Published in final edited form as:

Cardiopulm Phys Ther J. 2019 January ; 30(1): 44–50. doi:10.1097/CPT.0000000000000092.

Inspiratory Muscle Training in Patients with Prolonged Mechanical Ventilation: Narrative Review

Shakeel Ahmed, PT¹, A. Daniel Martin, PhD, PT¹, and Barbara K. Smith, PhD, PT^{1,2}

¹Departments of Physical Therapy University of Florida, Gainesville, FL, USA

²Departments of Pediatrics, University of Florida, Gainesville, FL, USA

Abstract

Patients with impending respiratory failure often require mechanical ventilation to optimize gas exchange. Although this form of assisted ventilation is required for survival, its persistent use results in diaphragm weakness and muscle fiber atrophy. There is strong evidence that mechanical ventilation alters the structure and function of the diaphragm, resulting in prolonged dependence on assisted ventilation and long-term consequences such as a delayed functional recovery, reduced quality of life and increased risk of mortality. This review summarizes the mechanisms underlying diaphragm dysfunction due to prolonged mechanical ventilation, highlights the role of inspiratory muscle exercise as a strategy to counter diaphragm weakness, and identifies the parameters of an evidence-supported exercise prescription for difficult to wean patients.

Introduction

Mechanical Ventilation (MV) is used to restore or enhance pulmonary gas exchange in patients who are unable to maintain adequate alveolar ventilation. Conditions that necessitate the use of MV include but are not restricted to neuromuscular diseases, respiratory failure secondary to chronic obstructive lung disease and following surgery with general anesthesia [1]. Despite its significance as a lifesaving intervention in intensive care units, MV has been associated with both short- and long-term deleterious consequences in patients who survive critical illness [2]. A high proportion of patients who require prolonged MV for more than 48 hours do not survive for 1 year, and those who survive have a significantly reduced functional status and quality of life [3]. Prolonged MV has a detrimental impact on the diaphragm, and this has been termed as Ventilator-Induced Diaphragmatic Dysfunction (VIDD) [4]. A large body of evidence illustrates that VIDD is a major contributor towards prolonged MV dependence and failure to wean from MV [5].

Address correspondence to: Barbara Smith, PhD, PT; P.O. Box 100154, Gainesville, FL 32610-0154.

Statement of Authorship: Each author has contributed substantially to the structure and composition of this manuscript, and we acknowledge responsibility for its contents

Notification of Conflicts of Interest: ADM is an external consultant for Lungpacer, which is developing an intravenous phrenic nerve pacing system.

Ethical Adherence: This review paper does not require Institutional Review Board approval.

The objectives of this review are to a) highlight the mechanisms underlying MV-induced diaphragm weakness, b) elucidate the clinical consequences of VIDD in humans and c) summarize exercise training to prevent or reverse diaphragm weakness.

Mechanisms of MV induced diaphragm weakness

The potential mechanisms underlying VIDD, summarized in Figure 1, are complex and often interrelated. The application of MV to correct acute alveolar hypoventilation creates passive inflation of the lungs for gas exchange, which can lead to inactivity of the diaphragm and ventilator-induced lung injury, and trigger a systemic inflammatory response [6]. Some underlying causes of critical illness/organ failure, including sepsis, chronic heart failure (CHF), and chronic obstructive pulmonary disease (COPD) appear to directly accelerate diaphragm dysfunction [7]. In result, measurable alterations in mitochondrial function, metabolism, and nutritional availability become apparent [5]. Dysfunction of metabolic and nutritional activity leads to a disruption in protein balance, observed as both a loss of protein synthesis and upregulation of proteolysis resulting in defects in diaphragm fiber cross-sectional area and excitation-contraction coupling [4, 6].

Metabolic and Nutritional Dysfunction in VIDD.

Clinical studies of VIDD have reported increased levels of diaphragm and/or circulating pro-inflammatory cytokines, which can in turn alter nutritional balance [8]. Prolonged invasive ventilation places patients at a high risk for both aspiration [9] and muscle weakness [10] and this often requires delays in feeding or an alternative means of nutrition [11]. Hyperglycemia in critical illness promotes reactive oxidative species (ROS) production and is strongly associated with respiratory muscle weakness, while aggressive insulin therapy may mitigate the severity of weakness [12].

