

## Review Article

# Inspiratory Muscle Rehabilitation Training in Pediatrics: What Is the Evidence?

Dharini M. Bhammar <sup>1</sup>, Harrison N. Jones <sup>2</sup>, and Jason E. Lang <sup>3</sup>

<sup>1</sup>Center for Tobacco Research, Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, OH, USA

<sup>2</sup>Department of Head and Neck Surgery & Communication Sciences, Duke University, Durham, NC, USA

<sup>3</sup>Division of Pulmonary and Sleep Medicine, Duke Children's Hospital and Health Center, Durham, NC, USA

Correspondence should be addressed to Dharini M. Bhammar; [dharini.bhammar@osumc.edu](mailto:dharini.bhammar@osumc.edu)

Received 16 February 2022; Revised 4 July 2022; Accepted 15 July 2022; Published 18 August 2022

Academic Editor: Paola Pierucci

Copyright © 2022 Dharini M. Bhammar et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Pulmonary rehabilitation is typically used for reducing respiratory symptoms and improving fitness and quality of life for patients with chronic lung disease. However, it is rarely prescribed and may be underused in pediatric conditions. Pulmonary rehabilitation can include inspiratory muscle training that improves the strength and endurance of the respiratory muscles. The purpose of this narrative review is to summarize the current literature related to inspiratory muscle rehabilitation training (IMRT) in healthy and diseased pediatric populations. This review highlights the different methods of IMRT and their effects on respiratory musculature in children. Available literature demonstrates that IMRT can improve respiratory muscle strength and endurance, perceived dyspnea and exertion, maximum voluntary ventilation, and exercise performance in the pediatric population. These mechanistic changes help explain improvements in symptomology and clinical outcomes with IMRT and highlight our evolving understanding of the role of IMRT in pediatric patients. There remains considerable heterogeneity in the literature related to the type of training utilized, training protocols, duration of the training, use of control versus placebo, and reported outcome measures. There is a need to test and refine different IMRT protocols, conduct larger randomized controlled trials, and include patient-centered clinical outcomes to help improve the evidence base and support the use of IMRT in patient care.

## 1. Introduction

Pulmonary rehabilitation (PR) is a class of treatments that aims to help patients suffering from chronic respiratory symptoms [1]. PR usually employs a combination of modalities that improves fitness, disease understanding, and lifestyle choices in ways that promote overall health and improved quality of life [1]. PR is most commonly prescribed for chronic obstructive pulmonary disease (COPD); however, PR can be effective in a number of other conditions, particularly those associated with dyspnea and fatigue, such as heart disease, interstitial lung disease, lung cancer, cystic fibrosis, and asthma [2–6]. To date, PR is rarely prescribed in pediatric conditions and may very well be underutilized.

In most cases, PR is prescribed by a physician and leverages the expertise and guidance of physical and respiratory therapists [7]. PR has the advantage of being practical in numerous settings and can be beneficial with a range of frequencies, ranging from daily to just a few times per month. PR involves a combination of whole-body exercise (e.g., walking, aerobics, cycling, and swimming) and skeletal muscle resistance or strength training to build strength and endurance of the heart, limb muscles, and respiratory muscles. PR can also include various forms of breathing exercises, including those that improve the strength and endurance of the respiratory muscles. Altogether, PR can relieve respiratory symptoms, reduce dyspnea, and increase mobility, endurance, and disease-related quality of life [8–11].

## 2. Respiratory Musculature

*2.1. Mechanics of Breathing.* The lungs cannot fulfill their gas exchange role without a mechanical apparatus (or pump) that expands the lungs and draws air into the lower airways. This complex apparatus includes the thoracic cage (made up of the spinal vertebrae, the ribs, and sternum), the lung pleura, and the respiratory muscles. The respiratory muscles are similar in nature to other skeletal muscles, and during quiet breathing, they work in unison to expand the thoracic cage and induce inhalation. Respiratory muscles have both voluntary and involuntary innervation and are thought to have greater resilience to fatigue than other skeletal muscles. The muscular diaphragm is the main driver of inhalation. During quiet involuntary breathing, the diaphragm mostly acts alone. As the diaphragm contracts, it flattens and descends into the abdominal cavity, leading to drops in intrapleural and alveolar pressures. Assuming airway patency, air moves from the atmosphere to the lower, subatmospheric pressures in the alveoli.

Exhalation, on the other hand, is a more passive process and results from the relaxation of the respiratory muscles. The diaphragm relaxes and ascends, allowing recoil of the lungs and thoracic cage to the resting volume known as functional residual capacity (FRC). During hyperventilation or volitional exhalation, the rectus abdominal muscles (and to some degree the internal intercostals, intercostales intimi, and subcostal muscles) promote thoracic recoil and forced exhalation. During volitional breathing or hyperventilation induced by exercise, exhalation is facilitated mainly by the abdominal muscles (rectus and transversus abdominal muscles and internal and external oblique muscles) and secondarily by the internal intercostals. Contraction of these muscles together actively augment the ascent of the diaphragm, raising the pleural and alveolar pressures and leading to rapid exhalation.

*2.2. Developmental and Pediatric Specific Issues with the Diaphragm and Respiratory Musculature.* Key developmental issues are involved in inspiration during health and disease. All respiratory muscles originally derive from embryonic (cranial and trunk) mesoderm. The embryonic and early-life development of the diaphragm is critical to normal respiration and can exhibit developmental defects that impair breathing efficiency. The muscular diaphragm develops as a thin sheet that is both a central tendon and emanating muscle connecting anteriorly to the costal cartilages of ribs 7–10 and xiphoid and posteriorly to the lumbar vertebral bodies, transverse processes, and the 11<sup>th</sup> and 12<sup>th</sup> ribs; it separates the thoracic from the abdominal cavity. After the diaphragm is fully developed, the descent of the diaphragm during contraction stabilizes and elevates the lowest ribs via its anterior connections. This is known as the bucket handle effect. It is thought that children have less efficient inspiratory motion due to incomplete diaphragmatic development [12, 13], which can lead to earlier fatigue and resulting dyspnea with activity. In addition, the increased thoracic compliance seen in children further makes inspiration less efficient. With respiratory

disease or when the body is under stress (i.e., during exercise), increased work of breathing and greater dyspnea can result. Additionally, the pediatric diaphragm sits more superiorly in the thoracoabdominal cavity with a reduced zone of apposition. Children's ribs are more horizontally aligned preventing a more efficient bucket-handle effect, raising the ribs up and out.

*2.3. Respiratory Muscle Fatigue.* Several factors can predispose respiratory muscles to fatigue in health and disease. Any factor that increases the energy demands of respiration impairs the capacity of the respiratory muscles to handle an increased ventilatory workload and quickly leads to respiratory muscle fatigue and dyspnea. Two common examples include restrictive lung disease (e.g., obesity, myopathy) and airway collapse and hyperinflation (e.g., asthma), both of which limit the respiratory muscles from handling increased ventilatory workload. Secondly, reduced energy reserves, malnutrition, or homeostatic problems, such as circulating acidosis or reactive oxygen species, can impair respiratory muscle function leading to fatigue. Lastly, deconditioning or atrophy (following severe illness or after prolonged mechanical ventilation), anemia, low cardiac output states, and hypoxemia all predispose to diaphragmatic dysfunction and fatigue. Table 1 shows the most common conditions that can affect the functioning of the respiratory muscles in childhood.

*2.4. Assessment of Respiratory Muscle Functioning.* More research is needed to understand how best to measure and follow changes in respiratory muscle functioning. The strength of the respiratory muscles can be quantified in the clinical setting easily by the maximum inspiratory pressure (MIP) at the mouth by manometry against a closed mouthpiece [14]. These tests require patient cooperation and maximal effort. Current guidelines recommend at least three inspiratory maneuvers with maximal effort within 10%. Typically, the MIP is measured at the initiation of inspiration from the lung's residual volume. Maximal expiratory pressure (MEP) measured at expiration from total lung capacity measures the strength of the expiratory muscles [15]. Some conditions such as obesity do not demonstrate uniformly reduced baseline inspiratory muscle strength (i.e., MIP) but display greater fatigue of respiratory muscles under stress. Though resting MIP is not a direct measure of fatigue, it is closely correlated with inspiratory muscle fatigue and exertional dyspnea [15–17]. Currently, there are no universally accepted measures of inspiratory muscle endurance or fatigue. Despite this, several procedures have been described in the research setting, but all have considerable limitations. Procedures that have been described but need further pediatric validation include various forms of incremental-load testing, constant-load testing, and time trials [14, 15].

*2.5. Pediatric Methods for Training the Inspiratory Muscles.* Training approaches for inspiratory muscles can broadly be separated into strength- or endurance-training approaches.

TABLE 1: Causes of respiratory muscle weakness or fatigue.

