Inspiratory muscle strength training

Evidence Summary

Inspiratory muscle training has been shown to improve exercise capacity, improve respiratory function, improve vascular function, and reduce respiratory complications in a wide variety of adult populations.

Neuroprotective Benefit: IMST has not been tested for cognitive outcomes but can improve respiratory function in individuals with neurodegenerative disease, and may mitigate vascular-related dementia risk factors.

Aging and related health concerns: Respiratory muscle training can improve respiratory capacity and improve outcomes in adults with chronic conditions. Some paradigms can also reduce blood pressure and improve vascular function.

Safety: Respiratory muscle training is safe and well-tolerated in a wide variety of adult populations. Frail individuals are most likely to experience adverse events. Training paradigms need to be tailored to the capacity of each individual.

Availability: OTC	**Dose**: A training paradigm of an inspiratory load at 75% of maximum for 30 inspiratory bouts (five sets of six breaths with one minute in between sets) (~5 minutes total) once per day.
Half-life: N/A	**BBB**: N/A
Clinical trials: Inspiratory muscle training has been tested in dozens of primarily small pilot studies (most have been ~10 to50 participants) and shown benefits in a variety of populations. Large scale (>200 participants), long duration (>1 year) studies are lacking.	**Observational studies**: Analyses of clinical studies indicates that inspiratory muscle training is associated with reduced risks for pulmonary complications.

What is it?

Inspiratory muscle strength training (IMST) is a form of respiratory muscle training [1]. Other types of respiratory muscle training include inspiratory endurance training and expiratory muscle training. Inspiratory muscle training uses the diaphragm and the accessory respiratory muscles, including the intercostal muscles and the sternocleidomastoid, to exert repeated inhalations against resistance, while expiration is not impeded. The resistance is achieved via inspiratory muscle training devices. These devices are generally classified by the FDA as class 1 medical devices, and thus exempt from regulatory processes, such as premarket notification requirements to demonstrate that a device is safe and effective. The Powerbreathe© Medic device has been approved for prescription by the National Health Service (NHS) in the UK.

Constant or tapered loading devices require that a target inspiratory pressure be achieved at the start of the inhalation, and then the degree of resistance is decreased, which allows for inspiration at higher lung volumes. Pressure threshold devices, which is the style that has been most frequently used in clinical trials, allow for inspiration only when the target pressure is reached. The same devices can be used for inspiratory muscle strength and endurance training, as the difference tends to be in the training paradigm, such as the target pressure and session duration. The target pressure is a percentage of an individual's maximal inspiratory pressure, which measures the strength of the respiratory muscles. Strength training paradigms are generally performed at higher target pressures for shorter duration, relative to endurance training paradigms. Expiratory muscle training is similar, but is based on maximal expiratory pressure, and requires either a separate device or a dual valve device.

Measures of respiratory strength, such as the maximal inspiratory pressure, are associated with mortality risk [2]. The traditional method of increasing respiratory function using aerobic exercise is not practical for all populations, particularly those with limited mobility or frailty, thus respiratory muscle training has been tested as an alternative and shown promise in these vulnerable populations [3]. Additionally, respiratory muscle training has been shown to further enhance respiratory function in exercise-competent populations when combined with exercise, even in trained athletes [4].
The training paradigms used across clinical studies have been highly variable, in part, because respiratory muscle training needs to be tailored to the capacity and goals of an individual [1]. Use of long sessions with high resistance loads could be detrimental in vulnerable populations [3], while the use of loads that are too low or sessions that are short may be insufficient to produce gains in healthy populations. Larger scale, longer duration studies are needed to determine the optimal training paradigms for different conditions [4].

A short duration, high-intensity form of IMST has recently been tested, and found to show relatively consistent results across studies in healthy adult populations [5]. This time-efficient protocol only takes about five minutes per day. The high-intensity IMST studies, and a large percentage of other inspiratory muscle training studies have used inspiratory threshold devices from PowerBreathe©. However, different devices are better suited for different types of respiratory muscle training protocols. Due to the heterogeneity in device and training paradigms across studies, head-to-head comparisons cannot be made, at this time. It is also unclear whether the combination of inspiratory and expiratory training is superior to inspiratory training alone, as the results have been mixed across studies. It may depend on the desired outcomes.

Neuroprotective Benefit: IMST has not been tested for cognitive outcomes but can improve respiratory function in individuals with neurodegenerative disease, and may mitigate vascular-related dementia risk factors.

Types of evidence:

- 2 systematic reviews on the use of respiratory muscle training in neurodegenerative diseases

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

The ability of IMST to impact cognition, rates of cognitive decline, and dementia risk have not yet been examined. Based on the ability of IMST to impact cardiovascular risk factors common to both cardiovascular disease and vascular dementia [1], it could potentially help reduce the risk of cognitive impairment related to vascular dysfunction.

Human research to suggest benefits to patients with dementia:

IMST has not yet been formally tested in dementia patients.

Inspiratory muscle training has been tested in patients with neurodegenerative diseases that can negatively impact respiratory function, including Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis [6; 7]. These training paradigms have shown benefits in improving respiratory strength and/or endurance, but impacts to neurological function were not evaluated.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The potential neuroprotective benefits of inspiratory muscle training stem from the proposed impacts of this technique on reducing vascular inflammation and oxidative stress [1], as these factors can negatively affect neuronal function.

APOE4 interactions: Not established

Aging and related health concerns: Respiratory muscle training can improve respiratory capacity and improve outcomes in adults with chronic conditions. Some paradigms can also reduce blood pressure and improve vascular function.