Mitochondrial Dysfunction in VIDD.

Mitochondrial dysfunction also occurs in human diaphragms exposed to MV, as measured by the number and function of mitochondria [13]. The function of key mitochondrial respiratory chain enzymes such as cytochrome-c oxidase and succinate dehydrogenase is significantly reduced in diaphragms exposed to MV [14]. Furthermore, the activity of the enzyme citrate synthase, a key marker of mitochondrial content, is also markedly decreased [13]. Deficient respiratory chain function permits excessive electron leakage from mitochondria, which results in increased ROS production [13, 14].

Role of ROS in VIDD.

With prolonged MV, electron transport chain (ETC) activity decreases and levels of ROS increase in human diaphragms [13]. Elevated levels of ROS enhance the expression of proteins which are needed to activate the ubiquitin-proteasome system and autophagy [15, 16]. ROS increase cytosolic calcium levels, which in turn activate the calpain and caspase 3 proteolytic pathways [4]. In contrast, administration of the Vitamin E analogue Trolox to rodents during the course of MV has been found to prevent MV-induced contractile impairments and proteolysis and attenuate contractile dysfunction of the diaphragm [17].

However, further study is needed to determine whether antioxidants can prevent or mitigate VIDD in humans.

Altered protein balance in the diaphragm

MV has been shown to slow down the rate of protein synthesis diaphragms of rats in as early as 6 hours following the start of MV [18]. To a large extent, regulation of protein synthesis is dependent on contractile activity of muscle, where an increased activity upregulates protein synthesis and decreased contractility suppresses protein synthesis [19]. As MV unloads the diaphragm by taking over the work of breathing, this state of partial or complete inactivity appears to impair synthesis of protein within the muscle. In addition to reduced protein synthesis, exposure to 12 or more hours of MV enhances protein degradation in diaphragms of rats and humans [17, 20]. Both in animal and human studies of prolonged MV, all major proteolytic systems, including the macroautophagy, calpain, caspase and the ubiquitin–proteasome systems are activated [20, 21].

VIDD: Diaphragm contractile dysfunction

The specific force-generating capacity of the diaphragm can be measured by the pressure response to supramaximal stimulation of the phrenic nerves [22]. The muscle fibers of diaphragms exposed to 12 or more hours of MV generate significantly less specific force, compared to patients exposed to less than 4 hours of MV support [23]. However, the rate of force decrement appears to be attenuated with assisted MV modes that permit synchronization of inspiratory efforts with the ventilator [24].

VIDD: Diaphragm fiber atrophy

In conjunction with weakness, structural and biochemical changes to the diaphragm have also been documented in humans on prolonged MV support. First reports of specific diaphragm atrophy came from post-mortem biopsies of neonates who received MV for 12 days or more before death. Significant diaphragm fiber atrophy was seen without evidence of atrophy in other peripheral muscles [25]. Similarly, specific diaphragm fiber atrophy was found in adult organ donors after 2–5 days of controlled MV [21]. Compared to controls who used < 2 hours MV for elective thoracic surgeries, the organ donors had significant atrophy of both slow and fast twitch diaphragm fibers. No atrophy was observed in the pectoralis major muscles of controls. Diaphragm fiber atrophy was associated with signs of increased oxidative stress and an increase in bio markers of muscle proteolysis [21]. Diaphragms of mechanically ventilated patients have also demonstrated the presence of oxidative stress-induced autophagy, and up regulation of the autophagic system was confined only to the diaphragm [20].

Clinical implications of MV induced diaphragmatic dysfunction in humans:

The cellular and molecular changes associated with MV induced diaphragmatic dysfunction have important consequences on the clinical outcomes of patients who are on prolonged MV. Failure to wean from MV is an important clinical consequence of VIDD in humans. An inadequate inspiratory muscle force is a major factor responsible for delayed weaning [26].

Difficulty in weaning from MV is encountered in approximately 20% to 25% of patients who receive MV [27].