Common classes	Examples/comments
Injury to spinal cord/diaphragmatic innervation	Trauma affecting spinal nerves C3–5
Arnold–Chiari malformations	Types I–IV
Guillain–Barre syndrome	Following acute infections, rarely vaccines
Myasthenic syndromes	
Muscular dystrophies	Duchenne, Becker, Myotonic, Limb-girdle
Spinal muscular atrophy	Types 1 (infantile onset), 2 (intermediate), 3/4 (mild, adult onset)
Multiple sclerosis	
Metabolic myopathy	Pompe, McArdle, mitochondrial
Airway diseases	COPD, asthma
Diaphragmatic disorders	Congenital diaphragmatic hernia, eventration
Cerebral vascular accidents (stroke)	
Critical illness	Prolonged ECMO, chronic mechanical ventilation
Inflammatory myopathy	Polymyositis, dermatomyositis
Iatrogenic (steroid myopathy, radiation injury)	
Poisoning/toxins	Botulism, narcotics
Infections	Polio, polio-like viruses, acute flaccid myelitis
Obesity	Restricted diaphragmatic motion and thoracic expansion

Note. COPD – chronic obstructive pulmonary disease and ECMO – extracorporeal membrane oxygenation.

Strength-training approaches generally involve higher external loads (intensity) with lower training volumes, while endurance-training approaches typically use lower external loads and higher training volumes [18]. Although training methods vary considerably, three primary methods have been used to train the respiratory muscles: (1) voluntary isocapnic hyperpnea (VIH), (2) flow-resistive loading, and (3) pressure-threshold loading.

**2.5.1. VIH Training.** VIH training typically requires vigorous hyperventilation for up to 30 minutes to target respiratory muscle endurance. To prevent hypocapnia, incorporation of a dead space rebreathing circuit or supplemental oxygen to avoid hypoxemia and maintain isocapnia is necessary. Training sessions generally occur at a frequency of 3–5 times per week at an intensity of 60–90% of maximal voluntary ventilation (MVV). A limitation of VIH is that high motivation is required as patients may find training to be strenuous and time-consuming [18–21]. Overall, VIH appears to enhance measures of respiratory muscle endurance but not strength [18, 22].

**2.5.2. Flow-Resistive Loading.** Flow-resistive loading provides the respiratory muscles an external load during ventilation through a variable diameter orifice. Traditionally, this is accomplished with the use of analog devices with adjustable dials, which allow the orifice surface area to be manipulated to change the flow and resulting load. For a given flow rate, the load increases as the orifice surface area decreases, although load also varies with flow rate. Therefore, in order to provide a quantifiable load, respiratory flow or pressure must be measured, which has led to the development of devices that provide electronic flow-resistive loading. For example, the K-series devices from POWER-breathe® provide an external load via an electronically controlled orifice that varies to achieve a target load or flow rate. Similarly, the PrO2™ device (Figure 1) provides a

respiratory load via a fixed 2 mm port, incorporates an integrated pressure transducer to quantify resistance, and uses a Bluetooth-connected smartphone app to provide targeted loads, biofeedback, and user adherence data.

**2.5.3. Pressure-Threshold Loading.** Pressure-threshold loading provides an external load to the respiratory muscles via ventilation through an orifice that remains closed with a spring-loaded valve or other methods until a target pressure is achieved (e.g., Threshold® IMT from Phillips Respirionics (Figure 2), EMST150™ with IA150™ from Aspire Products (Figure 3)). This approach allows delivery of a quantifiable and adjustable external load that is relatively independent of flow rate using simple and relatively inexpensive equipment. A limitation is that once the target pressure is achieved, the training resistance remits. Additional details about training devices including commercial product examples, strengths, and limitations can be found in Table 2.

The purpose of this narrative review is to summarize the currently available literature on the various types of IMRT protocols utilized in pediatric populations including youth athletes, children with neuromuscular disease, children with asthma, and children with obesity and to summarize the effectiveness of IMRT protocols on pulmonary and performance outcomes.

### 3. Effectiveness of Inspiratory Muscle Rehabilitation Training

**3.1. Description of Literature Search.** A PubMed search was performed using the search terms “inspiratory training” or “inspiratory muscle training” AND “children” or “child” or “pediatric” AND the appropriate population of interest such as “athletes,” “neuromuscular disease,” “obesity,” or “asthma” between January and March 2022. By screening the title and abstract, we were able to identify original prospective studies with full text available in English in children

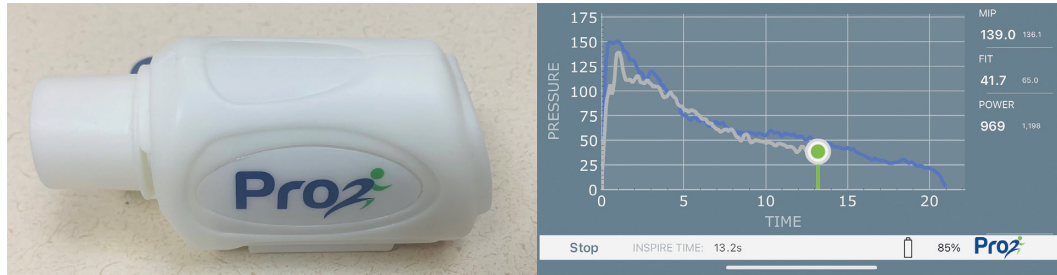


FIGURE 1: PrO<sub>2</sub><sup>™</sup> IMRT device (left) with user biofeedback (right) in PrO<sub>2</sub><sup>™</sup> Fit app via Bluetooth connection.



FIGURE 2: Threshold<sup>®</sup> IMT from Phillips Respironics provides pressure-threshold loading from 9 to 41 cm H<sub>2</sub>O resistance.



FIGURE 3: EMST150<sup>™</sup> with IA150<sup>™</sup> from Aspire Products provides pressure-threshold loading from 30 to 150 cm H<sub>2</sub>O resistance.

<18 years that included an IMRT intervention that was described in sufficient detail so as to be reproducible. IMRT was defined as an intervention that involved loading the inspiratory muscles with an external device to improve inspiratory muscle strength and/or endurance. The references and citations of each article identified with the search were also screened. Study quality was assessed using the National Heart, Lung, and Blood Institute's tailored quality assessment tools [23] with individual study quality assessments provided in Supplemental Tables 1–3.

**3.2. IMRT in Pediatric Athletes.** We performed a review of the literature on the use of inspiratory muscle training in pediatric-age athletes (Table 3). Most pediatric IMRT studies have involved swimmers [24–28], including one in disabled swimmers [29]. One study was on soccer players [30]. Wells and colleagues examined the effects of six weeks of moderate-intensity IMRT followed by six weeks of high-intensity IMRT compared with six weeks of sham (or placebo) followed by six weeks of moderate-intensity IMRT in national-level competitive swimmers [24]. They reported improvements in MIP and MEP as well as inspiratory and expiratory muscle power output during the respiratory muscle endurance test after 12 weeks in both groups with no differences between the groups. In this study, there was no effect

of IMRT on dyspnea or swim performance assessed with an incremental swimming test protocol. The increase in MIP after IMRT was consistent among the studies in swimmers [25–29] and in the study in soccer players [30].

Although the performance was not improved after IMRT in the national-level competitive swimmers, IMRT improved 50-meter and 200-meter swim performance in short- and middle-distance swimmers training 20 hours/week [26], 100-meter and 200-meter performance in swimmers training 10 hours/week but not in those training 14–19 hours/week [27], and apnea max (maximum distance swum after inspiration) in fin-swimmers [28]. Running performance was improved in soccer players after IMRT, more so than in the control training group [30]. Ratings of perceived exertion and dyspnea were reportedly lower after IMRT in swimmers [25, 26]. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>) improvements were noted in most [24, 26, 29, 30] but not all [25, 28] studies that included spirometry.

**3.3. IMRT in Children with Neuromuscular Diseases.** We performed a review of the literature on IMRT in children with neuromuscular diseases. Several studies were excluded due to insufficient details regarding the specifics of their training protocol or outcomes [31–38]. Of the eight included studies (Table 4), five included children with muscular dystrophy, of which four involved children with Duchenne muscular dystrophy (DMD) [39–42] and one involved children with limb girdle muscular dystrophy (LGMD) or spinal muscular atrophy (SMA) [43]. In the four studies with DMD patients, respiratory training occurred frequently from twice daily to 5 times per week for an overall duration of 5–6 weeks. Topin and colleagues [41] and Takaso and colleagues [42] both used pressure-threshold loading at an intensity of 30% MIP. DiMarco and colleagues [39] and Martin and colleagues [40] both used flow-resistive loading developed in-house at an intensity that could be tolerated for 5–15 minutes in the former or ventilation to exhaustion in less than 3 minutes in the latter. Training intensity was defined temporally by DiMarco et al. (15–20 minutes), while Martin and colleagues required 3 efforts to exhaustion. Additionally, Martin et al. required subjects to complete maximum isometric inspiratory/expiratory maneuvers over their range of vital capacity for 30 minutes. Overall, based on their training intensity and volume, these 4 studies in DMD seemed to target respiratory muscle endurance more than

TABLE 2: Types of inspiratory muscle rehabilitation training.