Types of evidence:
- 3 meta-analyses of clinical studies testing respiratory muscle training in healthy adults
- 3 systematic reviews and meta-analyses of clinical studies in stroke
- 3 systematic reviews and meta-analyses of clinical studies in postoperative patients
- 2 systematic reviews and meta-analyses in asthma
- 2 systematic reviews and meta-analyses in heart failure
- 2 systematic reviews and meta-analyses of clinical studies in athletes
- 1 systematic review and meta-analysis of clinical studies in obstructive sleep apnea
- 1 systematic review and meta-analysis of clinical studies in MS and ALS
- 1 systematic review of clinical studies in Parkinson's disease
- 1 systematic review and meta-analysis of clinical studies in COPD
- 1 meta-analysis of clinical studies in Duchene muscular dystrophy
- 1 systematic review and meta-analysis of clinical studies in spinal cord injury
- 1 systematic review and meta-analysis of clinical studies in critically ill adults
- 1 retrospective analysis of clinical studies testing high-intensity IMST in healthy adults
- 3 clinical trials in healthy adults
- 2 RCTs in obstructive sleep apnea
- 1 RCT in stable asthma
- 1 RCT in heart failure
- 1 RCT in long covid

Cardiovascular: BENEFITS FOR BLOOD PRESSURE AND ENDOTHELIAL FUNCTION
High-intensity IMST has been shown to reduce blood pressure in old and young men and women [5]. The reductions seen for this short (~five minutes/day) intervention were on par or exceeded the effects seen from other lifestyle interventions, such as aerobic exercise. The mechanism appears to involve reductions in vascular inflammation and oxidative stress, though the impact of the intervention on related plasma markers has been inconsistent [1]. The regulation of the autonomic nervous system also appears to play a role. Longer duration, large-scale studies are needed to determine the full scope of cardiovascular benefits from IMST, and which populations are most likely to benefit.

Blood pressure: A retrospective analysis of seven studies (n=248 participants) testing IMST at 75% maximum inspiratory pressure (PImax) (30 breaths per day, five to seven days per week) for six weeks in adults found that this training had a large effect on systolic blood pressure (Standardized mean difference [SMD] SMD 1.82) relative to sham interventions, which corresponds to a reduction of 9 ± 6 mmHg from baseline [5]. Diastolic blood pressure also showed a mean reduction of 4 ± 4 mmHg from baseline with IMST. The effects on systolic blood pressure were most pronounced in older adults. The effects on blood pressure were not significantly associated with improvements in respiratory muscle strength, based on gains to maximal inspiratory pressure.

In an RCT (NCT03266510) testing IMST at high (75% PImax) or low (15% PImax) resistance for six weeks in middle age to older adults (n=36) (age 50 to 79) with elevated systolic blood pressure (≥120 mmHg), the high resistance training significantly reduced resting systolic blood pressure (from 135±2 mm Hg to 126±3 mm Hg, P<0.01), and had a more modest effect on diastolic blood pressure (from 79±2 mm Hg to 77±2 mm Hg, P=0.03) [8]. The reduction in systolic blood pressure was largely maintained for at least six weeks after the end of the study (128±4 mm Hg, P<0.01). Similar trends were seen with daytime, nighttime, and 24-hour blood pressure measures. The IMST intervention involved 30 breaths per day, with five sets of six inspiratory bouts with one minute rest between sets using the POWERbreathe© K3 series inspiratory muscle training device.

In healthy young adults (age: 22 ± 2 years), a single bout of high resistance (75% PImax, five sets of six inspiratory bouts) IMST using a Hans Rudolph 2600 series two-way nonrebreathing valve with flow limitation cap did not significantly affect blood pressure [8]. However, it did lower heart rate from 85.4 ± 13.6 beats/min to 68.4 ± 11.7 beats/min, and muscle sympathetic nerve activity (MSNA) from 6.8 ± 1.1 bursts/15 s bin to 3.6 ± 0.6 bursts/15 s bin. The autonomic nervous system impacts blood pressure by regulating vascular tone. Activation of the sympathetic nervous system leads to vasoconstriction, while the parasympathetic nervous system promotes vasodilation. MSNA tends to increase with age, and is an important contributor to blood pressure during exercise. Thus, the decrease in MSNA seen with IMST is indicative of an effect on sympathetic drive, which may partially underlie the effect on blood pressure seen in longer duration studies. In this study, the effect on MSNA lasted longer in females.

Endothelial function: The effect of IMST on endothelial function was assessed in the RCT (NCT03266510) testing IMST in middle age to older adults with systolic hypertension [9]. Brachial artery flow mediated dilation (FMDBA) as expressed as a percent change in brachial artery diameter was found to be about 45% higher relative to baseline with the IMST intervention. The effect was greatest in postmenopausal women without hormonal replacement therapy (57%). This is particularly notable because this group of women tends to be the least responsive to the vascular benefits of aerobic exercise. However, unlike the effects on blood pressure, the effect on FMDBA was not sustained after training cessation. Reductions in the bioavailability of nitric oxide drive aging-related vascular endothelial dysfunction. High levels of reactive oxygen species (ROS), which are a common feature of aged tissues, negatively impact the induction of endothelial nitric oxide synthase (eNOS). Human umbilical vein endothelial cells cultured with serum derived from study participants showed higher levels of nitric oxide bioavailability with the IMST intervention (+17% vs +7% sham). The cells treated with serum from IMST participants also exhibited greater eNOS activation (p-eNOSser1177), and lower levels of ROS activity. Plasma metabolomics indicated an increase in levels of L-ornithine (1.33±0.09-fold change), which is a precursor for the nitric oxide substrate, L-arginine. Other notable impacted metabolites included the microbial metabolite indole (1.31±0.17-fold change), which has been reported to lower blood pressure, and the short-chain fatty acid, hexanoic acid (1.36±0.16-fold change), which is reported to have anti-inflammatory properties. A general anti-inflammatory effect of the IMST intervention was indicated by a 30% reduction in plasma C-reactive protein, although other circulating inflammation-related markers, such as IL-6 and TNFα, were not affected. Arterial stiffness, as measured by carotid artery compliance, and the beta stiffness index, was also not significantly impacted by the IMST intervention. However, at six weeks, the intervention may have been too short, as other lifestyle interventions require at least three months to show effects on these measures [1].

