

Effect of Flow-Resistive Inspiratory Muscle Training on The Severity of Exercise-Induced Bronchoconstriction and Cycling Time-Trial Performance

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1.0 Background & Rationale

EIB is a multifactorial condition characterized by airway inflammation, hyperresponsiveness, and airway narrowing following a bout of exercise in those with and without previous asthma diagnosis (1-9). Common techniques used to invoke bronchoconstriction and diagnose EIB are exercise and eucapnic voluntary hyperpnea (EVH). EVH is the method recommended by the International Olympic Committee to diagnose EIB in athletes (4, 10-12). Positive EIB diagnosis is defined as a $\geq 10\%$ drop in forced expiratory volume in 1 second (FEV₁) after an EVH challenge compared to baseline (4, 8, 9). The severity of EIB can be classified in the following manner: Mild EIB is characterized as $\geq 10\%$ drop in post-EVH FEV₁, moderate is a $\geq 25\%$ drop in post-EVH FEV₁, and severe EIB is a $\geq 50\%$ drop in post-EVH FEV₁, according to the American Thoracic Society Guidelines (4, 8, 13).

Elite athlete populations appear to have a high prevalence of EIB ranging from 10 to 60% for EIB and 17% for asthma, particularly in endurance sports such as running, cycling, rowing, and swimming (1, 2, 4, 7, 9, 11, 14). Carlsen et al., (2) reported 67 out of 597 American Olympic athletes in the 1984 Los Angeles summer Olympic Games had asthma or exercise-induced asthma. In the 1996 Olympics, asthma prevalence in cyclists and mountain bikers was 45%, while EIB was not documented in weightlifters and divers. EIB-positive athletes commonly experience symptoms such as wheezing, coughing, shortness of breath, dyspnea, and chest tightness during or after exercise (1, 4, 6, 15-17). Symptoms may last up to a few minutes or hours post-exercise but are reversible and manageable with medication (1-9). The mechanisms postulated to cause EIB are airway dehydration and high ventilation rates during exercise, leading to increased airway dryness and airway osmolarity, and a subsequent release of inflammatory mediators from airway cells, such as leukotrienes, prostaglandins, and histamine (1, 2, 4, 6-8). These inflammatory mediators can subsequently cause edema, constriction of airway smooth muscle, and increased mucus production (1, 2, 4, 6-8).

Treatment options for EIB heavily include pharmacological strategies, while non-pharmacological strategies are scarce. The most common pharmacological treatments are short-acting β_2 -agonists (SABA) (1, 4, 6, 8, 9, 15, 18, 19). SABAs stimulate airway β_2 -receptors causing relaxation of smooth muscle, and thereby dilating the airways. Inhaled forms like salbutamol or albuterol are commonly prescribed and taken 5-20 minutes before exercise (1, 4, 6, 8, 9). However, frequent use of SABAs may result in medication tolerance leading to a reduced efficacy in attenuating bronchoconstriction (1, 4, 8). There is emerging evidence that non-pharmacological therapies may be used to supplement traditional therapies to reduce the severity of EIB and minimize exercise respiratory symptoms (1, 4, 6, 8, 9, 15, 18-21). One of these non-pharmacological interventions that is the most available and cost-effective is inspiratory muscle training (IMT) (1-9, 22). This technique aims to increase the strength and endurance of the diaphragm and accessory muscles of respiration. Flow-resistive IMT typically consists of taking voluntary inspirations against a resistive load across an entire range of vital capacity while at rest (11, 23-32). This loading protocol requires the athlete to breathe through a 2mm diameter orifice in the device, which increases the pressure required to produce a given airflow (26, 29, 30, 33-35). IMT is typically performed in a laboratory or at home with an IMT device several times a week for 6 to 12 weeks (26, 29, 30, 33-35).