Device type	Subtypes	Commercial products	Strengths	Limitations
Voluntary isocapnic hyperpnea	N/A	SpiroTiger	Real-time biofeedback	Relatively expensive and complex equipment Limited portability Training is strenuous and time-consuming
Flow-resistive loading	Analog	Breather, P-Flex	Inexpensive Highly portable Highly programmable	Load varies with flow rate Limited biofeedback capability
	Digital	POWERbreathe K-series	Automated data collection Real-time biofeedback with Breathe-Link software for K4/K5 KH1 allows measurement of MIP Wide range of resistance (5–200 cm H <sub>2</sub> O) Highly portable Highly programmable	Relatively expensive Full functionality for K4/K5 devices requires a computer, which increases cost and decreases portability
		PrO2	Automated data collection Real-time biofeedback provided via smartphone app Measurement of MIP	Relatively expensive Full functionality requires a smartphone/tablet and an app
Pressure-threshold loading	N/A	Threshold IMT	Inexpensive Highly portable Load is relatively independent of flow rate Calibration markings are easy to interpret and set	Limited biofeedback capability Available load is low range and narrow (9–41 cm H <sub>2</sub> O)
		Analog devices from POWERbreathe (e.g., Medic, Classic, Plus)	Inexpensive Highly portable Load is relatively independent of flow rate Relatively wide range of loads available	Limited biofeedback capability Can be difficult to determine range of load for various models Ordinal calibration markings do not quantify load
		EMST75/150 with IA150	Relatively inexpensive Highly portable Load is relatively independent of flow rate (mm) Relatively wide range of loads available (5–75 cm H <sub>2</sub> O with EMST75; 30–150 cm H <sub>2</sub> O with EMST150)	Limited biofeedback capability For inspiratory training, both expiratory device (EMST75 or EMST150) and inspiratory adapter (IA150) are required Calibration markings to quantify load may be difficult to interpret

Note. MIP – maximal inspiratory pressure and EMST – expiratory muscle strength training.

strength, except for the study from Martin and colleagues that specifically targeted both strength and endurance.

Improvements in inspiratory muscle endurance were noted in all three of the studies which included endurance measures including improved MVV [39], the duration that MIP/MEP maneuvers could be sustained  $\geq 90\%$  [40], and time-to-exhaustion testing [41]. Inspiratory muscle strength (MIP) did not improve in three of the studies [39–41]. Takaso et al. [42] reported improvements in forced vital capacity. Yeldan et al. [43] studied inspiratory pressure-threshold loading 2 times per day for 12 weeks in patients with LGMD and SMA. Training intensity was 30% MIP, and volume was 15 minutes/session. Based on MIP, inspiratory muscle strength improved, though FVC and FEV<sub>1</sub> were unchanged.

The population of interest in the three remaining studies were children with infantile-onset Pompe disease (IOPD) including a before-and-after trial in 9 subjects [44] and 2 case studies involving three participants [45, 46]. Smith et al. [44] used inspiratory pressure-threshold loading twice per week for 90 days. The intensity was the highest tolerated load in which they generated at least 50% of their unassisted tidal volume for a volume of 3–4 sets of 6–10 repetitions. Jones et al. [45] and Crisp et al. [46] used inspiratory and expiratory pressure-threshold loading 5 times per week for 12 weeks. Training intensity was 60–70% MIP/MEP and volume was 3 sets of 25 inspiratory and expiratory repetitions. Results from Smith et al. [44] differed based on the mechanical ventilation status of participants. For those on full mechanical ventilation, no changes in peak inspiratory flow,

TABLE 3: Inspiratory muscle rehabilitation training (IMRT) in youth athletes.

Citation	Study Design	Population	Intervention	Outcomes	Limitations
Wells et al. 2005 [24]	RCT	National-level competitive swimmers, 15.6 ± 1.3 years, n = 34 (20 females, 14 males)	<p>Duration: 12 weeks</p> <p>Frequency: 10 sessions/week</p> <p>Intensity: 50% weeks 1–3 and 60% weeks 3–6 for MIP and MEP; 70% weeks 7–9 and 80% weeks 10–12 for MIP and MEP</p> <p>Volume: 10 breaths per session</p> <p>Type: inspiratory and expiratory flow-resistive loading</p> <p>Equipment: PowerLung</p> <p>Control: sham IMRT (10% MIP and MEP) for 6 weeks followed by moderate IMRT (50% weeks 7–9 and 60% weeks 10–12 for MIP and MEP)</p> <p>(Both groups continued regular swim training; only first 6 weeks represent differences between IMRT and sham)</p>	<p>At 6 weeks, no change in MIP and MEP in IMRT or sham groups; at 12 weeks, <math>\Delta</math>MIP = 14.4 cmH<sub>2</sub>O and <math>\Delta</math>MEP = 20 cmH<sub>2</sub>O in females (combining IMRT and sham subjects) with no changes in males</p> <p>MVV<sub>15</sub>, FEV<sub>1</sub>, and FVC increased in both IMRT and sham groups after 12 weeks; no difference between IMRT and sham at 6 weeks</p> <p>No differences in performance (swim velocity) or dyspnea</p>	No statistical between-group comparisons reported

TABLE 3: Continued.

Citation	Study Design	Population	Intervention	Outcomes	Limitations
Kilding et al. 2010 [25]	RCT	Club-level competitive swimmers $n = 16$ (6 females, 10 males)	<p>Duration: 6 weeks</p> <p>Frequency: 7 days/week</p> <p>Intensity: 50% MIP. Instructed to increased load periodically so that 30 breaths could only just be completed</p> <p>Volume: 30 breaths, twice a day</p> <p>Type: pressure threshold loading</p> <p>Equipment: POWER-breathe</p> <p>Control: sham IMRT, 60 slow protracted breaths once daily at 15% MIP</p>	<p><math>\Delta</math>MIP = 10.5 cmH<sub>2</sub>O in IMRT group vs. 0.3 cmH<sub>2</sub>O in sham group</p> <p>Swim time improved for 100 m and 200 m time trials, but not for 400 m time trial</p> <p>Rating of perceived exertion decreased across a range of intensities</p> <p>FVC, FEV<sub>1</sub>, PEF: No change</p> <p>MEP not reported</p>	
Lemaitre et al. 2013 [26]	Controlled before and after study	Swimmers, 13–18 yr, avg. training 45–48 wk/yr, 20 h/wk $n = 20$ (7 females, 13 males)	<p>Duration: 8 weeks</p> <p>Frequency: 5 days per week</p> <p>Intensity: 60% of MVV<sub>12</sub></p> <p>Volume: 30 min</p> <p>Type: voluntary isocapnic hyperpnea (respiratory muscle endurance training or RMET)</p> <p>Equipment: SpiroTiger</p> <p>Control: usual training only</p>	<p><math>\Delta</math>MIP = <math>\approx</math>25 cmH<sub>2</sub>O in RMET group vs. no change in control group</p> <p><math>\Delta</math>MEP = <math>\approx</math>25 cmH<sub>2</sub>O in RMET group vs. no change in control group</p> <p>Competition swim time on 50 m and 200 m improved</p> <p>Respiratory endurance test breathing duration increased from 16 to 24.6 min</p> <p><math>V_{E\max}</math> and maximum breathing frequency increased</p> <p>Rating of perceived exertion and rating of perceived dyspnea reduced during the 50 m and 200 m race</p> <p>FVC (% pred) and MVV increased</p>	MIP and MEP reported in figures (absolute values not reported)

TABLE 3: Continued.

Citation	Study Design	Population	Intervention	Outcomes	Limitations
Lomax et al. 2019 [27]	RCT	Swimmers, two groups based on training distance (low and high) $n = 33$ (15 females, 18 males)	Duration: 6 weeks Frequency: 7 days/wk Intensity: 50% MIP. Instructed to increased load periodically so that 30 breaths could only just be completed Volume: 30 breaths, twice a day Type: pressure threshold loading Equipment: POWER-breathe Control: usual swim training only	$\Delta$ MIP = $\approx 55$ cmH <sub>2</sub> O (high-training IMRT group), $\approx 35$ cmH <sub>2</sub> O (low-training IMRT group) and $\approx 20$ cmH <sub>2</sub> O (high-training control group) No change in MEP 100 m and 200 m swimming times improved in the low-training IMRT group only	MIP reported in figures (pre and post absolute values not reported). 36% improvement in MIP (combined for high and low-training IMRT groups) reported in text of article
Okrzymowska et al. 2019 [29]	RCT	Disabled swimming division athletes, 16–20 yr $n = 16$ (8 females, 8 males)	Duration: 8 weeks Frequency: 5 days/week Intensity: 30% MIP in week 1, increased to 40% in weeks 2 and 3, 50% in weeks 4 and 5, and 60% in weeks 6–8 Volume: 30 breaths, 5 min in week 1 increased to 15 min in week 8, twice a day Type: pressure threshold loading Equipment: philips respironics Control: usual swim training only	$\Delta$ MIP = 33 cmH <sub>2</sub> O (IMRT group) and 16 cmH <sub>2</sub> O (control group) FVC, FEV <sub>1</sub> , and PEF increased in IMRT group MEP increased in both groups	



TABLE 3: Continued.