Respiratory function: BENEFIT
Respiratory muscle training has been shown to improve respiratory muscle strength, respiratory muscle endurance, functional capacity, and quality of life in a wide variety of groups [1]. Its ability to impact lung function appears to be mixed or marginal, suggesting that the respiratory benefits stem from improving the function of the respiratory muscles, rather than the lungs. IMST is primarily designed to improve respiratory muscle strength, and based on measures of maximal inspiratory pressures, this technique has successfully been used in a wide variety of populations, from the critically ill to elite athletes, to improve respiratory muscle strength. Individuals with weaker respiratory strength have shown the most benefit in trials [4], however, this may be a reflection of the training protocols not being adequately tailored to the individual in these studies. While there is likely a ceiling effect at play, individuals with higher baseline aerobic capacity may require more intense (i.e. higher resistance and/or longer duration) training sessions to see a similar degree of improvement. Since impaired respiratory capacity negatively impacts other organ systems, the preservation of respiratory capacity appears to impact overall health outcomes in many chronic conditions.

Maximal inspiratory pressure is measured via an easy to perform, non-invasive test involving a forceful inspiration against an occluded mouthpiece. The device is calibrated by a manometer, in which pressure is measured by the distance moved by water in a glass tube, which is why inspiratory and expiratory pressure readings are given by the units cmH_2O. Based on a systematic review of 22 studies (n=840), reference ranges were established for maximal inspiratory pressure in healthy adults [10]. The reference ranges are relatively wide due to variability across studies. Reference values do not appear to vary by ethnicity [11].

Healthy adults: A regression analysis of 46 studies using different forms of respiratory muscle training in healthy adults found that less fit individuals showed greater relative benefit compared to trained athletes (6.0% per 10mL/kg· min decrease in maximal oxygen uptake, 95% confidence interval [CI] 1.8 to 10.2%; p = 0.005), and that respiratory strength training and endurance training showed a similar degree of benefit [4]. The combination of inspiratory and expiratory muscle strength training was superior to inspiratory strength training alone, based on six studies (+12.8%, 95% CI 3.6 to 22.0%; p = 0.006).
In healthy older adults (>60 years old), a meta-analysis of seven studies (n=212 participants) found that inspiratory muscle strength training using a threshold inspiratory loading device from 30 to 80% PImax from five to eight weeks improved maximal inspiratory muscle pressure, with an average increase of 26.3 ± 4.9 cm H_2O compared to an increase of 3.7 ± 4.1 cm H_2O in controls, resulting in an effect size of 3.03 (95% CI 2.44 to 3.61; p < 0.001) [12]. The impact on functional (exercise) capacity was less clear, as the increase in walking distance on the 6-minute walk test (24.7 ± 22.1 m vs. 9 ± 8.6 m) was not significant, but this was based on only three studies (n=101), with very high heterogeneity across the studies. Similarly, a meta-analysis of seven RCTs examining inspiratory muscle training from 30 to 80% PImax in older adults (age 64-88) found that this type of training increased inspiratory muscle strength as well as diaphragmatic thickness, based on ultrasound [13]. There did not appear to be a significant effect on pulmonary measures, based on spirometry, and due to heterogeneity in study designs, clear trends on other outcomes could not be established.
A meta-analysis of six studies (n=117) examining the effect of IMST with the PowerBreathe® threshold device on respiratory parameters in athletes found that significant improvements up to 54% in maximum inspiratory pressure were seen within four weeks of training, while improvements in maximal volume of oxygen (VO_2max) were seen within six weeks, and associated with the gains in maximum inspiratory pressure [14]. A study in healthy young adults (age 21.1 ± 2.5; n=10) found that IMST at 75% PImax with a low-volume, high-intensity paradigm of 30 inspirations/day, five days/week for six weeks using a Hans Rudolph 2600 series two-way nonrebreathing valve with flow limitation cap led to significant gains in respiratory muscle endurance on tests to exhaustion (from 362.0 ± 46.6 s to

663.8 ± 110.3 s; p = 0.003) coupled with increases in respiratory muscle work (from −9445 ± 1562 mmHg.s to −16648 ± 3761 mmHg.s; p = 0.069) [15].

Heart Failure: A meta-analysis of 13 RCTs testing inspiratory muscle training at maximal loads between 30 and 100% for between four and 12 weeks long found that this type of training improved maximal inspiratory pressure (+25.12 cmH_2O, 95% CI 15.29 to 34.95), and exercise capacity based on distance walked in the 6-minute walk test (+81.18 m; 95% CI 9.73 to 152.63) in patients with heart failure [16]. Maximum oxygen consumption (VO_2max) was also increased by 3.75 mL/kg/min (95% CI 2.98 to 4.51) and quality of life increased based on the Minnesota living with heart failure questionnaire (MLHFQ) (−20.68, 95% CI −29.03 to −12.32) in the 12-week long intervention studies. Most studies did not see improvements in pulmonary function. Similarly, a meta-analysis of 13 RCTs assessing exercise training interventions in patients with heart failure with preserved ejection fraction found that inspiratory muscle training improved peak oxygen uptake (Mean difference [MD] 2.72 ml/kg/min, 95% CI 1.44 to 3.99; p <0.001). Inspiratory muscle training also improved the ventilation/carbon dioxide ratio slope (MD 3.36 ml/kg/min, 95% CI –6.17 to –0.54; p = 0.019) [17], in which higher slopes are associated with a greater risk for cardiopulmonary morbidity [9].
An RCT tested inspiratory muscle strength and endurance training paradigms using the POWERbreathe® Classic low resistance threshold device for eight weeks in patients with heart failure plus a pacemaker (n=36) [18]. The IMST paradigm was done at 50% maximum inspiratory pressure for 10 to 15 diaphragmatic breaths per set with a 10 to 15 second break between sets for 30 minutes. The endurance training protocol (IMET) was done at 30% maximum inspiratory pressure for 20 to 25 diaphragmatic breaths per set with a 10 to 15 second rest between sets for 30 minutes. Both groups showed improvements in maximum inspiratory pressure (IMST: +26.20 ± 14.91 cmH_2O; IMET: +24.28 ± 13.22 cmH_2O), maximum expiratory pressure, respiratory muscle endurance, peripheral muscle strength, 6-minute walk test and incremental shuttle walk test walking distances, dyspnea, quality of life, physical activity level, and fatigue scores. There were no significant differences in these measures between the two paradigms, and no significant improvements on measures of pulmonary function.

