

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

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Patients with impending respiratory failure often require mechanical ventilation (MV) 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 MV 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 MV, 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. (**Cardiopulm Phys Ther J. 2018;0:1–7**) *Key Words: ventilator-induced diaphragm dysfunction, prolonged mechanical ventilation, inspiratory muscle strength training*

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 after surgery with general anesthesia.¹ Despite its significance as a lifesaving intervention in intensive care units (ICUs), 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 toward prolonged MV dependence and failure to wean from MV.⁵

The objectives of this review are to (1) highlight the mechanisms underlying MV-induced diaphragm weakness, (2) elucidate the clinical consequences of VIDD in humans, and (3) summarize exercise training to prevent or reverse diaphragm weakness.

MECHANISMS OF MECHANICAL VENTILATION-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

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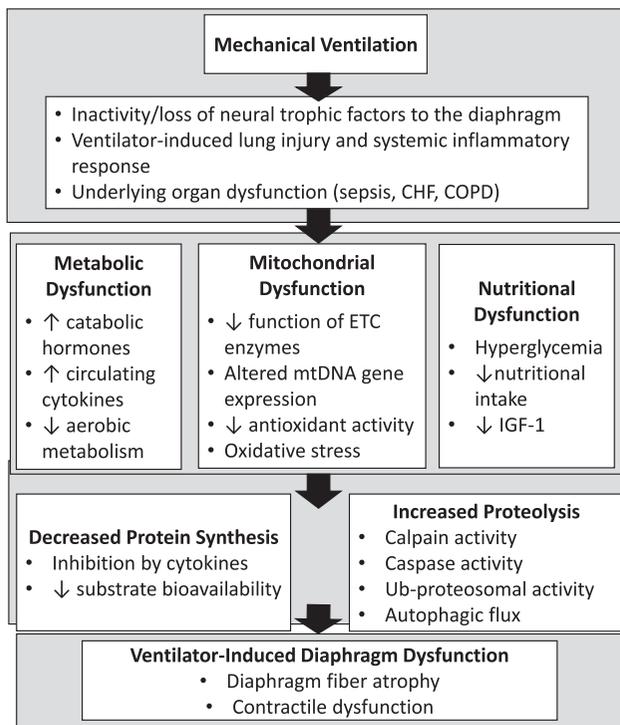
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creates passive inflation of the lungs for gas exchange, which can lead to inactivity of the diaphragm and ventilator-induced lung injury, and trigger a systemic inflammatory response.⁶ Some underlying causes of critical illness/organ failure, including sepsis, chronic heart failure (CHF), and chronic obstructive pulmonary disease (COPD) seem 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 Ventilator-Induced Diaphragmatic Dysfunction

Clinical studies of VIDD have reported increased levels of diaphragm and/or circulating proinflammatory cytokines, which can in turn alter nutritional balance.⁸ Prolonged invasive ventilation places patients at a high risk of both aspiration⁹ 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, whereas aggressive insulin therapy may mitigate the severity of weakness.¹²



ETC: electron transport chain; mtDNA: mitochondrial DNA; IGF: insulin like growth factor; CHF: Chronic Heart Failure; COPD: Chronic Obstructive Pulmonary Disease

Fig. 1. Potential mechanisms of VIDD. VIDD, ventilator-induced diaphragmatic dysfunction.

Mitochondrial Dysfunction in Ventilator-Induced Diaphragmatic Dysfunction

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 Reactive Oxidative Species in Ventilator-Induced Diaphragmatic Dysfunction

With prolonged MV, electron transport chain activity decreases and levels of ROS increase in human diaphragms.¹³ Elevated levels of ROS enhance the expression of proteins that are needed to activate the ubiquitin–proteasome system and autophagy.^{15,16} Reactive oxidative species increase cytosolic calcium levels, which in turn activate the calpain and caspase 3 proteolytic pathways.⁴ By 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

Mechanical ventilation has been shown to slow down the rate of protein synthesis diaphragms of rats in as early as 6 hours after 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 seems 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}

VENTILATOR-INDUCED DIAPHRAGMATIC DYSFUNCTION: 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 with patients exposed to less than 4 hours of MV support.²³ However, the rate of force decrement seems to be attenuated with assisted MV modes that permit synchronization of inspiratory efforts with the ventilator.²⁴

VENTILATOR-INDUCED DIAPHRAGMATIC DYSFUNCTION: 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 to 5 days of controlled MV.²¹ Compared with controls who used <2 hours of 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 biomarkers of muscle proteolysis.²¹ Diaphragms of mechanically ventilated patients have also demonstrated the presence of oxidative stress-induced autophagy, and upregulation of the autophagic system was confined only to the diaphragm.²⁰

CLINICAL IMPLICATIONS OF MECHANICAL VENTILATION-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 AS A REHABILITATIVE TOOL IN VENTILATOR-INDUCED DIAPHRAGMATIC DYSFUNCTION