Citation	Study Design	Population	Intervention	Outcomes	Limitations
Vašíčková et al. 2017 [28]	Randomized controlled trial (parallel arm with control group receiving the IMRT intervention after a 1-month washout)	Club-level fin-swimmers $n = 20$ (did not report sample size by sex)	<p>Duration: 4 weeks</p> <p>Frequency: 7 days/week</p> <p>Intensity: 30% MIP and MEP and increased by 2 cm H<sub>2</sub>O every week until maximum possible resistance on the threshold devices</p> <p>Volume: 10 maximal inspirations and 10 maximal expirations (strength) + 15 min of continuous breathing against resistance (endurance)</p> <p>Type: pressure threshold loading (inspiratory and expiratory)</p> <p>Equipment: philips respironics</p> <p>Control: usual swim training (with IMRT completed in second phase after washout)</p>	<p>MIP increased by 20.8% in the IMRT group vs. 1.5% in the control group (post 4 weeks)</p> <p>MEP increased by 10.6% in the IMRT group vs. 5.1% decrease in the control group (post 4 weeks)</p> <p>Length able to swim for one inspiration increased by 27.4% (IMRT in first phase), 20.7% (IMRT in second phase)</p> <p>FVC, FEV<sub>1</sub>, PEF: no change</p>	Results reported as median values; absolute values not reported for MIP and MEP
Mackala et al. 2019 [30]	RCT	Club-level competitive junior soccer players $n = 16$ males	<p>Duration: 8 weeks</p> <p>Frequency: 5 days/week</p> <p>Intensity: 40% MIP in week 1, increased by 5% every week to 80% in week 8</p> <p>Volume: 5 repetitions in week 1 to 15 repetitions in week 8, each repetition was 45 s of IMRT followed by a 15 s break, twice a day</p> <p>Type: pressure threshold loading</p> <p>Equipment: philips respironics</p> <p>Control: usual training only</p>	<p><math>\Delta</math>MIP = 44 cmH<sub>2</sub>O (IMRT group) vs. 11 cmH<sub>2</sub>O (control group)</p> <p><math>\Delta</math>MEP = 41 cmH<sub>2</sub>O (IMRT group) vs. 4 cmH<sub>2</sub>O (control group)</p> <p>Running test distance increased by 5% in IMRT group vs. 2.1% in the control group (both changes were statistically significant)</p> <p>FVC improved in IMRT group</p> <p>FEV<sub>1</sub> improved in both groups</p>	

Note. RCT—randomized control trial, MIP—maximal inspiratory pressure, MEP—maximal expiratory pressure, MVV<sub>12</sub>—Maximal voluntary ventilation measured by assessing ventilation during maximal voluntary effort for 12 seconds and extrapolating to calculate maximal ventilation in liters per minute, FEV<sub>1</sub>—forced expiratory volume in 1 second, FVC—forced vital capacity, PEF—peak expiratory flow, and V<sub>Emax</sub>—maximal ventilation.

TABLE 4: Inspiratory muscle rehabilitation training (IMRT) in children with neuromuscular disease.

Citation	Study design	Population	Intervention	Outcomes
DiMarco et al. 1985 [39]	Before-and after-trial	Various NMD: DMD ( $n=5$ ) LGMD ( $n=5$ ) FSHMD ( $n=1$ )	Duration: 6 weeks	MIP: no $\Delta$
		$N=11$ (did not report sample size by sex)	Frequency: 2 x/day Intensity: Inspiratory resistance tolerated for >5 minutes and <15 minutes Volume: 15–20 minutes/session Type: inspiratory flow-resistive loading Equipment: developed in-house	MEP: no $\Delta$ VC: no $\Delta$ Maximum voluntary ventilation (MVV): 30% MVV: $\uparrow 128 \pm 81\%$ , $p < 0.01$ 50% MVV: $\uparrow 107 \pm 36\%$ , $p < 0.01$ 70% MVV: $\uparrow 85 \pm 40\%$ , $p < 0.01$ 90% MVV: $\uparrow 75 \pm 24\%$ , $p < 0.01$
Martin et al. 1986 [40]	Cross-over trial	DMD	Duration: 5 weeks Frequency: 5 days/week Intensity: maximum isometric inspiratory/expiratory maneuvers at 20% intervals over VC range (strength training) or resistive IMT/EMT via various diameters of tubing that led to exhaustion in <3 minutes (endurance training)	MIP: no $\Delta$ MEP: no $\Delta$ VC: no $\Delta$
		$N=18$ males	Volume: 30 minutes (strength training); ventilation to exhaustion 3 x (endurance training) Type: isometric inspiratory/expiratory maneuvers against occluded tube (strength training); Inspiratory/expiratory flow-resistive loading (endurance training) Equipment: developed in-house	Inspiratory endurance (duration of MIP $\geq 90\%$ ): $\uparrow 8.5 \pm 8.1$ seconds, $p < 0.01$ Expiratory endurance (duration of MEP $\geq 90\%$ ): $\uparrow 6.1 \pm 5.1$ seconds, $p < 0.01$
Topin et al. 2002 [41]	RCT	DMD $N=16$ males	Duration: 6 weeks Frequency: 2 x/day Intensity: 30% MIP Volume: 10 minutes/session Type: inspiratory pressure-threshold resistance Equipment: threshold IMT (Control: sham-IMT 5% MIP)	MIP: no $\Delta$ FVC: no $\Delta$ Inspiratory muscle endurance ( $T_{lim}$ ): $\uparrow$ from $307.6 \pm 126.6$ to $448.4 \pm 176.7$ , $p < 0.05$
Yeldan et al. 2008 [43]	Non-RCT with alternating allocation	LGMD ( $n=17$ ), BMD ( $n=6$ ) recruited	Duration: 12 weeks Frequency: 2 x/day Intensity: 30% MIP	VC: no $\Delta$ FVC: no $\Delta$ FEV <sub>1</sub> : no $\Delta$
		$N=21$ completed (8 females, 13 males)	Volume: 15 minutes/session Type: inspiratory pressure-threshold resistance (Control: breathing exercises)	MIP: $\uparrow 37.5 \pm 22.8$ cmH <sub>2</sub> O (IMRT group) vs. $10.3 \pm 12.1$ cmH <sub>2</sub> O (control group), $p = 0.05$ MEP: no $\Delta$
Takaso et al. 2010 [42]	Before-and after-trial	DMD $N=17$ males	Duration: 6 weeks Frequency: daily Intensity: 30% MIP Volume: 3 sets of 15 repetitions Type: inspiratory pressure-threshold resistance Equipment: threshold IMT	%FVC: increased from $21.5 \pm 3.1$ to $26.4 \pm 2.8\%$ MIP and MEP not measured

TABLE 4: Continued.

Citation	Study design	Population	Intervention	Outcomes
Jones et al. 2014 [45]	Case report	IOPD	Duration: 12 weeks	MIP: ↑ from 17 cmH <sub>2</sub> O to 26 cmH <sub>2</sub> O (in subject 1) and from 22 cmH <sub>2</sub> O to 34 cmH <sub>2</sub> O (in subject 2)
		N = 2 (1 female, 1 male)	Frequency: 5 x/week Intensity: 60–70% MIP/MEP Volume: 3 sets of 25 inspiratory and expiratory repetitions Type: inspiratory/expiratory pressure-threshold resistance equipment: threshold IMT, threshold PEP, EMST 150	MEP: ↑ from 16 cmH <sub>2</sub> O to 20 cmH <sub>2</sub> O (in subject 1) and from 43 cmH <sub>2</sub> O to 80 cmH <sub>2</sub> O (in subject 2) Peak cough flow (subject 2 only): ↑  FVC: no Δ
Smith et al. 2017 [44]	Before-and-after trial	IOPD 2–15-years-old	Duration: 12 weeks	Subjects on full MV: PIF, tidal volume, inspiratory time, expiratory time, duty cycle: no Δ
		N = 9 (did not report sample size by sex)	Frequency: 3 x/week Intensity: highest tolerated load in which they generated at least 50% of unassisted tidal volume Volume: 3-4 sets of 6–10 repetitions Type: inspiratory pressure-threshold resistance Equipment: threshold PEP, AccuPEEP	Subjects on partial/no MV: ↑ PIF at 5 cmH <sub>2</sub> O  Pre-post IMRT MIP not reported
Crisp et al. 2020 [46]	Case report	IOPD	Duration: 12 weeks	MIP: ↑ 10.1 cmH <sub>2</sub> O (after 12 weeks; 1 <sup>st</sup> treatment phase)
		N = 1 female	Frequency: 5 x/week Intensity: 60–70% MIP/MEP Volume: 3 sets of 25 inspiratory and expiratory repetitions Type: inspiratory/expiratory pressure-threshold resistance Equipment: threshold IMT, Threshold PEP, EMST 150	MEP: ↑ 35.2 cmH <sub>2</sub> O (after 12 weeks; 1 <sup>st</sup> treatment phase)  Peak cough flow: ↑

Note. RCT—randomized controlled trial, NMD—neuromuscular disease, DMD—duchenne muscular dystrophy, LGMD—limb-girdle muscular dystrophy, FSHMD—fascioscapulothoracic muscular dystrophy, MIP—maximal inspiratory pressure, MEP—maximal expiratory pressure, VC—vital capacity, IMT—inspiratory muscle training, EMT—expiratory muscle training, FVC—forced vital capacity, FEV<sub>1</sub>—forced expiratory volume in 1 s, BMD—Becker muscular dystrophy, IOPD—infantile-onset Pompe disease, MV—mechanical ventilation, PIF—peak inspiratory flow, and EMST—expiratory muscle strength training.

tidal volume, inspiratory time, and expiratory time were noted. For subjects on partial or no mechanical ventilation, peak inspiratory flow and tidal volume improved. In the case studies from Jones et al. [45] and Crisp et al. [46], increases in MIP, MEP, and peak cough flow were noted.