Noninvasive measures such as ultrasonography have been used to study the impact of prolonged MV on the structure of the diaphragm. Diaphragms undergo significant thinning within 48 hours of MV, and on average, the mechanically-ventilated diaphragm becomes thinner by 6% per day [28]. Hence, cellular changes such as ROS-induced muscle damage, activation of proteolytic pathways, mitochondrial and contractile dysfunction translate over time into clinically measurable outcomes such as muscle wasting and decreased force-generating capability of the diaphragm. These deficits manifest as difficulty or failure to wean.

Inspiratory muscle strength training (IMST) as a rehabilitative tool in VIDD:

Inspiratory muscle training applies a load to the muscles of inspiration, with the goal to oppose the catabolic effects of MV and diaphragm inactivity, thereby improving fiber activation, cross sectional area, and contractile force. Similar to other peripheral muscles, the diaphragm is susceptible to atrophy and hypertrophy with changes in activation and loading [29]. In a rodent model of respiratory training that briefly loads the diaphragm via intermittent tracheal occlusions, training increased the cross sectional area of diaphragm and parasternal fast, glycolytic fibers [30]. Diaphragm fiber hypertrophy cannot be readily measured in clinical populations, but there is some evidence that the accessory muscles of respiration may hypertrophy following respiratory strengthening exercises [31]. The global strength of the inspiratory muscles can be estimated using maximal inspiratory pressure (MIP), a non-invasive, quick, and inexpensive maximal voluntary contraction test [32]. MIP is a common outcome measure for studies evaluating the effects of IMST. Additionally, MIP is used as a basis to establish a patient's inspiratory exercise training intensity.

The first use of inspiratory exercises in mechanically ventilated patients was reported by Aldrich et al in 1980's. These studies used flow-dependent inspiratory resistive training, in which the exercise load was dependent on a patient's inspiratory flow rate and breathing pattern [33]. Patients initiated training at 15–20% of their peak negative inspiratory pressure, and individual training durations were progressed from 5 minutes to 30 minutes [34]. Seventy-five percent of the sample was successfully weaned from MV, and these individuals had a 24% improvement in their MIP [33]. The inspiratory resistive training protocol used by Aldrich was designed to enhance inspiratory muscle endurance to a greater extent than strength, and this form of resistive inspiratory muscle training has shown to activate the accessory muscles of inspiration more than the diaphragm [35]. Subsequent animal and human studies have identified diaphragm weakness as a primary limiting factor for weaning [36, 37]. Hence, exercise protocols for enhancing diaphragm strength may be more beneficial than endurance exercise to facilitate ventilator weaning.

The type and intensity of inspiratory muscle exercises can impact study outcomes for difficult to wean patients. For example, Caruso studied the effect of twice-daily inspiratory muscle loading on inspiratory muscle strength, weaning duration, and rate of reintubation [38]. Inspiratory muscle loads were delivered by adjusting the triggering threshold of the

ventilator. Training duration started at 5 minutes and increased by 5 minutes in consecutive sessions, until the duration reached 30 minutes [38]. At extubation, no significant differences in MIP were found between the training and control groups. The duration of weaning and rates of reintubation were also similar in both groups [38]. Since the training type was a reduction of sensitivity of the ventilator trigger, patients did not need to sustain a high inspiratory pressure for the entire duration of a breath. Instead, they were only required to briefly overcome the pressure threshold setting to trigger the ventilator, and then received a large mechanical breath. The lack of a sustained inspiratory training load may explain the failure to improve strength.

In contrast to exercises designed to enhance inspiratory muscle endurance, most evidence-based strengthening exercise regimens have utilized pressure-threshold inspiratory muscle training (IMT)[39, 40]. Pressure-threshold IMST devices house a spring loaded, flow independent, one-way valve to ensure consistent resistance throughout inspiration, which may preferentially activate the diaphragm [35]. Early reports were case series describing threshold IMST regimens that based training intensity upon the patient's reported level of exertion during exercise. These reports identified a significant increase in the MIP at weaning, as compared to the start of IMST [40].