In healthy individuals, the most notable effects of IMT are an increase in diaphragm thickness and strength, a decrease in exertional dyspnea, and a decrease in respiratory and limb locomotor muscle deoxygenation during exercise (20, 23-27, 29, 36-42). The use of IMT

in asthma has been shown to improve inspiratory muscle strength, reduce dyspnea, medication use, and asthma symptoms (11, 17, 23-27, 29-32). Importantly, Turner et al., (31) has shown that pressure threshold IMT improved exercise tolerance by 16% and reduced the perception of dyspnea by 16% during cycling exercise performed at $\sim 70\%$ $\text{VO}_{2\text{max}}$ until exhaustion. Following IMT, inspiratory muscle strength and endurance increased 28% and 16%, respectively, and VO_2 decreased by 6% at minute 4 and 12% at the end of a constant load cycling exercise. It was speculated that the decrease in dyspnea perception might be due to increased inspiratory muscle strength, while the reduced VO_2 observed during constant load cycling exercise following IMT may be related to changes in strength and/or operating lung volumes during exercise (31).

Weiner et al., (43) found a proportional correlation between perception of dyspnea and β_2 -agonist use in individuals with mild to moderate asthma (44). Thus, decreased β_2 -agonist use decreased perception of dyspnea (Borg scale). In support, Weiner et al., (45) found individuals with mild asthma improved their inspiratory muscle strength, which was associated with a decrease in the modified Borg scale for dyspnea perception during a resistive breathing test. Furthermore, β_2 -agonist use decreased in the high β_2 -agonist user group in the last four weeks of training. Duruturk et al., (46) found that respiratory muscle strength, measured by maximal inspiratory pressure (MIP), increased after IMT in asthmatics. In addition, distance walked in a 6-minute test was improved, fatigue decreased, and dyspnea score decreased in the IMT group.

EIB may result in decreased exercise tolerance and performance, dynamic hyperinflation (DH), and decreased inspiratory muscle strength, leading to the onset of exertional dyspnea (ED) (19). ED is defined as the perception of the intensity and difficulty of breathing (15, 18, 19, 47-50). Common mechanisms leading to ED are chest tightness and work or effort of breathing (47). Work or effort of breathing has been theorized to be related to the respiratory system's central and peripheral coupling of muscle tone regulation, while chest tightness represents the degree of bronchoconstriction (15, 19, 47). The underlying mechanism responsible for ED is thought to involve dynamic hyperinflation (DH) of the lungs. DH occurs when there is a progressive increase in end-expiratory lung volume (EELV) during exercise with bronchoconstriction due to air trapping. This increase in EELV constrains tidal volume (V_T) closer to total lung capacity and the steeper, non-compliant region of the pressure-volume relationship between the lung and chest wall where elastic loading is greater to overcome (19, 32, 36, 37, 50-52). When there is a decrease between the volume of air to exhale, complete exhalation time, and frequency of inspirations, EELV increases (19, 32, 36, 37, 51), resulting in the immoderate elastic stretch of the inspiratory muscles forcing the muscles to function outside their optimal scope (15, 19, 49). The muscles then become weak, which results in a greater perception of dyspnea with the additional respiratory muscle work needed to overcome elastic loading forces (15, 19).

If EIB is not diagnosed and treated, a decrease in an athlete's performance may be detrimental to their athletic success. The athlete may have exacerbated symptoms, such as wheezing, increased mucus production, and coughing during exercise and excessive fatigue post-exercise. Due to leftward shifts in the pressure-volume curve with dynamic hyperinflation, respiratory muscle work increases, and respiratory muscle fatigue sets in (1-5, 9, 16, 18, 23, 26, 35, 53). Repeated mechanical contraction and resulting metabolites (e.g. hydrogen ions, potassium ions, bradykinin, phosphate, and prostaglandins) produced by fatiguing respiratory muscles stimulates signals from the group III/IV phrenic nerve afferents. This enhances sympathetic efferent signals to limb skeletal muscles, resulting in a redirection of blood flow from the lower limb muscles to the respiratory muscles – a phenomenon termed respiratory

muscle metaboreflex (9, 18). Therefore, respiratory muscle oxygen uptake increases at the expense of decreased locomotor oxygen uptake. In response, the locomotor skeletal muscles' metaboreceptors send afferent signals to the brain (also known as the central governor), increasing the sensation of fatigue, and decreased motor unit drive to the limb locomotor muscles, resulting in exercise performance decrement (5, 9, 18, 26, 32, 35, 44, 47, 53-55).