Overall, respiratory training appeared to improve respiratory muscle endurance and is likely to offer benefits in children with neuromuscular diseases considering the effects of respiratory muscle fatigue under stress on the morbidity and mortality in this population. Additionally, training appeared to be well-tolerated with no reported adverse events [39,43,45,46]. However, the lack of focus on patient-centered clinical end points in these studies highlights the need for additional research on these populations.

**3.4. IMRT in Children with Airways Disease.** A Cochrane review involving 115 adult patients was published in 2013 summarizing the results of 5 studies employing IMRT in

patients with asthma [47]. The IMRT sessions in these 5 Cochrane studies lasted between 10 and 30 minutes, and IMRT regimen duration ranged from 3 to 12 weeks. IMRT was consistently well-tolerated and consistently improved inspiratory strength measured by MIP. However, definitive clinical conclusions regarding asthma outcomes were not possible due to the relatively small number of subjects and heterogeneous end points across studies. This Cochrane review included two studies in which IMRT increased inspiratory muscle strength in adults with mild [48] and mild-to-moderate asthma [49] who were high consumers of inhaled  $\beta_2$  agonists (>1 puff/day) for breakthrough asthma symptoms. The increased inspiratory muscle strength has seen following IMRT correlated closely with a decrease in dyspnea with exercise (measured by Borg scoring) and a decrease in  $\beta_2$ -agonist consumption [49]. Since this 2013 review, two additional IMRT studies in adults with asthma ( $n = 81$ ) demonstrated reduced dyspnea, respiratory symptoms, and activity impairment with IMRT [50, 51]. These

TABLE 5: Inspiratory muscle rehabilitation training (IMRT) in children with asthma.

Citation	Study design	Population	Intervention	Outcomes
Lima et al. 2008 [52]	RCT	8–12-year-old patients with new referral for asthma and on no asthma treatment presenting with uncontrolled symptoms  N = 50 (34 females, 16 males)	Duration: 7 weeks  Frequency: 2 x/week Intensity: 40% MIP  Volume: 50 min sessions Type: inspiratory pressure threshold resistance Equipment: respironics threshold IMT (Control intervention: education without IMRT; all participants started monthly visits and asthma education; participants could be started on ICS or ICS/LABA and adjusted monthly)	Significant improvements in IMRT versus control seen in MIP ( $\Delta$ MIP = 62 cmH <sub>2</sub> O [IMRT group] vs. 0 cmH <sub>2</sub> O [control group]; $p < 0.0001$ ), MEP ( $\Delta$ MEP = 31 cmH <sub>2</sub> O [IMRT group] vs. 0 cmH <sub>2</sub> O [control group]), and PEF; daytime and nocturnal symptoms, activity limitation, and asthma attacks IMRT effects on MIP, MEP, and PEF were generally durable after 7 weeks off IMRT  No differences between groups in emergency room treatment and hospitalization
Elnaggar 2020 [53]	RCT	12–16-year-old patients with past diagnosis of asthma, clinically stable asthma on daily controller  N = 31 (11 females, 20 males)	Duration: 12 weeks  Frequency: 3 x/week Intensity: 40% MIP, reassessed every week Volume: 15 breaths with 10 s rest intervals for 15 min + continuous breathing for 5 min for endurance (total: 20 min sessions) Type: inspiratory pressure threshold resistance Equipment: respironics threshold IMT (Placebo control: IMT at 5% MIP and similar frequency, volume, and duration) Both groups received a conventional respiratory rehabilitation program	Significant improvement in IMRT vs. placebo seen in FEV <sub>1</sub> ( $p = 0.003$ ), FVC ( $p = 0.001$ ), FEV <sub>1</sub> /FVC ( $p = 0.004$ ), MIP ( $\Delta$ MIP = 17 cmH <sub>2</sub> O [IMRT group] vs. 11 cmH <sub>2</sub> O [placebo group]; $p = 0.002$ ), MEP ( $\Delta$ MEP = 19 cmH <sub>2</sub> O [IMRT group] vs. 11 cmH <sub>2</sub> O [placebo group]; $p = 0.004$ ), and asthma control test score ( $p = 0.001$ ) adjusted to the pretreatment values

Note. RCT—randomized controlled trial, IMT—inspiratory muscle training, ICS—inhaled corticosteroid, LABA—long-acting beta agonist, MIP—maximum inspiratory pressure, MEP—maximum expiratory pressure, PEF—peak expiratory flow, and SABA—short-acting beta agonist.

data emphasize the promise that inspiratory muscle rehabilitation has for patients with asthma with excess dyspnea and high  $\beta_2$ -agonist bronchodilator use. There were no studies describing exacerbation events that required the use of reliever medication, emergency department visits, or hospital admissions. This 2013 Cochrane review strongly recommended that studies on children be conducted in the future.

To date, only two IMRT studies have been published in pediatric asthma [52, 53], which were not included in the Cochrane review (Table 5). The first, by Lima and colleagues, was a randomized controlled study involving 50 children with asthma allocated to 1 of 2 groups: an IMRT group, comprising 25 children, and a control group, comprising 25 children who submitted to monthly medical

visits and education on asthma [52]. The IMRT was performed using a pressure threshold load of 40% of MIP. All children completing IMRT spent the first 25 minutes doing diaphragmatic breathing, fractionated breathing, and pursed-lip breathing sitting and in the supine position (each exercise was performed in a series of 10 repetitions). Next, pressure-threshold loading IMRT was performed for 25 minutes using a spring-loaded adjustable resistance valve device. During the first 20 minutes, inspirations were performed repeatedly in a series of 10 repetitions for 60 seconds each, separated by 60 second rest periods. During the final 5 minutes, IMRT was performed continuously without rest. The IMRT resistance load was 40% of MIP, which was calculated at the beginning of each session. The active intervention lasted for 7 weeks. The 25

TABLE 6: Inspiratory muscle rehabilitation training (IMRT) in children with obesity.

Citation	Study Design	Population	Intervention	Outcomes
LoMauro et al. 2016 [61]	Before-and-after trial	12–17-year-old children with obesity (BMI $z > 2$ ) enrolled in a multidisciplinary body weight reduction program  (Mean BMI = 36 kg/cm <sup>2</sup> )  N = 11 males	Duration: 3 weeks  Frequency: 5 x/week  Intensity: 50–60% MVV  Volume: 12–18 min sessions, 25 inspirations, 1 session/d  Type: eucapnic hyperventilation  Equipment: Spiro 141 Tiger® All participants underwent a body weight reduction program including energy-restricted diet, psychological and nutritional counseling and aerobic physical activity	Body weight reduction program with IMRT was associated with improved exercise performance (peak work rate increased by 26 W; $p = 0.003$ ) and lung and chest wall volume recruitment (inspiratory capacity reduced by 290 ± 550 mL)  Dyspnea and leg discomfort during exercise were reduced FVC improved by 4% predicted ( $p = 0.019$ )  During exercise, abdominal ribcage hyperinflation was delayed and led to 15% increased exercise capacity and reduced dyspnea at high workloads ( $p < 0.05$ ) without ventilatory and metabolic changes  MIP and MEP not reported
Salvadego et al. 2017 [59]	Non-randomized parallel group trial	15–19-year-old sedentary adolescents with a BMI $> 97^{\text{th}}$ percentile enrolled in a multidisciplinary body weight reduction program  (mean BMI ≈ 39 kg/cm <sup>2</sup> )  N = 17 males	Duration: 3 weeks  Frequency: 5 x/week Intensity: 50–60% MVV Volume: 12–18 min sessions, 25 inspirations, 1 session/d Type: eucapnic hyperventilation Equipment: Spiro Tiger® (Control: No IMRT) All participants underwent a body weight reduction program including energy-restricted diet, psychological and nutritional counseling and aerobic physical activity	IMRT group had significantly greater PEF ( $\Delta\text{PEF} = 13\%$ predicted [IMRT group] vs. 3% predicted [control group]), reduced oxygen cost of exercise and dyspnea ratings during exercise completed above the gas exchange threshold compared with the control group  MIP and MEP not reported

TABLE 6: Continued.