Martin et al (2011) conducted the first randomized trial of the effect of IMST on inspiratory strengthening and MV weaning [41]. The researchers compared IMST to a SHAM training regimen, in difficult to wean patients. IMST was delivered using threshold devices at the highest pressure setting that enabled the patients to consistently open the valve, while the SHAM group used a resistive device modified to provide no pressure overload during inspiration. Both groups performed 4 sets of 6–10 breaths, 5 days a week, and all subjects also underwent progressively lengthening breathing trials with minimal or no MV support, as tolerated. Researchers found a significant improvement of MIP following IMST, but not with SHAM training. Importantly, 71% of IMST group patients were weaned, whereas only 47% in the SHAM group were weaned [41].

Subsequent clinical studies in difficult to wean patients have largely confirmed the strengthening and weaning benefits first reported in by Martin et al. The preponderance of the evidence reveals IMST elicits significant improvements in MIP and weaning-related outcomes, as compared to standard care [41–43]. Table 1 summarizes the IMST exercise prescription frequency, intensity, type, time, volume and progression, as supported by clinical studies of IMST to date. In patients who are difficult to wean from MV and cannot tolerate higher inspiratory loads, a protocol emphasizing high-volume of exercise at lower intensities (15%–30% MIP) may be used, whereas patients who are unable to tolerate longer duration of training, a brief, yet intense load (50% MIP – highest load tolerated) may be sufficient induce adaptations.

Recent reports caution that patients who are successfully weaned from MV still tend to have residual inspiratory muscle weakness after discharge from intensive care [44, 45]. Therefore, clinicians should evaluate the MIP of patients who are successfully weaned after a prolonged period of MV and prescribe IMST when inspiratory weakness is identified. Since IMST has shown to enhance exercise capacity and reduce dyspnea in disorders which present with

inspiratory muscle weakness such as COPD and CHF [46, 47], an IMST prescription could help further enhance respiratory strength and exercise capacity in patients who have just successfully weaned from MV [48]. It should be further noted that difficulty weaning is only one of many serious problems that can compromise ICU patients. Among patients who weaned after a prolonged reliance on MV, post-weaning IMST significantly improved MIP and quality of life over usual care [48]. However, the rate of reintubation, post-ICU length of stay and readmission rate did not differ between the groups. Although IMST itself was not associated with adverse events, the intervention group experienced a higher hospital mortality rate that was attributed to their underlying critical illness [48].

Skeletal muscle damage is known to occur following high intensity, unaccustomed exercise and the same is true with the muscles of inspiration [46]. Healthy individuals reported delayed-onset muscle soreness (DOMS) in their anterior neck muscles 24 hours following a 60-minute bout of continuous inspiratory threshold loading, at an intensity of 70% of MIP [46]. DOMS was accompanied by an elevation of slow skeletal troponin I, a biomarker of skeletal muscle injury. However, creatine kinase levels and the force generating capacity of these muscles were not altered [49]. In contrast to the high volume of muscle loading required to induce inspiratory muscle DOMS in the healthy sample, the intensity and duration of clinical IMST is substantially lower and therefore, the risk for DOMS is low. In general, IMST protocols for VIDD have not been associated with serious adverse effects, and the benefits appear to outweigh the risks for most individuals [40, 41, 48, 50, 51].

Phrenic nerve stimulation:

While IMT has been shown to be safe and effective for strengthening patients with VIDD, its use is restricted to patients who are alert and cooperative. In contrast, many patients who are ventilator dependent may initially require periods of sedation or have an altered cognitive state. Unfortunately, an altered arousal limits the ability to participate in “early mobilization” of the respiratory muscles, via IMST. One solution to this conundrum is to exercise the diaphragm with functional electrical stimulation. Permanent phrenic-diaphragm pacing systems are commercially approved to manage ventilator-dependent patients with high cervical spinal cord injury and amyotrophic lateral sclerosis. Permanent phrenic-diaphragm pacing systems may involve a thoracoscopic muscle stimulation approach, or a thoracic phrenic cuff stimulation method. In the thoracoscopic approach, the phrenic nerves are stimulated via electrodes implanted on the diaphragm muscle near each phrenic nerve and turned on via an external controller. An alternative approach involves placement of cervical or intrathoracic cuff electrodes directly on the phrenic nerves, connected to a subcutaneous receiver, and operated with an external antenna and stimulation controller. There is strong evidence in difficult to wean patients with cervical spinal injury showing that phrenic-diaphragm pacing improves gas exchange and promotes early weaning from MV [52, 53]. Other potential indications of phrenic-diaphragm pacing are currently under investigation, including congestive heart failure, chronic obstructive airway disease, Pompe disease, and congenital central hypoventilation syndrome, as well as post-surgical ventilator weaning. Detailed information is available on clinicaltrials.gov (NCT01815554, NCT02354651, NCT03088020, NCT00769678, NCT03083418).