It has been postulated that EIB may be exacerbated by exercise. Price et al., (9) described that airflow limitation due to increasing exercise ventilation rates might cause airway stress, dynamic hyperinflation, and decreased respiratory muscle efficiency (1-9). The resultant ventilation-perfusion mismatch may reduce alveolar gas exchange. Therefore, this change in oxygen kinetics and an increase in an athlete's perception of effort and symptoms, due to dynamic hyperinflation and airway stress, may result in reduced exercise capacity (1-5, 9, 16, 18, 23, 26, 35).

To our knowledge, no study has been conducted assessing the impact of IMT on EIB severity, ED, and cycling time-trial performance. A review by Shei et al., (30) noted that studies examining the impact of IMT on asthma have all demonstrated an increase in inspiratory muscle strength (maximal inspiratory pressure, MIP) and endurance (sustained maximal inspiratory pressure). In addition, it has been observed that the reduction in the perception of dyspnea following and during exercise leads to a reduction in SABA use and fewer asthma symptoms (30, 43-45). Shei et al., (30) also noted the lack of data available to explain the impacts of IMT on exercise performance and tolerance in athletes with EIB. Interestingly, Price et al., (9) suggested that more prolonged duration exercise with specific aerobic demands could provoke airway obstruction and hinder performance.

Due to the lack of studies examining the impact of IMT on the severity of EIB and exercise performance, the specific aim of this study is to assess the efficacy of flow-resistive IMT on EIB severity and symptoms, SABA medication use, operating lung volumes, respiratory and limb locomotor muscle deoxygenation during constant-load cycling exercise, femoral blood flow, exertional dyspnea, and cycling time-trial performance. It is hypothesized that eight weeks of IMT will reduce EIB's severity and symptoms, respiratory and limb locomotor muscle deoxygenation, improve operating lung volumes, and exertional dyspnea and improve cycling time-trial performance.

2.0 Objective(s)

2.1 Primary Objective

Aim 1a. To examine the effect of flow-resistive inspiratory muscle training on the severity of exercise-induced bronchoconstriction (EIB) after inspiratory muscle training (IMT). More specifically, the pre- and post-values of the percentage drop in forced expiratory volume in 1 second (FEV₁) from the eucapnic voluntary hyperpnea (EVH) test before and after IMT will be measured.

We hypothesize IMT will reduce the severity of EIB. We anticipate there will be differences in the percentage drop in FEV₁ after EVH testing, resulting in a lessening of EIB severity.

Aim 1b. To examine the effects of flow-resistive inspiratory muscle training on the strength and endurance of the inspiratory muscles. More specifically, the pre-

to post-values of maximum inspiratory pressure and sustained maximum inspiratory pressure before and after IMT will be measured.

We hypothesize IMT will increase the maximum inspiratory pressure and sustained maximum inspiratory pressure post-training. We anticipate there will be differences in the MIP and SMIP values, resulting in the improvement of inspiratory muscle strength and endurance.

Aim 1c. Evaluate differences in constant load parameters and 16-km cycling time-trial completion time and power output before and after IMT.

We hypothesize power output will increase during constant load cycling after training. In addition, subjects time-trial time performance will improve and power output will increase after IMT.

2.2 Secondary Objective

Aim 2a. To assess whether IMT affects an individual's perception of exertional dyspnea and leg fatigue during constant load cycling and a 16-km cycling time-trial.

We hypothesize that individuals will have a reduced perception of exertional dyspnea after IMT, compared to pre-training.

Aim 2b. To examine the effects of IMT on the deoxygenation of the respiratory and limb locomotor muscles during constant load cycling and a 16-km cycling time-trial.

We hypothesize the deoxygenation of the respiratory and limb locomotor muscles will be reduced after IMT.

Aim 2c. To examine the effects of IMT on femoral blood flow (FBF) of the limb locomotor muscles during constant load cycling.

We hypothesize the decrease in demand for respiratory muscle blood flow after IMT would elicit vasodilation of limb locomotor muscles and optimize blood flow after IMT. IMT has the potential to attenuate the respiratory muscle metaboreflex. By measuring femoral blood flow, it will help inform us whether this is the case - such that more blood flow goes to limb locomotor muscles after IMT.

Aim 2d. To examine the effects of IMT on operating lung volumes during constant load cycling and a 16-km cycling time-trial.

We hypothesize the operating lung volumes during exercise will be improved after IMT.