Inspiratory muscle training (IMT) 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 through intermittent tracheal occlusions, training increased the cross-sectional area of fast glycolytic fibers in the diaphragm and parasternal muscles.³⁰ Diaphragm fiber hypertrophy cannot be readily measured in clinical populations, but there are some evidence that the accessory muscles of respiration may hypertrophy after respiratory strengthening exercises.³¹ The global strength of the inspiratory muscles can be estimated using maximal inspiratory pressure (MIP), a noninvasive, quick, and inexpensive maximal voluntary contraction test.³² Maximal inspiratory pressure is a common outcome measure for studies evaluating the effects of inspiratory muscle strength training (IMST). In addition, 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 1980s. 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% to 20% of their peak negative inspiratory pressure, and individual training durations were progressed from 5 to 30 minutes.³³ 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 IMT has shown to activate the accessory muscles of inspiration more than the diaphragm.³⁴ Subsequent animal and human studies have identified diaphragm weakness as a primary limiting factor for weaning.^{35,36} 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.³⁷ 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.³⁷ 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.³⁷ Because 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 used pressure-threshold IMT.^{38,39} Pressure-threshold IMST devices house a spring-loaded, flow-independent, 1-way valve to ensure consistent resistance throughout inspiration, which may preferentially activate the diaphragm.³⁴ Early reports were case series describing threshold IMST regimens that based training intensity on 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.³⁹

Martin et al⁴⁰ (2011) conducted the first randomized trial of the effect of IMST on inspiratory strengthening and MV weaning. The researchers compared IMST with a SHAM training regimen, in difficult to wean patients. Inspiratory muscle strength training was delivered using threshold devices at the highest pressure setting that enabled the patients to consistently open the valve, whereas the SHAM group used a resistive device modified to provide no pressure overload during inspiration. Both groups performed 4 sets of 6 to 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 after IMST, but not with SHAM training. Importantly, 71% of IMST group patients were weaned, whereas only 47% in the SHAM group were weaned.⁴⁰

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.⁴⁰⁻⁴² 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 to 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.^{43,44} 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. Because IMST has shown to enhance exercise capacity and reduce dyspnea in disorders, which present with inspiratory muscle weakness such as COPD and CHF,^{45,46} an IMST prescription could help further enhance respiratory strength and exercise capacity in patients who have just successfully weaned from MV.⁴⁷ 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, postweaning IMST significantly improved MIP and quality of life over usual care.⁴⁷ 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.⁴⁷

Skeletal muscle damage is known to occur after high-intensity, unaccustomed exercise, and the same is true with the muscles of inspiration.⁴⁵ Healthy individuals reported delayed-onset muscle soreness (DOMS) in their anterior neck muscles 24 hours after a 60-minute bout of continuous inspiratory threshold loading, at an intensity of 70% of MIP.⁴⁵ Delayed-onset muscle soreness 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.⁴⁸ 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 are substantially lower, and therefore, the risk of DOMS is low. In general, IMST protocols for VIDD have not been associated with serious adverse effects, and the benefits seem to outweigh the risks for most individuals.^{39,40,47,49,50}

PHRENIC NERVE STIMULATION

Although 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. By 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, through 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 through electrodes implanted on the diaphragm muscle near each phrenic nerve and turned on through an external controller. An alternative approach involves placement of cervical or intrathoracic cuff electrodes directly on the phrenic nerves, connected to

TABLE 1

Inspiratory Muscle Strength Training (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 and ratings of dyspnea, and/or perceived exertion Before and after: maximal inspiratory pressure
Contraindications	Pressure support > 15 cm H ₂ O, PEEP > 10 cm H ₂ O, and PaO ₂ < 60 mm Hg
Commonly used inspiratory threshold loading devices for IMST	1. Threshold IMT (Respironics, Inc., Murrysville, PA) 2. POWERbreathe (POWERbreathe International, Ltd., Warwickshire, United Kingdom)

BP, blood pressure; EKG, electrocardiogram; HR, heart rate; IMST, inspiratory muscle strength training; IMT, inspiratory muscle training; MIP, maximal inspiratory pressure; PaO₂, partial pressure of oxygen in arterial blood; PEEP, positive end expiratory pressure; RPE, ratings of perceived exertion; RR, respiratory rate; SpO₂, oxygen saturation (pulse oximetry).

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.^{51,52} 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 postsurgical ventilator weaning. Detailed information is available on clinicaltrials.gov (NCT01815554, NCT02354651, NCT03088020, NCT00769678, NCT03083418).

Phrenic-diaphragm stimulation seems 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.⁵³ Brief periods of diaphragm stimulation while the patient is on MV seem to significantly reduce oxidative stress⁵⁴ and improve mitochondrial respiration in the diaphragm.⁵⁵ However, because 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 uses 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.⁵⁶ 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.⁵⁶ Although transvenous phrenic nerve stimulation was shown to be safe in sedated and mechanically ventilated humans,⁵⁷ 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. Although 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 and 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,^{58,59} 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 seems to promote ventilator weaning. Furthermore, clinical IMST exercise prescription seems 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 IMST or diaphragm functional electrical stimulation to prevent or reduce the severity of VIDD.

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