants showed a progressive increase in end-inspiratory lung volume (EELV) as exercise duration increased; however, those in the IMT group exhibited a tendency toward a reduction in the degree of hyperinflation during the first five minutes of exercise following IMT, as well as a significant attenuation at that point.

Following intervention, there was a comparable trend for EILV to decrease in the IMT group. According to earlier studies, a rise in EELV during intentional hyperpnea raised the oxygen cost of ventilation and the elastic work of breathing (21).

The findings of the Lima et al. study are consistent with those of studies involving adults with obstructive illnesses (16,22), demonstrating that following particular IMT, IMS improved, leading to a corresponding improvement in clinical status. An evaluation of a respiratory treatment program in eight distinct locations was conducted by a multicenter, randomized, cross-over controlled research (23).

In addition to breathing exercises and instructional materials, the program featured IMT, relaxation methods, bronchial hygiene practices, and leisure activities. Exercise tolerance and patient quality of life were shown to have significantly improved.

Table 1: characteristics and main findings of the included studies

Citation	Study design	Study participants	Outcomes measures	Intervention	Findings
Turner et al. (25)	Quasi experimental	Mild to moderate asthma	Exertional dyspnea and IMS	IMT	Following the intervention, there was no discernible difference in Time to the limit of exercise tolerance (Tlim), respiratory muscle exhaustion, or the placebo group's experience of dyspnea. A substantial 16% decrease in dyspnea during exercise was also observed. Despite the extended Tlim, the exercise-induced decline in intervention group was reduced from 10% before to IMT to 6% following IMT. The levels of pulmonary function in the placebo and IMT groups did not alter. IMT improves exercise tolerance, lessens the sensation of dyspnea, and attenuates inspiratory muscle fatigue. According to these results, IMT could be a useful addition to asthma treatment that helps increase this group's engagement and adherence to exercise regimens. Breathlessness, however, is also a significant indicator of bronchoconstriction, therefore if this symptom is unusually low, care should be taken.
Lima et al. (26)	RCT	Uncontrolled asthma	Emergency department visits, asthma symptoms and IMS	Breathing exercises, IMT	In addition to enhancing peak expiratory flow and severity factors, programs using IMT and respiratory workouts can boost the mechanical efficiency of the respiratory muscles.
Sampai o et al. (27)	RCT	Clinical diagnostic of asthma	IMS	IMT	In the intervention group PImax: Pre vs Post; $p < 0.05$ PEmax: Pre vs Post; $p < 0.05$ No significant changes in PEmax and PImax

Weiner et al. (16)	RCT	Mild to moderate asthma	Consumption of β_2 -agonist, IMS and lung function	IMT	The mean daily consumption of beta2-agonists and the baseline maximum inspiratory pressure did not exhibit a strong association with each other, nor with the perception of dyspnea (POD). Nonetheless, a noteworthy association was seen between the POD and the average daily intake of beta2-agonists. The decline in POD and the reduction in beta2-agonist intake were strongly linked with the increase in IMS following inspiratory muscle training.
Delgado et al. (24)	RCT	Controlled asthma	Exercise capacity and IMS	Inspiratory muscle training (IMT)	Intervention group Plmax (cmH ₂ O): pre vs post ($p < 0.05$) 6MWT (m): pre vs post ($p < 0.05$) No changes in pulmonary function:
Weiner et al. (28)	RCT	Mild to moderate asthma	β_2 -agonist consumption, IMS, and lung function.	IMT	In the female individuals, mean daily 2-agonist intake and POD were considerably greater, whereas baseline Plmax was significantly lower. By the conclusion of the twentieth training week, Plmax was on par with the male participants. A statistically significant reduction in mean daily 2-agonist usage and POD, comparable to that observed in male patients, was linked to an increase in Plmax.

CONCLUSION

This systematic review demonstrates that inspiratory muscle training (IMT) is an effective adjunctive intervention for patients with asthma, consistently improving inspiratory muscle strength without adverse effects. Beyond enhancing Plmax, IMT was associated with reductions in dyspnea perception and β_2 -agonist use, and in some cases, improved exercise tolerance and decreased healthcare utilization.