3.0 Outcome Measures

3.1 Primary Outcome Measures

Outcomes of interest is the severity of exercise-induced bronchoconstriction (EIB), inspiratory muscle strength and endurance, and cycling performance.

EIB severity will be measured using the pre- and post-values of the percentage drop in forced expiratory volume in 1 second (FEV₁) obtained from the eucapnic voluntary hyperpnea (EVH) test before and after IMT.

Inspiratory muscle strength and endurance will be measured using the flow-resistive trainer device that will record maximum inspiratory pressure and sustained maximum inspiratory pressure for 8 weeks.

Cycling performance will be summarized by pre- to post-values in power output, time, and speed time to complete the time-trial and constant loads before and after IMT.

3.2 Secondary Outcome Measures

The secondary outcomes of interest include exertional dyspnea and leg fatigue, deoxygenation of respiratory and limb locomotor muscles, and operational lung volumes.

Exertional dyspnea and leg fatigue will be summarized by the separate and cumulative pre- and post-values of perceived scores before and after IMT.

Deoxygenation of respiratory and limb locomotor muscles will be summarized by pre- and post-values of respiratory and limb deoxygenation values via NIRS protocol before and after IMT.

Femoral blood flow will be summarized by pre- and post-values of blood flow values via Doppler ultrasound protocol before and after IMT.

Operation lung volumes to assess the degree of dynamic hyperinflation will be measured using flow volume loops and inspiratory capacity (IC) maneuvers. Respiratory mechanical constraint will be calculated by the tidal volume (V_T)/IC ratio to indicate the degree of dynamic hyperinflation, further implicating the potential of EFL ([56-60](#)).

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Male and female, between the ages of 18 to 35 years.
- Required to be a competitive recreational or college athlete and have at least 1-2 years of cycling or biking experience.
- Body Mass Index (BMI) of 18.5 to 28 kg/m²

- Considered “moderately to highly active” by the International Physical Activity Questionnaire (IPAQ).
- Have clinically treated mild to moderate persistent asthma and/or exercise-induced bronchoconstriction (EIB), with a resting forced expiratory volume in 1 second (FEV₁) > 65% of predicted.
- A ≥ 10% drop in FEV₁ after eucapnic voluntary hyperpnea (EVH).
- Prescribed short-acting β_2 -agonists (SABAs) by a physician.
- Comfortable not taking SABA before experimental visits.

4.2 Exclusion Criteria

- History of smoking or recreational smoking, cardiovascular disease, renal disease, neurological disease, and metabolic disease.
- Currently taking asthma maintenance medications (e.g., corticosteroids and leukotriene modifiers)
- Any injuries in the past 6 months.
- Taking SSRI's (antidepressants and anxiety medication), ADD/ADHD medication, and chronically consume pain medication (Aleve, Tylenol, CBD, etc).
- Resting blood pressure of > 130mmHg systolic or 90 mmHg diastolic.
- Resting Pulse rate of > 100 bpm.
- Regularly consuming fish oil supplements or eating more than one fish meal per week

5.0 Study Design

The study design is a randomized, single-blind parallel group study. Participants will complete a formal screening visit and five experimental visits. The five experimental visits will occur each day ± 1 hour, at least 24 hours apart, and ≥ 2 hours postprandial.

The participants were required to visit the laboratory 5 times to complete the experimental tests. *Visit 1.* Participants underwent pulmonary function testing (PFT) and completed a eucapnic voluntary hyperpnea (EVH) challenge to diagnose EIB. *Visit 2.* Participants completed an incremental cycle ergometer test to determine VO_{2peak}. Male participants began with a 3-minute warm-up at 60W (61). After the warm-up, the test started at 100W and increased by 30W every minute until exhaustion (33, 61). A participant's VO_{2peak} was determined as the highest 30-second average VO₂ value (33, 61). All participants had a 1-hour rest period before the 16-km familiarization time-trial. *Visit 3.* Each participant completed two 8-minute constant-load exercise bouts, one at moderate intensity and another at submaximal intensity, and had a 1-hour rest period before the 16-km time-trial. After visit 3, participants were randomly assigned to either an IMT or a sham-IMT (control) group using a random number generator (1 = IMT, 2 = sham-IMT). Participants used a flow-resistive inspiratory muscle trainer (Pro2Fit, Smithfield, Rhode Island) in order to complete eight weeks of IMT, performed three times a week, prior to any exercise training that day. After 8 weeks of the IMT or Sham-IMT intervention, participants returned to the laboratory to repeat the PFTs, the EIB diagnosis via EVH, the familiarization time-trial, and the constant-load and performance time-trial post-IMT for *Visit 4* and *Visit 5*.