Stroke: A meta-analysis of nine studies found that respiratory muscle training done between 20 to 40 minutes per day, five to seven times per week for at least six weeks was associated with short term improvements in respiratory muscle function in stroke patients [19]. There were significant improvements in inspiratory muscle strength (SMD 0.65, 95% CO 0.17 to 1.13; based on nine studies n=344), inspiratory muscle endurance (SMD 1.19, 95% CI 0.71 to 1.66; based on three studies, n=81), diaphragm thickness (SMD 0.9, 95% CI 0.43 to 1.37; based on three studies, n=79), and peak expiratory

flow (SMD 0.55, 95% CI 0.03 to 1.08; based on three studies n=84). There were no consistent effects on pulmonary function, nor were the improvements maintained in the medium term. The combination of inspiratory and expiratory training appeared to be superior to inspiratory training alone in this analysis. A meta-analysis of 19 studies (n=943 participants) examined the impact of respiratory muscle training consisting of inspiratory muscle training or a combination of inspiratory and expiratory muscle training beginning at 30% P1max/PEmax on respiratory function in stroke patients [20]. Significant improvements were seen in maximal expiratory pressure (pooled effect size [ES] 0.55, 95% CI 0.12 to 0.98), maximal inspiratory pressure (ES 0.84, 95% CI 0.44 to 1.24), and functional capacity based on the 6-minute walk test (pooled ES 0.39, 95% CI 0.05 to 0.74). Improvements were also seen in pulmonary function, including the first second forced expiratory volume (FEV1) (pooled ES 0.57, 95% CI 0.24 to 0.90), and forced vital capacity (FVC) (pooled ES 0.32, 95% CI 0.06 to 0.58). Significant effects were not seen on the Barthel index of activities of daily living, the Berg balance scale, or measures of dyspnea. On the majority of outcomes, there were no significant differences in the effect sizes for inspiratory only compared to inspiratory plus expiratory training studies.
A meta-analysis of five trials (n=263 participants) using respiratory muscle training via threshold devices (generally about 30 minutes per week, five times per week) in stroke patients with respiratory weakness found that this training increased maximal inspiratory pressure by 7 cmH_2O (95% CI 1 to 14) and maximal expiratory pressure by 13 cmH_2O (95% CI 1 to 25) [21]. The respiratory training was also associated with a reduction in the risk for respiratory complications (Relative risk [RR] 0.38, 95% CI 0.15 to 0.96).

Critically ill: Inspiratory muscle training has been used in a critical care setting, particularly for preventing mechanical ventilation and helping to wean patients off ventilation [3]. A systematic review and meta-analysis of 28 studies (n=1,185 participants) assessed the efficacy and safety of inspiratory muscle training in critically ill patients (age 35- 82). An improvement in maximal inspiratory pressure was seen in RCTs, with an average increase of 6 cmH_2O (95% CI 5 to 8), as well as an increase in maximal expiratory pressure (9 cmH_2O, 95% CI 5 to 14). This type of training was also associated with a shorter duration of ventilation (4.1 days, 95% CI 0.8 to 7.4), and a shorter duration of weaning from ventilation (2.3 days, 95% CI 0.7 to 4.0).

Neurodegenerative diseases: Respiratory dysfunction is a common feature of many neurodegenerative diseases in later stages of the disease course. Studies suggest the respiratory muscle training may help improve respiratory function in these patients, though it may not be as effective once severe degeneration of respiratory-controlling neurons and/or muscle has taken place.

A meta-analysis of nine RCTs (n=194), in which six included patients with multiple sclerosis and three included patients with amyotrophic lateral sclerosis examined the impact of respiratory (inspiratory and/or expiratory) muscle training on respiratory parameters [7]. Significant increases were seen in maximal inspiratory pressure (23.50 cmH_2O, 95% CI 7.82 to 39.19; based on eight studies, n=194) and maximal expiratory pressure (12.03 cmH_2O, 95% CI 5.50 to 18.57; based on seven studies, n=175). The effects on measures of pulmonary function (FEV1, FVC) were inconsistent. A systematic review of studies examining the impact of respiratory training on patients with Parkinson's disease found that three RCTs testing IMST saw significant positive effects on their primary outcomes, including maximal inspiratory pressure, inspiratory muscle endurance, and peak subglottic pressure [6]. A meta-analysis of six RCTs (n=124 participants) tested inspiratory muscle training ranging from 10 to 30 minutes per day at 40% to 80% maximum inspiratory pressure for four to eight weeks in adults with spinal cord injury [22]. A significant improvement was seen on maximum inspiratory pressure (MD 15.72 cmH_2O, 95% CI 5.02, 26.41; $p = 0.004$) relative to controls, but there were no significant effects on physical or mental quality of life, and maximal expiratory pressure, though variation in the latter may have been impacted by the location of the spinal injury. Improvements in inspiratory muscle endurance and strength were seen in patients with the neuromuscular disorder Duchenne muscular dystrophy based on a meta-analysis of six studies including 100 patients, though the effects did not reach statistical significance [3]. Based on the variability across patients, the intervention may need to be administered early in the disease course to be effective.