Phrenic-diaphragm stimulation appears to directly counter some known contributors to VIDD. Mechanisms of phrenic nerve stimulation have been investigated with temporary stimulation during cardiac surgeries, which significantly improves the fiber force generation of mechanically-ventilated, stimulated diaphragms [54]. Brief periods of diaphragm stimulation while the patient is on MV appear to significantly reduce oxidative stress [55] and improve mitochondrial respiration in the diaphragm [56]. However, since phrenic-diaphragm pacing systems and temporary intraoperative stimulation require invasive surgical procedures, they may not be suitable for many critically ill patients.

Transvenous phrenic nerve pacing is a less-invasive emerging technology that utilizes central catheters placed in the left subclavian vein. Phrenic pacing catheters contain multiple closely-spaced embedded electrodes positioned near the phrenic nerves and are controlled by an external pulse generator [57]. The transvenous pacing technique efficaciously attenuated VIDD in mechanically ventilated animal models, as measured by a preserved diaphragm thickness and myofiber cross-sectional area, along with improved fatigue resistance [57]. While transvenous phrenic nerve stimulation was shown to be safe in sedated and mechanically ventilated humans [58], this technology is not yet approved for commercial use. Further studies are needed to evaluate its efficacy to mitigate VIDD.

Summary:

Mechanical ventilation is an important lifesaving intervention for critically ill patients. Though MV improves gas exchange and maintains adequate oxygenation, it also results in structural and functional alterations in the diaphragm which further increase dependency on MV. As this review has highlighted, VIDD is a result of a combination of cellular and biochemical alterations occurring within the diaphragm. Increased oxidative stress, activation of proteolytic systems, autophagy and the consequent contractile dysfunction render the diaphragm incapable of handling the work of breathing. This results in difficulty in weaning the patients from ventilatory support.

As prolonged MV is found to escalate cost of hospitalization, reduce quality of life of patients and is associated with high risk of mortality, preventing or significantly reducing the severity of VIDD needs to be given serious consideration as a therapeutic goal in all patients who require short or long term MV support. Inspiratory muscle training is a low-cost [59, 60], evidence-based rehabilitation intervention. The preponderance of the evidence illustrates that short duration, high-intensity daily IMST results in significant strengthening of the inspiratory muscles and appears to promote ventilator weaning. Further, clinical IMST exercise prescription appears safe even for critically ill, difficult to wean patients. Early studies of diaphragm/phrenic nerve stimulation also show initial promise for patients who may not be able to complete voluntary IMST. Future clinical physical therapy practice may include a greater role for inspiratory muscle strength training or diaphragm functional electrical stimulation to prevent or reduce the severity of VIDD.

Acknowledgments

Acknowledgements: This work was supported by (*blinded*).

Funding Sources: R01 AR072328 to ADM and R21 HD090752 to BKS.

References:

1. Esteban A, et al., How is mechanical ventilation employed in the intensive care unit? An international utilization review. *Am J Respir Crit Care Med*, 2000 161(5): p. 1450–1458. [PubMed: 10806138]
2. Hermans G, et al., Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*, 2014 190(4): p. 410–20. [PubMed: 24825371]
3. Chelluri L, et al., Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med*, 2004 32(1): p. 61–9. [PubMed: 14707560]
4. Powers SK, et al., Ventilator-induced diaphragm dysfunction: cause and effect. *Am J Physiol Regul Integr Comp Physiol*, 2013 305(5): p. R464–77. [PubMed: 23842681]
5. Jubran A, Critical illness and mechanical ventilation: effects on the diaphragm. *Respir Care*, 2006 51(9): p. 1054–61; discussion 1062–4. [PubMed: 16934168]
6. Petrof BJ, Jaber S, and Matecki S, Ventilator-induced diaphragmatic dysfunction. *Curr Opin Crit Care*, 2010 16(1): p. 19–25. [PubMed: 19935062]
7. Jung B, et al., Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Medicine*, 2016 42(5): p. 853–861. [PubMed: 26572511]
8. Englert JA and Rogers AJ, Metabolism, Metabolomics, and Nutritional Support of Patients with Sepsis. *Clinics in Chest Medicine*, 2016 37(2): p. 321–31. [PubMed: 27229648]
9. Brodsky MB, et al., Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. *J Crit Care*, 2014 29(4): p. 574–9. [PubMed: 24631168]
10. Mirzakhani H, et al., Muscle weakness predicts pharyngeal dysfunction and symptomatic aspiration in long-term ventilated patients. *Anesthesiology*, 2013 119(2): p. 389–97. [PubMed: 23584384]
11. Kim H, et al., Why patients in critical care do not receive adequate enteral nutrition? A review of the literature. *J Crit Care*, 2012 27(6): p. 702–13. [PubMed: 23084129]
12. de Jonghe B, et al., Intensive care unit-acquired weakness: risk factors and prevention. *Crit Care Med*, 2009 37(10 Suppl): p. S309–15. [PubMed: 20046115]
13. Picard M, et al., Mitochondrial dysfunction and lipid accumulation in the human diaphragm during mechanical ventilation. *Am J Respir Crit Care Med*, 2012 186(11): p. 1140–9. [PubMed: 23024021]
14. Picard M, et al., Metabolic Oversupply and Mitochondrial Dysfunction as a Cause of Diaphragmatic Failure after Mechanical Ventilation. *Faseb Journal*, 2012 26.
15. Bruells CS, et al., Negative pressure ventilation and positive pressure ventilation promote comparable levels of ventilator-induced diaphragmatic dysfunction in rats. *Anesthesiology*, 2013 119(3): p. 652–62. [PubMed: 23838714]
16. Smuder AJ, et al., Crosstalk between autophagy and oxidative stress regulates proteolysis in the diaphragm during mechanical ventilation. *Free Radic Biol Med*, 2018 115: p. 179–190. [PubMed: 29197632]
17. Betters JL, et al., Trolox attenuates mechanical ventilation-induced diaphragmatic dysfunction and proteolysis. *Am J Respir Crit Care Med*, 2004 170(11): p. 1179–1184. [PubMed: 15374845]
18. Shanely RA, et al., Mechanical ventilation depresses protein synthesis in the rat diaphragm. *Am J Respir Crit Care Med*, 2004 170(9): p. 994–9. [PubMed: 15297271]
19. Gibson J, Smith K, and Rennie M, Prevention of disuse muscle atrophy by means of electrical stimulation: maintenance of protein synthesis. *The Lancet*, 1988 332(8614): p. 767–770.
20. Hussain SN, et al., Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med*, 2010 182(11): p. 1377–86. [PubMed: 20639440]
21. Levine S, et al., Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*, 2008 358(13): p. 1327–35. [PubMed: 18367735]