6.0 Study Procedures

All study procedures are being conducted for research purposes only.

Specific Measures:

Pulmonary function testing & EIB Diagnosis: Pulmonary function testing was performed in accordance with the American Thoracic Society (2, 8, 62, 63). Maximal expiratory flow-volume (MEFV) loops were assessed to determine the degree of EFL using a handheld computerized pneumotachograph spirometer before and after the eucapnic voluntary hyperpnea (EVH) challenge, and using a metabolic cart (Vmax Encore System; CareFusion, Yorba Linda, CA) before and after exercise testing. The test included a forced vital capacity (FVC) maneuver in order to determine the participants FEV₁, FVC, peak expiratory flow (PEF), forced expiratory flow after 25 and 75% of FVC (FEF_{25-75%}), and FEV₁/FVC. Prior to exercise testing, spirometry was performed in triplicate, selecting the three best maneuvers with FEV₁ within 0.15 L. Prior to the EVH challenge, participants completed five maneuvers, and the average of the three best maneuvers with FEV₁ within 0.15 L was analyzed (63).

The EVH challenge is used as a surrogate for an exercise challenge to diagnose EIB. After establishing a baseline FEV₁, the target ventilation rate was calculated (L/min) (FEV₁ × 30) and is maintained by the participant for 6 minutes while breathing dry air from a Douglas bag (5% CO₂, 21% O₂, balance N₂) (4, 10, 11, 64) through a two way non-rebreathing valve (Hans-Rudolph, Shawnee, KS). Spirometry was performed after completion of the EVH challenge to assess changes in FEV₁ at 5-minute intervals over 30 minutes (8, 30). Participants with ≥ a 10% drop in FEV₁ (eq. 1) were deemed to have tested positive for EIB (65). Severity is characterized into three categories: mild, moderate, and severe. Mild is indicated as ≥ 10%, and less than 25%, moderate is ≥ 25%, and less than 50%, and severe is ≥ 50%, according to the American Thoracic Society Guidelines (8, 13, 38, 64).

$$\text{Percentage Drop FEV}_1 = \left[\left(\frac{\text{FEV}_1 \text{ Baseline} - \text{lowest value FEV}_1 \text{ EVH}}{\text{FEV}_1 \text{ Baseline}} \right) \times 100 \right] \quad [1]$$

Inspiratory Muscle Training (IMT) & Sham-IMT Training: A flow-resistive IMT protocol, as described previously (26, 29, 30, 33-35), was used in this study. Participants used the Pro2Fit (Smithfield, Rhode Island) flow-resistive inspiratory muscle trainer to complete 8 weeks of IMT, performed three times a week with 24 hours between sessions, and did not perform any aerobic exercise training that day. The training device consists of a handheld unit interfaced with a tablet or smartphone via a wireless Bluetooth connection. The test of incremental respiratory endurance (TIRE) protocol requires users to exhale forcefully to residual volume and immediately inhale maximally (maximum inspiratory pressure, MIP) against a 2mm diameter leak, and sustain the inhalation until task failure. The area under the pressure-time curve generated by MIP is known as sustained maximal inspiratory pressure (SMIP). Participants were required to complete 3 SMIP maneuvers during each training session and use the best of the 3 for that day's training template (corresponding to about 80% SMIP) via the Pro2Fit software. Participants must match or exceed the SMIP template with each increasing

level of the work-rest ratio. Work at each level consists of 6 breaths, for a total of 36 breaths. If six breaths are completed, the next level starts. Rest intervals will progressively shorten as training continues, from 40 seconds to 30-, 20-, 15-, 10-, and 5-seconds. The training session is terminated if participants are unable to match at least 90% of the training template for two consecutive breaths or have completed all 36 breaths (25). The 30% SMIP used for the sham-IMT group has previously been shown not to elicit any training adaptations (26, 29, 30, 33-35). Compliance was assessed by summing the number of recorded sessions for each participant and dividing by the total number of prescribed sessions.