Asthma: A meta-analysis of 11 studies (n=270 participants) examining respiratory training interventions in individuals with asthma found that inspiratory muscle training increased maximal inspiratory pressure (MD 21.95 cmH_2O, 95% CI 15.05 to 28.85), but did not significantly impact expiratory pressure, or measures of pulmonary function, including FEV1 and FVC [23]. A beneficial impact on exercise capacity was seen in studies using a training regimen with >50% PImax for at least six weeks. Impacts on asthma symptoms/exacerbations and use of rescue medication were inconsistent or absent. Similarly, a Cochrane systematic review of five RCTs (n=113 participants) testing inspiratory training devices in adults with asthma indicated a positive impact on maximal inspiratory pressure (MD 13.34 cmH_2O, 95% CI 4.70 to 21.98, based on four studies, n=84), but not on expiratory or pulmonary measures [24]. The impact on exacerbations or use of rescue medication was not adequately addressed in the included studies. An RCT tested inspiratory muscle training at 30 breaths per day at the limit of tolerance relative to conventional breathing exercises (i.e. diagrapmagnitc and pursed lip breathing) at 50-60% PImax for 12 weeks [25]. Inspiratory muscle training resulted in a greater increase in respiratory muscle strength, based on maximal inspiratory pressure, by +29.84% (95% CI 71.19 to 101.03%) and +16.92% (95% CI

82.45 to 99.38%), respectively. Benefits were similar between the groups for other measures, such as asthma control and exercise capacity.

COPD: A meta-analysis involving 37 studies testing inspiratory muscle training ranging from 30 to 80% PImax for one week to one year in patients with chronic obstructive pulmonary disease (COPD) found that the intervention led to clinically relevant improvements in maximal inspiratory pressure (MD 12.00 cmH_2O, 95% CI 10.02 to 13.97), the Baseline Dyspnea Index (MD 2.30, 95% CI 1.67 to 2.93), the Saint George's Respiratory Questionnaire for quality of life (MD -2.40, 95% CI -4.89to 0.09), and exercise capacity based on the 6-minute walk test (MD 42.68 m, 95%CI 16.90 to 68.47) [26]. However, these benefits overlapped with those from pulmonary rehabilitation, and did not offer additional or synergistic benefits relative to pulmonary rehabilitation alone.

Long-Covid: An RCT testing respiratory muscle training using the POWERbreathe KH1© device for two 20-minute sessions per day six times per week for eight weeks in patients with long covid (n=88) (NCT04734561) found that the intervention improved inspiratory and expiratory muscle strength and endurance, and reduced dyspnea approximately five-fold [27]. However, there were no statistically significant improvements in exercise tolerance or fatigue. Combined inspiratory and expiratory training was superior to inspiratory training alone, in this study.

Athletic/Exercise performance: BENEFIT TO AEROBIC CAPACITY
IMST was originally investigated as an ergogenic aid to enhance athletic performance [1]. A systematic review and meta-analysis of 46 studies examining the effect of respiratory muscle training on exercise performance found that respiratory muscle training improves exercise performance in healthy adults (SMD 1.11, 95% CI 0.61 to 1.61; $p < 0.001$) [4]. The improvements were seen in both sedentary adults and professional athletes, though effect sizes were larger for the former, and consistent across a wide array of sports, including cycling, running, rowing, and swimming. A systematic review and meta-analysis of six studies (n=117) testing inspiratory muscle training using a PowerBreathe© threshold training device in athletes found that significant improvements were seen in maximal aerobic capacity, as measured by VO_2max, following six weeks of training (ratio of means 1.12, 95% CI 0.93 to 1.35) [15]. The improvement in aerobic capacity was associated with gains in maximal inspiratory pressure, such that those who showed increases of ≥21.5% were more likely to also show gains in VO_2max. Resistance to fatigue was also seen with training, as measured by a decrease in blood lactate concentrations, particularly in those who had achieved a maximal inspiratory pressure gain of ≥6.8%. A separate meta-analysis of nine studies (n=191) testing respiratory muscle training paradigms in soccer players, also

showed significant enhancements in maximal inspiratory pressure and maximal oxygen consumption with training [28]. Significant impacts to measures of pulmonary function were not seen.
The impact on exercise and athletic performance is thought to stem primarily from the mitigation of the muscle metaboreflex [1; 14]. When respiratory muscles fatigue, the body redistributes blood from the skeletal muscles to the respiratory muscles, leading to reduced oxidative capacity and higher rates of lactate production in the locomotor muscles, resulting in fatigue. The strengthening of the respiratory muscles allows for lower rates of fatigue with prolonged exertion, such that the blood can continue to supply the skeletal muscles at the level required to maintain exercise performance.

Sleep apnea: POTENTIAL BENEFIT FOR SLEEP AND RESPIRATORY STRENGTH
A meta-analysis of seven studies (n=185 participants) examined the effects of inspiratory muscle training at 30 to 70% PImax for six to 12 weeks in patients with obstructive sleep apnea [29]. Improvements were seen on the Epworth sleepiness scale (−4.45 points, 95% CI −7.64 to −1.27; $p = 0.006$), the Pittsburgh sleep quality index (−2.79 points, 95% CI −4.19 to −1.39; $p < 0.0001$), and in maximal inspiratory pressure (−29.56 cmH_2O, 95% CI −53.14 to −5.98; $p = 0.01$). However, consistent improvement was not seen on the apnea/hypopnea index (AHI) (MD −2.09 events/h, 95% CI −9.40 to 5.23; $p = 0.58$).
An RCT tested high-intensity IMST of 75% PImax relative to 15% PImax at 30 breaths per day (five sets of six breaths, with one minute break in between sets) five days/week for six weeks using the POWERbreathe training device© (K3 Series) in older adults (age 60-80) with moderate severity obstructive sleep apnea (n=25) (NCT02709941) [30]. In the high-intensity group (75% PImax) there were reductions in resting systolic blood pressure (−8.82 ± 4.98 mmHg), nighttime systolic blood pressure (−12.00 ± 8.20 mmHg), diastolic blood pressure (−4.69 ± 2.81 mmHg), and mean arterial blood pressure (−6.06 ± 1.03 mmHg) relative to baseline. There was also a reduction in muscle sympathetic nerve activities (MSNA), suggestive of an effect on autonomic function (6.97 ± 2.29 bursts/min−1). These effects were not seen in participants in the low-intensity group (15% PImax). Neither intervention significantly impacted measures of awake and resting oxygen desaturations, sleep duration, pulmonary function, heart rate, or baroreceptor sensitivity.
A separate RCT tested IMST with or without continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea (n=65) for 12 weeks (NCT04457583) [31]. The IMST intervention involved progressive resistive loads of 40-70% PImax using the POWERbreathe® classic for 30 breaths once per day. With the IMST intervention, maximal inspiratory pressure increased relative to baseline in both the CPAP (from 82 cmH_2O, 95% CI 62 to 104; to 95 cmH_2O, 95% CI 77 to 121) and non-CPAP users (from 93 cmH_2O, 95% CI 66 to 120; to 129 cmH_2O, 95% CI 79 to 148). Median AHI was also reduced in