Citation	Study Design	Population	Intervention	Outcomes
Alemayehu et al. 2018 [60]	RCT	15–18-year-old sedentary adolescents with a BMI >97 <sup>th</sup> percentile enrolled in a multidisciplinary body weight reduction program	Duration: 3 weeks	IMRT group had significantly greater improvement in time to exhaustion and peak exercise intensity during a treadmill test
		(Mean BMI = 40 kg/cm <sup>2</sup> )	Frequency: 5 x/week	IMRT had greater reduction in heart rate and oxygen cost of exercise below and above the gas exchange threshold and in dyspnea ratings above the gas exchange threshold
		N = 16 males	Intensity: 50–60% MVV Volume: 12–18 min sessions, 25 inspirations, 1 session/d Type: eucapnic hyperventilation Equipment: Spiro Tiger® (Control: no IMRT) All participants underwent a body weight reduction program including energy-restricted diet, psychological and nutritional counseling and aerobic physical activity	MIP and MEP not reported

Note. BMI–body mass index, MVV–maximal voluntary ventilation, FVC–forced vital capacity, and PEF–peak expiratory flow.

participants in each intervention group were generally similar. The mean age in both groups was just under 10 years. At 49 and 90 days, the IMRT group had significantly improved MIP, MEP, and PEF from baseline, which were significantly improved over that of the control group. Children undergoing IMRT experienced a mean 127% improvement from baseline in MIP (standardized effect size (SES) improvement of 10.7) at 90 days and 76% improvement from baseline in PEF (SES improvement of 2.6) at 90 days. Once IMRT was discontinued, improvements in MIP, MEP, and PEF remained stable after 7 weeks. There were clear numeric reductions from baseline in the frequency of asthma attacks, nocturnal and diurnal symptoms, and reported activity limitation in IMRT-treated children not seen in the control arm.

More recently in 2020, Elnaggar investigated the efficacy of IMRT on lung function, respiratory muscle strength, and asthma symptoms in asthmatic children [53]. Elnaggar used a randomized placebo-controlled assessor-blinded study of 34 children with asthma and randomized participants to receive either the IMRT at 40% of the MIP for 20 minutes/session, 3 times per week, over 12 consecutive weeks (IMRT group;  $n = 17$ ) or placebo IMRT at 5% of MIP (placebo group;  $n = 17$ ). Both interventional groups received a conventional respiratory rehabilitation program. The researchers reported significant post-treatment differences between the IMRT and placebo groups in FEV<sub>1</sub> ( $P = 0.003$ ), FVC ( $P = 0.001$ ), FEV<sub>1</sub>/FVC ( $P = 0.004$ ), MIP ( $P = 0.002$ ), and MEP ( $P = 0.004$ ), adjusted to the pretreatment values, in favor of the IMRT group. In addition, IMRT was associated with significant improvement in asthma symptom scores

measured by the validated Asthma Control Test (ACT) ( $P = 0.001$ ). Elnaggar concluded that the incorporation of IMRT in children with asthma can improve respiratory function, enhance respiratory muscle strength, and improve children's perception of asthma symptoms.

**3.5. IMRT in Children with Obesity.** Studies that have examined the effects of IMRT in overweight and obese adults have reported improved exercise performance [54–57], MIP [56–58], respiratory muscle endurance [54, 55], and reduced exertional dyspnea [54, 55]. Three studies have examined the effects of IMRT in adolescents with obesity, all from the same research group in Italy [59–61] (Table 6). The IMRT protocol was completed at 50–60% MVV, 1 session per day, 5 days per week, with each session lasting 12–18 minutes. LoMauro et al. reported significant weight loss (3.5 kg), improvements in exercise performance and FVC, and reduced dyspnea and leg discomfort during exercise after a 3-week multidisciplinary body weight reduction program that included IMRT [61]. However, since the program included diet, aerobic exercise, and psychological and nutrition counseling in addition to the IMRT component, it is impossible to tease out the independent effects of IMRT. In two studies that differed on the mode of exercise (i.e., cycling vs. walking), three weeks of IMRT combined with a multidisciplinary weight loss program was effective in reducing the oxygen cost of exercise during moderate-intensity walking and vigorous-intensity walking and cycling when compared with a multidisciplinary weight loss program alone; both interventions resulted in similar weight loss [59, 60]. IMRT

combined with a multidisciplinary weight loss program also resulted in improved peak performance, reduced exertional dyspnea ratings, higher FVC, and a reduced slow component of oxygen uptake during vigorous-intensity exercise [59, 60]. The slow component of oxygen uptake during vigorous-intensity exercise is partly due to the increased oxygen cost of breathing [62], and a greater slow component can be associated with reduced exercise tolerance [63]; improvements in the slow component of oxygen uptake could therefore have beneficial implications for exercise tolerance for the pediatric obese population.

#### 4. Clinical Considerations

IMRT appears to represent a viable non-pharmacologic option for patients in need of improving their exercise tolerance and reducing dyspnea. The exact mechanisms by which IMRT reduces asthma symptoms remain poorly defined. For children with asthma, we speculate that IMRT improves disease control through improved lung function, reduced airway closure, and reduced respiratory muscle fatigue leading to reduced frequency of dyspnea, which previously was perceived as asthma symptoms. While there have not been any published reports on the effectiveness of IMRT in children with obesity and asthma, a special population that experiences a high symptom burden [64], favorable results showing that IMRT improves performance and reduces dyspnea in nonasthmatic children with obesity are encouraging. IMRT has major advantages: it is simple, safe, and inexpensive, and is generally very attractive to many patients interested in a nonpharmacologic therapy. For patients who experience significant dyspnea or exercise intolerance with consequent physical activity avoidance, IMRT could be a precursor to the implementation of a home- or center-based exercise program. A careful assessment by a healthcare professional to evaluate differential diagnoses for dyspnea and/or exercise intolerance, a baseline test of inspiratory muscle strength, and a cardiopulmonary exercise test could help identify patients who have reduced inspiratory muscle strength and/or impaired breathing mechanics; these are the patients that may benefit most from IMRT. Follow-up testing, regular contact between the healthcare professional and patient, and documentation of the effectiveness of IMRT through clinical audits could inform clinical practice models [65].

#### 5. Future Directions

Relatively few children have been formally studied with high-quality IMRT utilizing randomization and blinding. Among studies included in this review, approximately half included both inspiratory and expiratory muscle training. It may be reasonable to hypothesize that expiratory muscle training would improve expiratory muscle strength (i.e., MEP). Although this hypothesis was supported by two randomized trials [26, 28] and two case reports [45, 46], it was not supported by two other randomized trials [24, 40]. In addition, three studies on obese youth included an inspiratory and expiratory training component but did not

measure inspiratory or expiratory muscle strength [59–61]. Interestingly, three randomized trials with an exclusive inspiratory training protocol nevertheless reported improvements in MEP [53]. Whether there is any additional benefit to including an expiratory muscle training component in pulmonary rehabilitation protocols remains unclear. Theoretically, since the inspiratory phase of breathing is active while the expiratory phase is mostly due to passive recoil except at higher ranges of ventilation, the benefit of training expiratory muscles is not readily apparent. However, studies that compare inspiratory training alone versus combined training in different youth populations may offer insights into this issue and inform interventions in the PR field. The optimal dose of IMRT regarding intensity (percent of MIP), repetitions and weekly frequency, and duration are poorly understood. Dose ranging and physiologic studies that describe potential mechanisms are needed to guide clinical practice, as are studies that include patient-centered clinical end points. Larger randomized controlled trials that evaluate IMRT effectiveness and look at mechanistic outcomes are also needed in the pediatric population in addition to trials that can offer insight into specific patient groups that may benefit most from IMRT.

#### 6. Conclusion

Dyspnea and exercise intolerance are common symptoms noted in pediatric patients with neuromuscular diseases, asthma, and obesity. Only a handful of studies have investigated the effects of IMRT on clinical outcomes and underlying physiological mechanisms in these pediatric patients. These studies demonstrate that IMRT is likely effective in improving respiratory muscle strength and reducing airway closure (i.e., higher FVC) and potentially in improving breathing mechanics and reducing dyspnea during exercise. These mechanistic changes can help explain improvements in symptomology and clinical outcomes, and they highlight our evolving understanding of the role of IMRT in pediatric patients.

#### Data Availability

Data sharing is not applicable to this article as no new datasets were created or analyzed in this study.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

#### Authors' Contributions

Dharini M. Bhammar contributed to conceptualization (supporting), methodology (supporting), visualization (equal), writing the original draft (equal), and reviewing and editing (lead). Harrison N. Jones contributed to conceptualization (supporting), methodology (supporting), visualization (equal), writing original draft (equal), and reviewing and editing (supporting). Jason E. Lang contributed to conceptualization (lead), methodology (lead), visualization

(equal), writing original draft (equal), and reviewing and editing (supporting).