Constant Load & Time-Trial Cycling Exercise: Before exercise, the participant adjusted the seat height on the cycle ergometer (Velotron, Velotron® Racermate, Seattle, WA), and then were fitted with a facemask (Hans-Rudolph, Shawnee, KS) and flow probe connected to a metabolic cart (Vmax® Encore, Vyair Medical, Mettawa, IL) and a Polar HR Monitor (Polar, Helsinki, Finland) underneath the sternum. Each participant completed two constant-load (CL) exercises with a 5-minute rest period in between, one at 15% below the gas exchange threshold (GET; CL1) and another at 15% above the gas exchange threshold (CL2), corresponding to 85% $\text{VO}_{2\text{peak}}$ (42). Males warmed up for 5 minutes at 60W, followed by a 5-minute rest (42, 66). After the 5-minute rest period, participants cycled at 5W for 2 minutes, immediately followed by a predetermined moderate workload. The moderate and submaximal workloads are determined from their GETs, estimated from changes in breath values using the modified V-slope method (42). Each participant completed a familiarization time-trial (TT) to learn the cycle gearing system and to reduce any further learning effects (61, 67). The cycle ergometer recorded each participant's power output (PO), speed, and time to complete the time-trial (33). The ergometer allows participants to vary their resistance and power output, with an electronic gearing system during the 16-km TTs, simulating an actual performance scenario.

Ratings of exertional dyspnea & leg fatigue: During constant-load cycling and the cycling time-trial, three modified Borg scales (0-10) were placed at arm's length, comfortably reachable by the participant on the cycle ergometer. Participants were asked to indicate their ratings of perceived breathing intensity, 0 indicating "not noticeable" and 10 indicating "maximal intensity imaginable". Secondly, participants were asked to rate perceived breathing unpleasantness, with 0 indicating "not unpleasant" and 10 indicating "maximal unpleasantness imaginable". Lastly, participants were asked to rate leg fatigue, with 0 indicating "not fatigued at all" and 10 indicating "total fatigue and exhaustion". Ratings were recorded every 2 minutes during each of the 8-minute constant loads and every 4 km during the 16-km time-trial.

Femoral Blood Flow (FBF): The limb blood flow protocol for the femoral artery, as previously described (65, 68-72), was used in the study. With participants at rest on the cycle ergometer with their right leg straight and relaxed, femoral artery diameter (as internal diameter) and blood velocity were measured 2-3 cm proximal to the superficial/deep bifurcation with an ultrasound Doppler system in triplex mode (Aplio 300; Toshiba Medical Systems Corporation), equipped with a linear array transducer functioning at an imaging frequency of 7.5 MHz. Blood velocity (cm/s) will be assessed with an insonation angle $\leq 60^\circ$, with the sample volume maximized and centered in real

time according to vessel size and position. With participants in an upright position, blood velocity and vessel radius (cm) were measured at rest prior to the start of exercise and during the last 10 seconds of the first constant load (CL1) and the second constant load (CL2). LBF (mL/min) was calculated using Equation 2.

$$LBF = \left[\left((\text{mean blood velocity (cm/s)}) \times \pi (\text{vessel radius (cm)})^2 \right) \times 60 \right] \quad [2]$$

Near-infrared spectroscopy (NIRS): As described previously ([28](#), [73-75](#)), near-infrared spectroscopy (NIRS) optode holders and optodes (OxiMon MKIII; Artinis Medical Systems, The Netherlands) were placed on the vastus lateralis of the participant's right leg and over the right 6th intercostal space at the anterior axillary line to monitor the deoxygenation status of the respiratory and limb locomotor muscle. Limb optode placement was approximately 15cm above the patella and 5cm lateral from the thigh's midline. Placement locations were marked with a semi-permanent marker, and holders were positioned to the skin surface with double-sided tape and covered with a black elastic bandage wrap to limit extraneous light from influencing the probe and to limit movement during exercise. The system emits NIR light to the target tissue via fiber-optic cables at wavelengths of 760 and 850nm. Optode separation distance within the optode holder for the vastus lateralis and anterior axillary line was 4cm (40mm). Light emitted from the fibers is half or less than half the distance between the emitter and the detector, allowing a depth of tissue of approximately 1-2cm. Skinfold measurements of the right mid-axillary and right thigh region determined the depth of tissue. A differential pathlength factor (DPF) of 4 was used. Light reflected from the tissue is detected by a photomultiplier tube and is recorded at a sampling rate of 50Hz. Based on a modified Beers-Lambert Law, concentrations were estimated for deoxygenated ([HHb]) hemoglobin and myoglobin in tissue. Resting values were obtained when the participant was sitting on the ergometer with the legs relaxed. Respiratory and limb deoxygenation were measured during each constant load and cycling time-trial. The collected data were filtered using OxySoft (Artinis Medical Systems, The Netherlands) to smooth the raw data.