Its effects on pulmonary function and expiratory muscle strength remain inconclusive, reflecting heterogeneity in study design and training protocols. These findings support the integration of IMT into comprehensive asthma management programs, particularly for patients with impaired inspiratory muscle performance.

References

- 1) Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med*. 2017 Sep;5(9):691–706.
- 2) Ehteshami-Afshar S, FitzGerald JM, Doyle-Waters MM, Sadatsafavi M. The global economic burden of asthma and chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis*. 2016 Jan 1;20(1):11–23.
- 3) McConnell AK. The role of inspiratory muscle function and training in the genesis of dyspnoea in asthma and COPD. *Prim Care Respir J*. 2005 Aug 1;14(4):186–94.
- 4) Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med*. 1994 Jul;150(1):11–6. doi: 10.1164/ajrccm.150.1.8025735
- 5) Barreiro E, Bustamante V, Cejudo P, Gáldiz JB, Gea J, de Lucas P, et al. Normativa SEPAR sobre disfunción muscular de los pacientes con enfermedad pulmonar obstructiva crónica. *Arch Bronconeumol*. 2015 Aug;51(8):384–95.
- 6) Shei RJ, Paris HLR, Wilhite DP, Chapman RF, Mickleborough TD. The role of inspiratory muscle training in the management of asthma and exercise-induced bronchoconstriction. *Phys Sportsmed*. 2016 Oct 1;44(4):327–34. doi: 10.1080/00913847.2016.1176546
- 7) Ramsook AH, Molgat-Seon Y, Schaeffer MR, Wilkie SS, Camp PG, Reid WD, et al. Effects of inspiratory muscle training on respiratory muscle electromyography and dyspnea during exercise in healthy men. *J Appl Physiol*. 2017 May 1;122(5):1267–75. doi: 10.1152/jappphysiol.00046.2017
- 8) Hutton B, Catalá-López F, Moher D. La extensión de la declaración PRISMA para revisiones sistemáticas que incorporan metaanálisis en red: PRISMA-NMA. *Med Clin (Barc)*. 2016 Sep;147(6):262–6.
- 9) Silva IS, Fregonezi GA, Dias F AL, Ribeiro CT, Guerra RO, Ferreira GM. Inspiratory muscle training for asthma. *Cochrane Database Syst Rev*. 2013 Sep 8.
- 10) Neves LF, Reis MH, Plentz RD, Matte DL, Coronel CC, Sbruzzi G. Expiratory and Expiratory Plus Inspiratory Muscle Training Improves Respiratory Muscle Strength in Subjects With COPD: Systematic Review. *Respir Care*. 2014 Sep;59(9):1381–8. doi: 10.4187/respcare.02793
- 11) McConnell A, Caine M, Donovan K, Toogood A, Miller M. Inspiratory Muscle Training Improves Lung Function and Reduces Exertional Dyspnoea in Mild/Moderate asthmatics. *Clin Sci*. 1998 Aug 1;95(s39):4P-4P.
- 12) Killian KJ, Summers E, Watson RM, O'Byrne PM, Jones NL, Campbell EJ. Factors contributing to dyspnoea during bronchoconstriction and exercise in asthmatic subjects. *Eur Respir J*. 1993 Jul;6(7):1004–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8370426>
- 13) Romer LM, McConnell AK, Jones DA. Effects of inspiratory muscle training on time-trial performance in trained cyclists. *J Sports Sci*. 2002 Jan 9;20(7):547–90. Available from: <https://www.tandfonline.com/doi/full/10.1080/026404102760000053>
- 14) Loughheed MD, Fisher T, O'Donnell DE. Dynamic Hyperinflation During Bronchoconstriction in Asthma. *Chest*. 2006 Oct;130(4):1072–81. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0012369215511422>
- 15) Martin J, Powell E, Shore S, Emrich J, Engel LA. The Role of Respiratory Muscles in the Hyperinflation of Bronchial Asthma 1– 3. *Am Rev Respir Dis*. 1980 Mar;121(3):441–7. Available from: <http://www.atsjournals.org/doi/10.1164/arrd.1980.121.3.441>