## Acknowledgments

The authors would like to thank Angela Dahlberg for her editing services. No funding was received for this research.

## Supplementary Materials

Scoring and quality of studies as well as adverse events for randomized controlled trials, pre-post intervention trials, and case reports/series are reported in Supplemental Tables 1, 2, and 3, respectively. (*Supplementary Materials*)

## References

- [1] M. A. Spruit, S. J. Singh, C. Garvey et al., "An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation," *American Journal of Respiratory and Critical Care Medicine*, vol. 188, no. 8, pp. e13–64, 2013.
- [2] M. L. Bruurs, L. J. van der Giessen, and H. Moed, "The effectiveness of physiotherapy in patients with asthma: a systematic review of the literature," *Respiratory Medicine*, vol. 107, no. 4, pp. 483–494, 2013.
- [3] L. P. Cahalin, R. Arena, M. Guazzi et al., "Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes," *Expert Review of Cardiovascular Therapy*, vol. 11, no. 2, pp. 161–177, 2013.
- [4] I. D. Rosero, R. Ramírez-Vélez, A. Lucia et al., "Systematic review and meta-analysis of randomized, controlled trials on preoperative physical exercise interventions in patients with non-small-cell lung cancer," *Cancers*, vol. 11, no. 7, p. 944, 2019.
- [5] W. D. Reid, E. L. Geddes, K. O'Brien, D. Brooks, and J. Crowe, "Effects of inspiratory muscle training in cystic fibrosis: a systematic review," *Clinical Rehabilitation*, vol. 22, no. 10-11, pp. 1003–1013, 2008.
- [6] N. Makhdami, M. Farooqi, C. Thom-Fernandes, and N. G. Raghavan, "Pulmonary rehabilitation in interstitial lung diseases," *Current Opinion in Pulmonary Medicine*, vol. 26, no. 5, pp. 470–476, 2020.
- [7] C. L. Rochester, I. Vogiatzis, A. E. Holland et al., "An official American thoracic society/European respiratory society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation," *American Journal of Respiratory and Critical Care Medicine*, vol. 192, no. 11, pp. 1373–1386, 2015.
- [8] R. Bianchi, F. Gigliotti, I. Romagnoli et al., "Impact of a rehabilitation program on dyspnea intensity and quality in patients with chronic obstructive pulmonary disease," *Respiration*, vol. 81, no. 3, pp. 186–195, 2011.
- [9] A. L. Ries, G. S. Bauldoff, B. W. Carlin et al., "Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines," *Chest*, vol. 131, no. 5, pp. 4S–42S, 2007.
- [10] L. Dowman, C. J. Hill, A. May, and A. E. Holland, "Pulmonary rehabilitation for interstitial lung disease," *Cochrane Database of Systematic Reviews*, vol. 2, Article ID CD006322, 2021.
- [11] M. A. Puhan, E. Gimeno-Santos, C. J. Cates, and T. Troosters, "Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease," *Cochrane Database of Systematic Reviews*, vol. 12, Article ID CD005305, 2016.
- [12] M. B. Hershenson, A. A. Colin, M. E. B. Wohl, and A. R. Stark, "Changes in the contribution of the rib cage to tidal breathing during infancy," *American Review of Respiratory Disease*, vol. 141, no. 4\_pt\_1, pp. 922–925, 1990.
- [13] C. Papastamelos, H. B. Panitch, S. E. England, and J. L. Allen, "Developmental changes in chest wall compliance in infancy and early childhood," *Journal of Applied Physiology*, vol. 78, no. 1, pp. 179–184, 1995.
- [14] S. American, "Thoracic society/European respiratory. ATS/ERS statement on respiratory muscle testing," *American Journal of Respiratory and Critical Care Medicine*, vol. 166, no. 4, pp. 518–624, 2002.
- [15] P. Laveneziana, A. Albuquerque, A. Aliverti et al., "ERS statement on respiratory muscle testing at rest and during exercise," *European Respiratory Journal*, vol. 53, no. 6, Article ID 1801214, 2019.
- [16] G. Scano, F. Gigliotti, R. Duranti, M. Gorini, A. Fanelli, and G. Marconi, "Control of breathing in patients with neuromuscular diseases," *Monaldi Archives for Chest Disease*, vol. 48, no. 1, pp. 87–91, 1993.
- [17] K. J. Killian and N. L. Jones, "Respiratory muscles and dyspnea," *Clinics in Chest Medicine*, vol. 9, no. 2, pp. 237–248, 1988.
- [18] A. K. McConnell, *Respiratory Muscle Training: Theory and Practice*, Churchill Livingstone Elsevier, London UK, 2013.
- [19] B. Rassler, G. Marx, S. Hallebach, P. Kalischewski, and I. Baumann, "Long-term respiratory muscle endurance training in patients with myasthenia gravis: first results after four months of training," *Autoimmune Diseases*, vol. 2011, pp. 1–7, 2011.
- [20] B. Rassler, G. Hallebach, P. Kalischewski, I. Baumann, J. Schauer, and C. M. Spengler, "The effect of respiratory muscle endurance training in patients with myasthenia gravis," *Neuromuscular Disorders*, vol. 17, no. 5, pp. 385–391, 2007.
- [21] S. Freitag, S. Hallebach, I. Baumann, P. Kalischewski, and B. Rassler, "Effects of long-term respiratory muscle endurance training on respiratory and functional outcomes in patients with Myasthenia gravis," *Respiratory Medicine*, vol. 144, pp. 7–15, 2018.
- [22] L. M. Romer and A. K. McConnell, "Specificity and reversibility of inspiratory muscle training," *Medicine & Science in Sports & Exercise*, vol. 35, no. 2, pp. 237–244, 2003.
- [23] L. National Heart and Blood Institute, "Study Quality Assessment Tools 2013," 2021, <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>.
- [24] G. D. Wells, M. Pyley, S. Thomas, L. Goodman, and J. Duffin, "Effects of concurrent inspiratory and expiratory muscle training on respiratory and exercise performance in competitive swimmers," *European Journal of Applied Physiology*, vol. 94, no. 5-6, pp. 527–540, 2005.
- [25] A. E. Kilding, S. Brown, and A. K. McConnell, "Inspiratory muscle training improves 100 and 200 m swimming performance," *European Journal of Applied Physiology*, vol. 108, no. 3, pp. 505–511, 2010.
- [26] F. Lemaitre, J. B. Coquart, F. Chavallard et al., "Effect of additional respiratory muscle endurance training in young well-trained swimmers," *Journal of Sports Science and Medicine*, vol. 12, no. 4, pp. 630–638, 2013.
- [27] M. Lomax, J. Kapus, P. I. Brown, and M. Faghy, "Impact of weekly swimming training distance on the ergogenicity of inspiratory muscle training in well-trained youth swimmers,"