the IMST intervention groups in both CPAP (from 53 events/hour, 95% CI 31 to 63, to 17 events/hour, 95% CI 15 to 40) and non-CPAP users (from 29 events/hour, 95% CI 21 to 34; to 21 events/hour, 95% CI 17 to 32). Improvements in sleep quality based on the Epworth sleepiness scale in CPAP (from 14, 95% CI 7 to 17; to 6, 95% CI 5 to 9) and non-CPAP users: (from 8, 95% CI 5 to 11; to 4, 95% CI 4 to 10) and in sleep quality based on the Pittsburgh Sleep Quality Index in CPAP (from 9, 95% CI 7 to 11; to 4, 95% CI 4 to 6) and non-CPAP users (from 6, 95% CI 4 to 9; to 5, 95% CI 3 to 7) were also seen in the IMST intervention groups.
Together these studies suggest that IMST may help improve sleep quality and respiratory muscle strength, but likely requires longer duration training (~12 weeks) for the benefits to become apparent. It is unclear how long the effects persistent following the termination of training. The effects may also be impacted by age and disease severity.

Postoperative complications: BENEFIT FOR REDUCING PULMONARY COMPLICATIONS
A Cochrane systematic review including 12 RCTs (n=695 participants) examined the impact of preoperative inspiratory muscle training using a threshold-loading device with loads between 10 and 60% PImax for the prevention of postoperative complications following elective cardiac or abdominal surgery [32]. The impact of preoperative inspiratory training on all-cause mortality during the postoperative period was unclear (RR 0.40, 95% CI 0.04 to 4.23; based on seven trials, n=443), but it was associated with reductions in collapsed lung (RR 0.53, 95% CI 0.34 to 0.82; based on seven trials, n=443), pneumonia (RR 0.45, 95% CI 0.26 to 0.77; based on 11 trials, n=675), and length of hospital stay (MD -1.33, 95% CI -2.53 to -0.13). A meta-analysis of 17 RCTs (n=853 participants) looked at the role of inspiratory muscle training on postoperative pulmonary complications in patients undergoing cardiac, pulmonary, or abdominal surgeries [33]. The majority of studies used the Powerbreathe® device with a load ranging from 15 to 40% maximal inspiratory pressure. The training was done preoperatively in 12 studies, postoperatively in three studies, and at both times points in two studies. Overall, the use of inspiratory muscle training was associated with reductions in postoperative pulmonary complications (RR 0.50, 95%CI 0.39 to 0.64), and the length of hospital stay (MD −1.41, 95%CI −2.07 to −0.75). Benefits were more apparent with the use of preoperative training. High-risk patients and those having pulmonary surgery appeared to be most impacted. Longer duration inspiratory training, especially when combined with exercise was most effective.
A meta-analysis of five RCTs (n=293 participants) including individuals undergoing cardiac surgery examined the impact of inspiratory muscle training, primarily done postoperatively, on respiratory measures [34]. There was a benefit to exercise capacity based on the distanced covered on the 6-minute walk test relative to control groups (MD 78.05 m, 95% CI, 60.92 to 95.18; based on four trials, n=196).

Benefits were also seen toward measures of pulmonary function, the FEV1(MD 5.80%, 95% CI 2.03 to 9.56) and FVC (MD 3.47%, 95% CI 0.57 to 6.36), however, these were based on the same two RCTs.

Safety: Respiratory muscle training is safe and well-tolerated in a wide variety of adult populations. Frail individuals are most likely to experience adverse events. Training paradigms need to be tailored to the capacity of each individual.

Types of evidence:

- 1 systematic review and meta-analysis of clinical studies in critically ill patients
- 1 Cochrane systematic review of clinical studies in postoperative patients
- 1 systematic review and meta-analysis of clinical studies in spinal cord injury
- 1 systematic review and meta-analysis in asthma
- 1 RCT in heart failure
- 1 RCT in adults with hypertension

Respiratory muscle training paradigms, including IMST, have consistently been well-tolerated in clinical studies, with high compliance rates amongst study participants. No adverse events were reported in the majority of inspiratory muscle training studies, and most studies that included a quality of life component found improvements on those measures [3; 22; 23]. Inspiratory muscle training did not result in shock or fainting when performed by stable patients with heart failure [18]. In an RCT including 36 older adults with hypertension testing high-resistance (75% PImax) IMST, there were two reported treatment-related adverse events, neck soreness and lightheadedness [35]. Both were of minor severity. The treatment effects are not long-lasting, as the intervention-related changes have generally been shown to subside within a few weeks of training cessation [19; 35].

Serious adverse events have only been reported in critically ill patient populations [3]. These have generally occurred in the context of prolonged flow resistive or threshold loading inspiratory muscle training in patients with breathing or circulatory abnormalities, resulting in paradoxical breathing, rapid breathing, oxygen desaturation, or hemodynamic instability. Thus, high intensity/resistance IMST paradigms may not be appropriate for frail populations.