Flow Limitation: At specific points during the exercise bout, participants were instructed to perform an inspiratory capacity (IC) maneuver, inspire to total lung capacity (TLC), and then exhale back to breathing normally. Respiratory mechanical constraint was calculated by the tidal volume (V_T)/IC ratio to indicate the degree of dynamic hyperinflation, further implicating the potential of EFL ([56-60](#)). In conditions characterized by pronounced mechanical constraint (e.g., COPD), IMT can reduce diaphragm activation and dyspnea ([76-78](#)). In asthma/EIB, however, resting spirometry is typically preserved and dynamic hyperinflation becomes prominent only under severe obstruction or near-maximal ventilation ([44](#), [51](#), [79-81](#)). Given that V_T generally reaches a mechanical ceiling when ~70% of IC is used and inspiratory reserve volume (IRV) approaches ~0.5–1.0 L, dyspnea intensity closely tracks this V_T /IC ratio rather than inspiratory strength per se ([56-60](#)).

7.0 Study Withdrawal/Discontinuation

Participants can voluntarily withdraw from the study at any time by contacting any of the researchers on the study via any available means (personal contact, email, phone,

etc.). If a researcher on the project wishes to withdraw a subject from the study, they will contact the individual directly (personal contact, email, phone, etc.). Possible indications for withdrawal by a researcher include: Concern that a participant could injure themselves by performing on of the exercise tasks in the study, results that do not meet the criteria for inclusion in the study, an abnormal response to exercise, an inability to complete the exercise tests, inability of a participant to complete a task properly to obtain valid measures, etc.

8.0 Statistical Considerations

Data analysis was conducted using GraphPad Prism (GraphPad Software LLC, San Diego, CA, USA). All dependent variables were assessed for normality using the Shapiro-Wilk test, and corresponding Q-Q plots were visually inspected. When the assumption of normality was not met, a non-parametric Wilcoxon signed-rank test was performed. To evaluate main and interaction effects, a two-way repeated-measures ANOVA was performed for each outcome variable, with time (pre, post) and group (IMT, Sham-IMT) as within- and between-participants factors, respectively. When missing data precluded a full factorial ANOVA, a mixed-effects model with restricted maximum likelihood (REML) was used to account for unbalanced datasets and preserve statistical power. Significance was set at $p < 0.05$ for all comparisons. Data are reported as means \pm standard deviations (SD) and mean differences (MD) with 95% confidence intervals (CI).

A statistical power analysis was performed to estimate sample size using G*Power 3.1.9.7 (University of Kiel, University of Düsseldorf, and University of Mannheim, Germany). Utilizing F tests for ANOVA determined that 20 participants total (10 = IMT, 10 = Sham-IMT) are needed in the proposed study for a power of 0.80, with an effect size of 0.25 and an $\alpha = 0.05$. Based on previous work by Turner et al., (31), Duruturk et al., (46), Shei et al., (29), Hursh et al., (33), and Faghy et al., (82), standard parameters of $1-\beta = 0.8$ and $\alpha = 0.05$ are suggested. However, due to the limitation of participant recruitment, only 11 participants completed the study. Given the modest sample size, these findings should be interpreted as preliminary and hypothesis-generating. Given the modest and imbalanced sample size, statistical findings were interpreted with emphasis on effect sizes and 95% confidence intervals rather than sole reliance on p values. Interaction effects were considered the primary test of intervention efficacy, whereas within-group changes were interpreted descriptively to characterize response patterns. Non-significant findings were not interpreted as evidence of no effect but rather as inconclusive within the constraints of the present sample.

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