- The Journal of Strength & Conditioning Research*, vol. 33, no. 8, pp. 2185–2193, 2019.
- [28] J. Vašíčková, K. Neumannová, and Z. Svozil, “The effect of respiratory muscle training on fin-swimmers’ performance,” *Journal of Sports Science and Medicine*, vol. 16, no. 4, pp. 521–526, 2017.
- [29] P. Okrzymowska, M. Kurzaj, W. Seidel, and K. Rożek-Piechura, “Eight weeks of inspiratory muscle training improves pulmonary function in disabled swimmers-A randomized trial,” *International Journal of Environmental Research and Public Health*, vol. 16, no. 10, p. 1747, 2019.
- [30] K. Mackała, M. Kurzaj, P. Okrzymowska, J. Stodółka, M. Coh, and K. Rożek-Piechura, “The effect of respiratory muscle training on the pulmonary function, lung ventilation, and endurance performance of young soccer players,” *International Journal of Environmental Research and Public Health*, vol. 17, no. 1, p. 234, 2019.
- [31] L. M. Stern, A. J. Martin, N. Jones, R. Garrett, and J. Yeates, “Training inspiratory resistance in Duchenne dystrophy using adapted computer games,” *Developmental Medicine and Child Neurology*, vol. 31, no. 4, pp. 494–500, 2008.
- [32] D. L. M. Stern, D. A. J. Martin, M. N. Jones, M. R. Garrett, and M. J. Yeates, “Respiratory training in Duchenne dystrophy,” *Developmental Medicine and Child Neurology*, vol. 33, no. 7, p. 649, 2008.
- [33] D. Vilozni, E. Bar-Yishay, I. Gur, Y. Shapira, S. Meyer, and S. Godfrey, “Computerized respiratory muscle training in children with Duchenne muscular dystrophy,” *Neuromuscular Disorders*, vol. 4, no. 3, pp. 249–255, 1994.
- [34] T. Wanke, K. Toifl, M. Merkle, D. Formanek, H. Lahrmann, and H. Zwick, “Inspiratory muscle training in patients with Duchenne muscular dystrophy,” *Chest*, vol. 105, no. 2, pp. 475–482, 1994.
- [35] D. Gozal and P. Thiriet, “Respiratory muscle training in neuromuscular disease: long-term effects on strength and load perception,” *Medicine & Science in Sports & Exercise*, vol. 31, no. 11, pp. 1522–1527, 1999.
- [36] E. Rodillo, C. M. Noble-Jamieson, V. Aber, J. Z. Heckmatt, F. Muntoni, and V. Dubowitz, “Respiratory muscle training in Duchenne muscular dystrophy,” *Archives of Disease in Childhood*, vol. 64, no. 5, pp. 736–738, 1989.
- [37] G. Winkler, U. Zifko, A. Nader et al., “Dose-dependent effects of inspiratory muscle training in neuromuscular disorders,” *Muscle & Nerve*, vol. 23, no. 8, pp. 1257–1260, 2000.
- [38] W. Koessler, T. Wanke, G. Winkler et al., “2 Years’ experience with inspiratory muscle training in patients with neuromuscular disorders,” *Chest*, vol. 120, no. 3, pp. 765–769, 2001.
- [39] A. F. DiMarco, J. S. Kelling, M. S. DiMarco, I. Jacobs, R. Shields, and M. D. Altose, “The effects of inspiratory resistive training on respiratory muscle function in patients with muscular dystrophy,” *Muscle & Nerve*, vol. 8, no. 4, pp. 284–290, 1985.
- [40] A. J. Martin, L. Stern, J. Yeates, D. Lepp, and J. Little, “Respiratory muscle training in Duchenne muscular dystrophy,” *Developmental Medicine and Child Neurology*, vol. 28, no. 3, pp. 314–318, 2008.
- [41] N. Topin, S. Matecki, S. Le Bris et al., “Dose-dependent effect of individualized respiratory muscle training in children with Duchenne muscular dystrophy,” *Neuromuscular Disorders*, vol. 12, no. 6, pp. 576–583, 2002.
- [42] M. Takaso, T. Nakazawa, T. Imura et al., “Surgical management of severe scoliosis with high-risk pulmonary dysfunction in Duchenne muscular dystrophy,” *International Orthopaedics*, vol. 34, no. 3, pp. 401–406, 2010.
- [43] I. Yeldan, H. N. Gurses, and H. Yuksel, “Comparison study of chest physiotherapy home training programmes on respiratory functions in patients with muscular dystrophy,” *Clinical Rehabilitation*, vol. 22, no. 8, pp. 741–748, 2008.
- [44] B. K. Smith, A. D. Martin, L. A. Lawson et al., “Inspiratory muscle conditioning exercise and diaphragm gene therapy in Pompe disease: clinical evidence of respiratory plasticity,” *Experimental Neurology*, vol. 287, no. Pt 2, pp. 216–224, 2017.
- [45] H. N. Jones, K. D. Crisp, T. Moss et al., “Effects of respiratory muscle training (RMT) in children with infantile-onset Pompe disease and respiratory muscle weakness,” *Journal of Pediatric Rehabilitation Medicine*, vol. 7, no. 3, pp. 255–265, 2014.
- [46] K. D. Crisp, L. E. Case, R. M. Kravitz, P. S. Kishnani, H. N. Jones, and retraining, “Training, detraining, and retraining: two 12-week respiratory muscle training regimens in a child with infantile-onset Pompe disease,” *Journal of Pediatric Rehabilitation Medicine*, vol. 13, no. 1, pp. 71–80, 2020.
- [47] I. S. Silva, G. A. F. Fregonezi, F. A. L. Dias, C. T. D. Ribeiro, R. O. Guerra, and G. M. H. Ferreira, “Inspiratory muscle training for asthma,” *Cochrane Database of Systematic Reviews*, vol. 9, Article ID CD003792, 2013.
- [48] P. Weiner, N. Berar-Yanay, A. Davidovich, R. Magadle, and M. Weiner, “Specific inspiratory muscle training in patients with mild asthma with high consumption of inhaled  $\beta_2$ -agonists,” *Chest*, vol. 117, no. 3, pp. 722–727, 2000.
- [49] P. Weiner, R. Magadle, M. Beckerman, and N. Berar-Yanay, “The relationship among the inspiratory muscle strength, the perception of dyspnea and inhaled beta2-agonists in patients with asthma,” *Canadian Respiratory Journal*, vol. 9, no. 5, pp. 307–312, 2002.
- [50] N. Duruturk, M. Acar, and M. I. Dogrul, “Effect of inspiratory muscle training in the management of patients with asthma: a randomized controlled trial,” *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 38, no. 3, pp. 198–203, 2018.
- [51] I. Lopez-de-Uralde-Villanueva, P. Candelas-Fernandez, B. de-Diego-Cano, O. Minguez-Calzada, and T. Del Corral, “The effectiveness of combining inspiratory muscle training with manual therapy and a therapeutic exercise program on maximum inspiratory pressure in adults with asthma: a randomized clinical trial,” *Clinical Rehabilitation*, vol. 32, no. 6, pp. 752–765, 2018.
- [52] E. V. N. C. L. Lima, W. L. Lima, A. Nobre, A. M. d. Santos, L. M. O. Brito, and M. d. R. d. S. R. Costa, “Treinamento muscular inspiratório e exercícios respiratórios em crianças asmáticas,” *Jornal Brasileiro de Pneumologia*, vol. 34, no. 8, pp. 552–558, 2008.
- [53] R. K. Elnaggar, “A randomized placebo-controlled study investigating the efficacy of inspiratory muscle training in the treatment of children with bronchial asthma,” *Journal of Asthma*, vol. 58, no. 12, pp. 1661–1669, 2021.
- [54] I. Frank, R. Briggs, and C. M. Spengler, “Respiratory muscles, exercise performance, and health in overweight and obese subjects,” *Medicine & Science in Sports & Exercise*, vol. 43, no. 4, pp. 714–727, 2011.
- [55] J. C. Villiot-Danger, E. Villiot-Danger, J. C. Borel, J. L. Pepin, B. Wuyam, and S. Verges, “Respiratory muscle endurance

- training in obese patients,” *International Journal of Obesity*, vol. 35, no. 5, pp. 692–699, 2011.
- [56] A. M. Edwards, G. P. Maguire, D. Graham, V. Boland, and G. Richardson, “Four weeks of inspiratory muscle training improves self-paced walking performance in overweight and obese adults: a randomised controlled trial,” *Journal of obesity*, vol. 2012, pp. 1–6, 2012.
- [57] Y.-C. Kuo, H.-L. Chang, C.-F. Cheng, T. Mündel, and Y.-H. Liao, “Six-week inspiratory resistance training ameliorates endurance performance but does not affect obesity-related metabolic biomarkers in obese adults: a randomized controlled trial,” *Respiratory Physiology & Neurobiology*, vol. 273, Article ID 103285, 2020.
- [58] M. C. Barbalho-Moulim, G. P. S. Miguel, E. M. P. Forti, F. do Amaral Campos, and D. Costa, “Effects of preoperative inspiratory muscle training in obese women undergoing open bariatric surgery: respiratory muscle strength, lung volumes, and diaphragmatic excursion,” *Clinics*, vol. 66, no. 10, pp. 1721–1727, 2011.
- [59] D. Salvadego, A. Sartorio, F. Agosti et al., “Respiratory muscle endurance training reduces the O<sub>2</sub> cost of cycling and perceived exertion in obese adolescents,” *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, vol. 313, no. 4, pp. R487–R495, 2017.
- [60] H. K. Alemayehu, D. Salvadego, M. Isola et al., “Three weeks of respiratory muscle endurance training improve the O<sub>2</sub> cost of walking and exercise tolerance in obese adolescents,” *Physiological reports*, vol. 6, no. 20, Article ID e13888, 2018.
- [61] A. LoMauro, A. Cesareo, F. Agosti et al., “Effects of a multidisciplinary body weight reduction program on static and dynamic thoraco-abdominal volumes in obese adolescents,” *Applied Physiology Nutrition and Metabolism*, vol. 41, no. 6, pp. 649–658, 2016.
- [62] D. Salvadego, A. Sartorio, F. Agosti et al., “Acute respiratory muscle unloading by normoxic helium–O<sub>2</sub> breathing reduces the O<sub>2</sub> cost of cycling and perceived exertion in obese adolescents,” *European Journal of Applied Physiology*, vol. 115, no. 1, pp. 99–109, 2015.
- [63] D. Salvadego, S. Lazzer, C. Busti et al., “Gas exchange kinetics in obese adolescents. Inferences on exercise tolerance and prescription,” *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, vol. 299, no. 5, pp. R1298–R1305, 2010.
- [64] J. E. Lang, M. J. Hossain, and J. J. Lima, “Overweight children report qualitatively distinct asthma symptoms: analysis of validated symptom measures,” *The Journal of Allergy and Clinical Immunology*, vol. 135, no. 4, pp. 886–893.e3, 2015.
- [65] A. E. Holland, N. S. Cox, L. Houchen-Wolloff et al., “Defining modern pulmonary rehabilitation. An official American thoracic society workshop report,” *Annals of the American Thoracic Society*, vol. 18, no. 5, pp. e12–e29, 2021.