22. Watson AC, et al., Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. *Crit Care Med*, 2001 29(7): p. 1325–31. [PubMed: 11445679]
23. Hussain SN, et al., Prolonged controlled mechanical ventilation in humans triggers myofibrillar contractile dysfunction and myofilament protein loss in the diaphragm. *Thorax*, 2016 71(5): p. 436–45. [PubMed: 27033022]
24. Sassoon CS, Zhu E, and Caiozzo VJ, Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med*, 2004 170(6): p. 626–32. [PubMed: 15201132]
25. Knisely AS, Leal SM, and Singer DB, Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. *J Pediatr*, 1988 113(6): p. 1074–7. [PubMed: 3142983]
26. Carlucci A, et al., Determinants of weaning success in patients with prolonged mechanical ventilation. *Crit Care*, 2009 13(3): p. R97. [PubMed: 19549301]
27. Esteban A, et al., A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med*, 1995 332(6): p. 345–50. [PubMed: 7823995]
28. Grosu HB, et al., Diaphragm muscle thinning in patients who are mechanically ventilated. *Chest*, 2012 142(6): p. 1455–60. [PubMed: 23364680]
29. Jackman RW and Kandarian SC, The molecular basis of skeletal muscle atrophy. *American Journal of Physiology-Cell Physiology*, 2004 287(4): p. C834–C843. [PubMed: 15355854]
30. Smith BK, et al., Chronic intrinsic transient tracheal occlusion elicits diaphragmatic muscle fiber remodeling in conscious rodents. *PLoS One*, 2012 7(11): p. e49264. [PubMed: 23133678]
31. Ramírez-Sarmiento A, et al., Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes. *American journal of respiratory and critical care medicine*, 2002 166(11): p. 1491–1497. [PubMed: 12406842]
32. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med*, 2002 166(4): p. 518–624. [PubMed: 12186831]
33. Aldrich TK and Karpel JP, Inspiratory muscle resistive training in respiratory failure. *The American review of respiratory disease*, 1985 131(3): p. 461–2. [PubMed: 3883864]
34. Aldrich TK and Karpel JP, Inspiratory muscle resistive training in respiratory failure. *Am Rev Respir Dis*, 1985 131(3): p. 461–2. [PubMed: 3883864]
35. Walterspacher S, et al., Activation of respiratory muscles during respiratory muscle training. *Respir Physiol Neurobiol*, 2017 247: p. 126–132. [PubMed: 29037769]
36. Hermans G, et al., Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. *Crit Care*, 2010 14(4): p. R127. [PubMed: 20594319]
37. Powers SK, et al., Mechanical ventilation results in diaphragmatic contractile dysfunction. *Faseb Journal*, 1998 12(4): p. A417–A417.
38. Caruso P, et al., Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. *Clinics*, 2005 60(6): p. 479–484. [PubMed: 16358138]
39. Sprague S.S.a.P.D.H., <Use of inspiratory strength training to wean six patients who were ventilator dependent.pdf> 2003.
40. Martin AD, et al., Use of inspiratory muscle strength training to facilitate ventilator weaning: a series of 10 consecutive patients. *Chest*, 2002 122(1): p. 192–6. [PubMed: 12114357]
41. Martin AD, et al., Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care*, 2011 15(2): p. R84. [PubMed: 21385346]
42. Cader SA, et al., Extubation process in bed-ridden elderly intensive care patients receiving inspiratory muscle training: a randomized clinical trial. *Clin Interv Aging*, 2012 7: p. 437–43. [PubMed: 23118533]
43. Cader SA, et al., Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomised trial. *J Physiother*, 2010 56(3): p. 171–7. [PubMed: 20795923]