Drug interactions: Interactions have not been established

Sources and dosing:

IMST is most commonly performed using a threshold-loading device. Devices that have been successfully tested in clinical studies include the inspiratory muscle trainer PFLEX from Respironics (discontinued), the inspiratory muscle trainer Respifit S, the inspiratory and expiratory muscle trainer Orygen Dual Valve, the respiratory muscle trainer SpiroTiger®, the respiratory muscle trainer TRAINAIR®, and the inspiratory muscle trainers from PowerBreathe©, including the PowerBreathe© classic and the K3 series. Head-to-head comparisons of the various devices have not been performed, so it is unclear if one of these devices is clinically superior. PowerBreathe© is the most extensively tested brand of inspiratory muscle trainer, and the trainer most frequently used in high-intensity IMST clinical studies. The primary protocol, which has resulted in benefits on measures of maximal inspiratory pressure and blood pressure in a variety of populations involves training at 75% PImax for 30 inspiratory bouts per day involving five sets of six breaths, with a one-minute break between sets for five to seven days per week. Improvements on some measures can be seen within six weeks, but others require at least 12 weeks. Aside from blood pressure, the maintenance of the beneficial effects appears to require continual use.

Research underway:

According to Clinicaltrials.gov, there are currently 129 active clinical trials testing inspiratory muscle training in numerous conditions, including Covid-19, heart failure, chronic kidney disease, postsurgical complications, COPD, lung transplant, obesity, and ventilated patients, among others. There are five studies specifically assessing IMST for various conditions, including stroke, chronic kidney disease, vascular parameters in postmenopausal women, blood pressure, and sleep apnea.

Search terms:
Pubmed, Google: Inspiratory muscle training, IMST

- Neurodegenerative disease, cardiovascular, aging, meta-analysis, systematic review, clinical trial

Websites visited for IMST:

- Clinicaltrials.gov

References:

1. Craighead DH, Freeberg KA, McCarty NP *et al.* (2021) Time-efficient, high-resistance inspiratory muscle strength training for cardiovascular aging. *Experimental gerontology* **154**, 111515https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9150656/.

2. van der Palen J, Rea TD, Manolio TA *et al.* (2004) Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax* **59**, 1063-1067https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1746892/.

3. Williamson E, Pederson N, Rawson H *et al.* (2019) The Effect of Inspiratory Muscle Training on Duchenne Muscular Dystrophy: A Meta-analysis. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association* **31**, 323-330https://pubmed.ncbi.nlm.nih.gov/31568374/.

4. Illi SK, Held U, Frank I *et al.* (2012) Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis. *Sports medicine (Auckland, NZ)* **42**, 707-724https://pubmed.ncbi.nlm.nih.gov/22765281/.

5. Craighead DH, Tavoian D, Freeberg KA *et al.* (2022) A multi-trial, retrospective analysis of the antihypertensive effects of high-resistance, low-volume inspiratory muscle strength training. *Journal of applied physiology (Bethesda, Md : 1985)* **133**, 1001-1010https://pubmed.ncbi.nlm.nih.gov/36107991/.

6. van de Wetering-van Dongen VA, Kalf JG, van der Wees PJ *et al.* (2020) The Effects of Respiratory Training in Parkinson's Disease: A Systematic Review. *Journal of Parkinson's disease* **10**, 1315-1333https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7683068/.

7. Ferreira GD, Costa AC, Plentz RD *et al.* (2016) Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis. *Physiotherapy* **102**, 221-228https://pubmed.ncbi.nlm.nih.gov/27026167/.

8. DeLucia CM, DeBonis DR, Schwyhart SM *et al.* (2021) Acute cardiovascular responses to a single bout of high intensity inspiratory muscle strength training in healthy young adults. *Journal of applied physiology (Bethesda, Md : 1985)* **130**, 1114-1121https://pubmed.ncbi.nlm.nih.gov/33600284/.

9. Torchio R, Mazzucco A, Guglielmo M *et al.* (2017) Minute ventilation to carbon dioxide output (V'E/V'CO2 slope) is the strongest death predictor before larger lung resections. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace* **87**, 817https://pubmed.ncbi.nlm.nih.gov/29424191/.

10. Sclauser Pessoa IM, Franco Parreira V, Fregonezi GA *et al.* (2014) Reference values for maximal inspiratory pressure: a systematic review. *Canadian respiratory journal* **21**, 43-50https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3938239/.

11. Sachs MC, Enright PL, Hinckley Stukovsky KD *et al.* (2009) Performance of maximum inspiratory pressure tests and maximum inspiratory pressure reference equations for 4 race/ethnic groups. *Respiratory care* **54**, 1321-1328https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3616895/.

12. Manifield J, Winnard A, Hume E *et al.* (2021) Inspiratory muscle training for improving inspiratory muscle strength and functional capacity in older adults: a systematic review and meta-analysis. *Age and ageing* **50**, 716-724https://pubmed.ncbi.nlm.nih.gov/33951159/.

13. Seixas MB, Almeida LB, Trevizan PF *et al.* (2020) Effects of Inspiratory Muscle Training in Older Adults. *Respiratory care* **65**, 535-544https://pubmed.ncbi.nlm.nih.gov/31662444/.

14. Fernández-Lázaro D, Gallego-Gallego D, Corchete LA *et al.* (2021) Inspiratory Muscle Training Program Using the PowerBreath(®): Does It Have Ergogenic Potential for Respiratory and/or Athletic Performance? A Systematic Review with Meta-Analysis. *International journal of environmental research and public health* **18**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8297193/.

15. DeLucia CM, Tavoian D, Debonis DR *et al.* (2022) A short course of high-resistance, low-volume breathing exercise extends respiratory endurance and blunts cardiovascular responsiveness to constant load respiratory testing in healthy young adults. *Respiratory physiology & neurobiology* **307**, 103974https://pubmed.ncbi.nlm.nih.gov/36180018/.

16. Azambuja ACM, de Oliveira LZ, Sbruzzi G (2020) Inspiratory Muscle Training in Patients With Heart Failure: What Is New? Systematic Review and Meta-Analysis. *Physical therapy* **100**, 2099-2109https://pubmed.ncbi.nlm.nih.gov/32936904/.