- 16) Weiner P, Magadle R, Beckerman M, Berar-Yanay N. The Relationship among the Inspiratory Muscle Strength, the Perception of Dyspnea and Inhaled Beta 2 -Agonists in Patients with Asthma. *Can Respir J*. 2002 Jan 3;9(5):307–12. Available from: <https://onlinelibrary.wiley.com/doi/10.1155/2002/746808>
- 17) el-Manshawy A, Killian KJ, Summers E, Jones NL. Breathlessness during exercise with and without resistive loading. *J Appl Physiol*. 1986 Sep 1;61(3):896–905. Available from: <https://www.physiology.org/doi/10.1152/jappl.1986.61.3.896>
- 18) Hallstrand TS, Bates PW, Schoene RB. Aerobic Conditioning in Mild Asthma Decreases the Hyperpnea of Exercise and Improves Exercise and Ventilatory Capacity. *Chest*. 2000 Nov;118(5):1460–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0012369215512257>
- 19) Kosmas EN. Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma. *Eur Respir J*. 2004 Sep 1;24(3):378–84. Available from: <http://erj.ersjournals.com/cgi/doi/10.1183/09031936.04.00113003>
- 20) O'DONNELL DE, REVILL SM, WEBB KA. Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2001 Sep 1;164(5):770–7. Available from: <https://www.atsjournals.org/doi/10.1164/ajrccm.164.5.2012122>
- 21) Collett PW, Perry C, Engel LA. Pressure-time product, flow, and oxygen cost of resistive breathing in humans. *J Appl Physiol*. 1985 Apr 1;58(4):1263–72. Available from: <https://www.physiology.org/doi/10.1152/jappl.1985.58.4.1263>
- 22) Weiner P, Berar-Yanay N, Davidovich A, Magadle R, Weiner M. Specific Inspiratory Muscle Training in Patients With Mild Asthma With High Consumption of Inhaled β_2 -Agonists. *Chest*. 2000 Mar;117(3):722–7. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S001236921532729X>
- 23) Cambach W, Chadwick-Straver R, Wagenaar R, van Keimpema A, Kemper H. The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. *Eur Respir J*. 1997 Jan 1;10(1):104–13. Available from: <http://erj.ersjournals.com/lookup/doi/10.1183/09031936.97.10010104>
- 24) Delgado, R., Silva, I., Silva, T. E., Fernandes, T., Lima Filho, N., Oliveira, V. H., ... & Ferreira, G. (2014). Inspiratory muscle training for asthma—A randomized controlled pilot study. *European Respiratory Journal*, 44(Suppl 58)..
- 25) Turner La, Mickleborough Td, McConnell Ak, Stager Jm, Tecklenburg-Lund S, Lindley Mr. Effect of Inspiratory Muscle Training on Exercise Tolerance in Asthmatic Individuals. *Med Sci Sport Exerc*. 2011 Nov;43(11):2031–8. Available from: <https://journals.lww.com/00005768-201111000-00003>
- 26) Lima EVNCL, Lima WL, Nobre A, Santos AM dos, Brito LMO, Costa M do R da SR. Treinamento muscular inspiratório e exercícios respiratórios em crianças asmáticas. *J Bras Pneumol*. 2008 Aug;34(8):552–8. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-37132008000800003&lng=pt&tlng=pt
- 27) Sampaio, L. M. M., Jamami, M., Pires, V. A., Silva, A. B., & Costa, D. (2002). Respiratory muscle strength in asthmatic patient submitted by respiratory muscle training and physical training. *Physiother Mag Univ Sao Paulo*, 9(2), 43-48..
- 28) Weiner P, Magadle R, Massarwa F, Beckerman M, Berar-Yanay N. Influence of Gender and Inspiratory Muscle Training on the Perception of Dyspnea in Patients With Asthma. *Chest*. 2002 Jul;122(1):197–201. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0012369216462999>