44. Chang AT, et al., Reduced inspiratory muscle endurance following successful weaning from prolonged mechanical ventilation. *Chest*, 2005 128(2): p. 553–9. [PubMed: 16100137]
45. Bissett B, et al., Weaned but weary: one third of adult intensive care patients mechanically ventilated for 7 days or more have impaired inspiratory muscle endurance after successful weaning. *Heart Lung*, 2015 44(1): p. 15–20. [PubMed: 25455911]
46. Mathur S, et al., Delayed onset muscle soreness after inspiratory threshold loading in healthy adults. *Cardiopulm Phys Ther J*, 2010 21(1): p. 5–12.
47. Wu J, Kuang L, and Fu L, Effects of inspiratory muscle training in chronic heart failure patients: A systematic review and meta-analysis. *Congenit Heart Dis*, 2018.
48. Bissett BM, et al., Inspiratory muscle training to enhance recovery from mechanical ventilation: a randomised trial. *Thorax*, 2016 71(9): p. 812–9. [PubMed: 27257003]
49. Foster GE, et al., Serum skeletal troponin I following inspiratory threshold loading in healthy young and middle-aged men. *Eur J Appl Physiol*, 2012 112(10): p. 3547–58. [PubMed: 22323298]
50. Bissett B and Leditschke IA, Inspiratory muscle training to enhance weaning from mechanical ventilation. *Anaesth Intensive Care*, 2007 35(5): p. 776–9. [PubMed: 17933168]
51. Smith BK, et al., Inspiratory muscle training in a child with nemaline myopathy and organ transplantation. *Pediatr Crit Care Med*, 2011 12(2): p. e94–8. [PubMed: 20407395]
52. Posluszny JA Jr., et al., Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. *J Trauma Acute Care Surg*, 2014 76(2): p. 303–9; discussion 309–10. [PubMed: 24458038]
53. Gonzalez-Bermejo J, et al., Can diaphragm pacing improve gas exchange? Insights from quadriplegic patients. *Eur Respir J*, 2014 43(1): p. 303–6. [PubMed: 24036240]
54. Ahn B, et al., Phrenic nerve stimulation increases human diaphragm fiber force after cardiothoracic surgery. *Am J Respir Crit Care Med*, 2014 190(7): p. 837–9. [PubMed: 25271750]
55. Mankowski RT, et al., Intraoperative hemidiaphragm electrical stimulation reduces oxidative stress and upregulates autophagy in surgery patients undergoing mechanical ventilation: exploratory study. *J Transl Med*, 2016 14(1): p. 305. [PubMed: 27784315]
56. Martin AD, et al., Effect of intermittent phrenic nerve stimulation during cardiothoracic surgery on mitochondrial respiration in the human diaphragm. *Crit Care Med*, 2014 42(2): p. e152–6. [PubMed: 24126442]
57. Reynolds SC, et al., Mitigation of Ventilator-induced Diaphragm Atrophy by Transvenous Phrenic Nerve Stimulation. *Am J Respir Crit Care Med*, 2017 195(3): p. 339–348. [PubMed: 27500981]
58. Reynolds S, et al., Diaphragm Activation in Ventilated Patients Using a Novel Transvenous Phrenic Nerve Pacing Catheter. *Crit Care Med*, 2017 45(7): p. e691–e694. [PubMed: 28441238]
59. medexsupply. Muscle trainers and resistance 2018; Available from: https://www.medexsupply.com/respiratory-asthma-management--muscle-trainers-and-resistance-respiratorics-threshold-pep-positive-expiratory-pressure-device-10-cs-x_pid-17493.html?pid=17493&gclid=EA1aIQobChMI97uCOprY2QIVGo_ICh3vXQVEEAkYBSABEgJLufD_BwE.
60. POWERbreathe. POWERbreathe plus : breathing training device 2018; Available from: <https://www.powerbreathe.com/plus>.

Figure 1:
Potential mechanisms of VIDD

Table 1.**IMST recommendations for patients on mechanical ventilation**

Parameter	Recommendation
Frequency	1–2 times per day, 5–7 days per week
Intensity	High volume, low intensity (15%–30% MIP) in patients who cannot tolerate higher inspiratory loads Brief, high intensity (30–40% MIP - Highest load tolerated) in patients who are unable to tolerate longer duration of training.
Type	Pressure threshold device
Time	Active intervals: 60–90 seconds Rest intervals: 1–5 minutes
Volume	5–10 breaths for 3–5 sets
Progression	Increase by 1–2 cm H ₂ O every 1–2 days, or up to 10% as tolerated Maintain RPE of 6–8 with opening of IMT valve
Monitoring	Daily: HR, BP, SpO ₂ , RR, EKG & ratings of dyspnea and/or perceived exertion Before and after: maximal inspiratory pressure
Contraindications	Pressure support > 15 cmH ₂ O, PEEP > 10 cmH ₂ O, PaO ₂ < 60 mmHg
Commonly used Inspiratory threshold loading devices for IMST	1. Threshold IMT (Respironics Inc; Murrysville, PA, USA) 2. POWERbreathe (POWERbreathe international Ltd, Warwickshire, England)

HR: Heart Rate, BP: Blood Pressure, SpO₂ : Oxygen saturation (Pulse oximetry), RR: Respiratory rate; EKG: electrocardiogram, RPE: Ratings of Perceived exertion ; MIP: Maximal Inspiratory Pressure, PEEP: Positive End Expiratory Pressure, PaO₂ : Partial pressure of oxygen in arterial blood, IMST: inspiratory muscle strength training