17. Zhuang C, Luo X, Wang Q *et al.* (2021) The effect of exercise training and physiotherapy on diastolic function, exercise capacity and quality of life in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Kardiologia polska* **79**, 1107-1115https://pubmed.ncbi.nlm.nih.gov/34472077/.

18. Katayıfçı N, Boşnak Güçlü M, Şen F (2022) A comparison of the effects of inspiratory muscle strength and endurance training on exercise capacity, respiratory muscle strength and endurance, and quality of life in pacemaker patients with heart failure: A randomized study. *Heart & lung : the journal of critical care* **55**, 49-58https://pubmed.ncbi.nlm.nih.gov/35472660/.

19. Fabero-Garrido R, Del Corral T, Angulo-Díaz-Parreño S *et al.* (2022) Respiratory muscle training improves exercise tolerance and respiratory muscle function/structure post-stroke at short term: A systematic review and meta-analysis. *Annals of physical and rehabilitation medicine* **65**, 101596https://pubmed.ncbi.nlm.nih.gov/34687960/.

20. Pozuelo-Carrascosa DP, Carmona-Torres JM, Laredo-Aguilera JA *et al.* (2020) Effectiveness of Respiratory Muscle Training for Pulmonary Function and Walking Ability in Patients with Stroke: A Systematic Review with Meta-Analysis. *International journal of environmental research and public health* **17**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7432552/.

21. Menezes KK, Nascimento LR, Ada L *et al.* (2016) Respiratory muscle training increases respiratory muscle strength and reduces respiratory complications after stroke: a systematic review. *Journal of physiotherapy* **62**, 138-144https://pubmed.ncbi.nlm.nih.gov/27320833/.

22. Woods A, Gustafson O, Williams M *et al.* (2022) The effects of inspiratory muscle training on inspiratory muscle strength, lung function and quality of life in adults with spinal cord injuries: a systematic review and Meta-analysis. *Disability and rehabilitation*, 1-12https://pubmed.ncbi.nlm.nih.gov/35931101/.

23. Lista-Paz A, Cousilla LB, Jácome C *et al.* (2022) Effect of respiratory muscle training in asthma: a systematic review and meta-analysis. *Annals of physical and rehabilitation medicine*, 101691https://pubmed.ncbi.nlm.nih.gov/35843501/.

24. Silva IS, Fregonezi GA, Dias FA *et al.* (2013) Inspiratory muscle training for asthma. *The Cochrane database of systematic reviews* **2013**, Cd003792https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7163283/.

25. Chung Y, Huang TY, Liao YH *et al.* (2021) 12-Week Inspiratory Muscle Training Improves Respiratory Muscle Strength in Adult Patients with Stable Asthma: A Randomized Controlled Trial. *International journal of environmental research and public health* **18**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8004228/.

26. Beaumont M, Forget P, Couturaud F *et al.* (2018) Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *The clinical respiratory journal* **12**, 2178-2188https://pubmed.ncbi.nlm.nih.gov/29665262/.

27. Del Corral T, Garrido RF, Plaza-Manzano G *et al.* (2022) Home-based respiratory muscle training on quality of life and exercise tolerance in long-term post-COVID-19: Randomized controlled trial. *Annals of physical and rehabilitation medicine*, 101709https://pubmed.ncbi.nlm.nih.gov/36191860/.

28. León-Morillas F, León-Garzón MC, Del Mar Martínez-García M *et al.* (2021) Effects of respiratory muscle training in soccer players: a systematic review with a meta-analysis. *Sportverletzung Sportschaden : Organ der Gesellschaft fur Orthopadisch-Traumatologische Sportmedizin* **35**, 154-164https://pubmed.ncbi.nlm.nih.gov/34261153/.

29. Torres-Castro R, Solis-Navarro L, Puppo H *et al.* (2022) Respiratory Muscle Training in Patients with Obstructive Sleep Apnoea: A Systematic Review and Meta-Analysis. *Clocks & sleep* **4**, 219-229https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9036269/.

30. Ramos-Barrera GE, DeLucia CM, Bailey EF (2020) Inspiratory muscle strength training lowers blood pressure and sympathetic activity in older adults with OSA: a randomized controlled pilot trial. *Journal of applied physiology (Bethesda, Md : 1985)* **129**, 449-458https://pubmed.ncbi.nlm.nih.gov/32730174/.

31. Azeredo LM, Souza LC, Guimarães BLS *et al.* (2022) Inspiratory muscle training as adjuvant therapy in obstructive sleep apnea: a randomized controlled trial. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas* **55**, e12331https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9529044/.

32. Katsura M, Kuriyama A, Takeshima T *et al.* (2015) Preoperative inspiratory muscle training for postoperative pulmonary complications in adults undergoing cardiac and major abdominal surgery. *The Cochrane database of systematic reviews* **2015**, Cd010356https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9251477/.

33. Kendall F, Oliveira J, Peleteiro B *et al.* (2018) Inspiratory muscle training is effective to reduce postoperative pulmonary complications and length of hospital stay: a systematic review and meta-analysis. *Disability and rehabilitation* **40**, 864-882https://pubmed.ncbi.nlm.nih.gov/28093920/.

34. Dsouza FV, Amaravadi SK, Samuel SR *et al.* (2021) Effectiveness of Inspiratory Muscle Training on Respiratory Muscle Strength in Patients Undergoing Cardiac Surgeries: A Systematic Review With Meta-Analysis. *Annals of rehabilitation medicine* **45**, 264-273https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8435466/.

35. Craighead DH, Heinbockel TC, Freeberg KA *et al.* (2021) Time-Efficient Inspiratory Muscle Strength Training Lowers Blood Pressure and Improves Endothelial Function, NO Bioavailability, and Oxidative Stress in Midlife/Older Adults With Above-Normal Blood Pressure. *Journal of the American Heart Association* **10**, e020980https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8403283/.

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.